

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
DILIA RODRIGUEZ D'ALEMAN

ASUNTO	Radicación	08 116 272
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	09095
	Folios	4

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐
No. Solicitud Internacional PCT/US2007/064911			
Fecha de Presentación Internacional 26/Marzo/2007			

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 comunica:

1. Documentos estudiados

Descripción:	Folios 5 a 40	30/Octubre/2008
Reivindicaciones:	Folios 41 a 55	30/Octubre/2008
Prioridad:	US 60/788,185	31/Marzo/2006
	US 11/688,016	19/Marzo/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "composiciones oftálmicas que comprenden alcaftadina y métodos para administrarlas" (modificado en el folio 71).

El problema planteado en esta solicitud consiste en la necesidad de suministrar nuevas terapias contra las alergias oculares que sean ventajosas en eficacia y duración de la acción, ofreciendo al mismo tiempo similares perfiles de seguridad.

Para resolver este problema técnico la solicitud en estudio proporciona una composición del compuesto alcaftadina.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 31/55.

4. Excepción a la Patentabilidad (Art 20 D 486 literal d)

El objeto de las reivindicaciones 1 – 51 y 62 – 118 no es patentable de acuerdo con el Art citado.

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Dentro del capítulo reivindicatorio se encuentran términos como hidrato, solvato y polimorfos que si bien se nombran en la descripción y son conocidos por la persona del oficio medianamente versada en la materia, no se encuentra soporte en la divulgación de dichas formas reclamadas y el procedimiento para su producción. Igualmente, los términos N-óxidos y profármacos no encuentran soporte en el capítulo descriptivo, por cuanto están relacionados de forma genérica y no define inequívocamente la estructura química de dichas formas, ni el método para su elaboración. Por tal motivo se sugiere al solicitante eliminar estos términos del alcance del capítulo reivindicatorio.

Las reivindicaciones 57 – 61 y 124 – 128 no tienen sustento en la descripción porque reclaman un kit que no se menciona en la descripción.

La reivindicación 61 presenta una dependencia incorrecta, porque se habla de un kit (producto) pero se define por una característica de proceso (esterilización). Se recuerda al solicitante que esta manera de reclamar “el producto por el proceso” es válida solo cuando el producto obtenido no se puede definir por sí mismo y en ese caso sus características inequívocamente no se pueden definir de otra manera, el cual no es el caso de la actual solicitud. Por lo tanto se sugiere que las reivindicaciones que definen el kit sean independientes de las reivindicaciones del proceso.

Las reivindicaciones 129 – 132 y 136 – 140 no son claras porque reclaman nuevamente la composición ya reclamada sin aportar ninguna característica técnica esencial al caracterizar las composiciones por su uso en el tratamiento de ciertas patologías. Se requiere al solicitante eliminarlas.

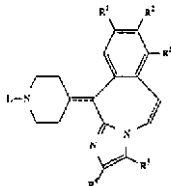
Las reivindicaciones 133 – 135 no son claras porque aunque reclaman una composición, se caracterizan como un método de tratamiento por la administración de alcaftadina. Se sugiere al solicitante eliminarlas

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: marzo 31 de 2006 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	US 5'468.743	Imidazo[2,1-b]benzazepine derivatives, compositions and method of use	21/noviembre/1995

D1 http://worldwide.espacenet.com/publicationDetails/biblio?DB=worldwide.espacenet.com&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=19951121&CC=US&NR=5468743A&KC=A
divulga (Abstract) un compuesto utilizado como antialérgicos de fórmula



7. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 52 consiste en una composición oftálmica que comprende alcaftadina.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
composición oftálmica	Composición (reivindicación 10)
alcaftadina	6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5-imidazo[2,1-b] [3] benzazepine-3-carboxaldehyde (reivindicación 5, compuesto 6)

Las características **esenciales** de la composición de la reivindicación 52 habían sido divulgadas previamente en D1 el cual enseña el compuesto 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5-imidazo[2,1-b] [3] benzazepine-3-carboxaldehyde (reivindicación 5, compuesto 6) y las composiciones que lo contienen en una cantidad terapéuticamente activa (reivindicación 10).

En consecuencia, la reivindicación 52 no es nueva a la luz de la divulgación del documento D1.

Las reivindicaciones dependientes 53 - 56 no mencionan alguna característica que haga nueva a la composición de la reivindicación 52, por lo cual también se considera que no son nuevas.

La reivindicación 119 consiste en una composición oftálmica que comprende el compuesto de formula II.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
Composición oftálmica	Composición (reivindicación 10)
Ácido 6,11-dihydro-11-(1-methyl-4-piperidiniliden)-5H-imidazo[2,1-b] [3] benzazepine-3-carboxílico	Ácido 6,11-dihydro-11-(1-methyl-4-piperidiniliden)-5H-imidazo[2,1-b] [3] benzazepine-3-carboxílico (Reivindicacion 5, compuesto 7)

Las características **esenciales** de la composición de la reivindicación 52 habían sido divulgadas previamente en D1 el cual enseña el compuesto ácido 6,11-dihydro-11-(1-methyl-4-piperidiniliden)-5H-imidazo[2,1-b] [3] benzazepine-3-carboxílico (Reivindicacion 5, compuesto 7) y las composiciones que lo contienen en una cantidad terapéuticamente activa (reivindicación 10).

En consecuencia, la reivindicación 119 no es nueva a la luz de la divulgación del documento D1.

Las reivindicaciones dependientes 120 – 123 no mencionan alguna característica que haga nueva a la composición de la reivindicación 119, por lo cual se considera que no son nuevas.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5'468.743	52 – 56, 119 – 140	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 (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de

no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
01 JUN. 2012

Elaborado por: María del Pilar Obando P.
Revisado por: Consuelo Leguizamon 

Effects of ACE inhibition and β -receptor blockade on energy metabolism in rats postmyocardial infarction

STEPHANIE HÜGEL, MICHAEL HORN, MARK DE GROOT, HELGA REMKES, CHARLOTTE DIENESCH, KAI HU, GEORG ERTL, AND STEFAN NEUBAUER
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Hügel, Stephanie, Michael Horn, Mark De Groot, Helga Remkes, Charlotte Dienesch, Kai Hu, Georg Ertl, and Stefan Neubauer. Effects of ACE inhibition and β -receptor blockade on energy metabolism in rats postmyocardial infarction. *Am. J. Physiol.* 277 (Heart Circ. Physiol. 46): H2167–H2175, 1999.—Chronic treatment with β -receptor blockers or angiotensin-converting enzyme (ACE) inhibitors in heart failure can reduce mortality and improve left ventricular function, but the mechanisms involved in their beneficial action remain to be fully defined. Our hypothesis was that these agents prevent the derangement of cardiac energy metabolism. Rats were subjected to myocardial infarction (MI) or sham operation. Thereafter, animals were treated with bisoprolol, captopril, or remained untreated. Two months later, cardiac function was measured in the isolated heart by a left ventricular balloon (pressure-volume curves), and energy metabolism of residual intact myocardium was analyzed in terms of total and isoenzyme creatine kinase (CK) activity, steady-state levels (ATP, phosphocreatine), and turnover rates (CK reaction velocity) of high-energy phosphates (^{31}P nuclear magnetic resonance) and total creatine content (HPLC). Bisoprolol and partially captopril prevented post-MI hypertrophy and partially prevented left ventricular contractile dysfunction. Residual intact failing myocardium in untreated, infarcted hearts showed a 25% decrease of the total, a 26% decrease of MM-, and a 37% decrease of the mitochondrial CK activity. Total creatine was reduced by 15%, phosphocreatine by 21%, and CK reaction velocity by 41%. Treatment with bisoprolol or captopril largely prevented all of these changes in infarcted hearts. Thus the favorable functional effects of β -receptor blockers and ACE inhibitors post-MI are accompanied by substantial beneficial effects on cardiac energy metabolism.

adrenergic antagonist; angiotensin-converting enzyme inhibitors; infarction; remodeling; energy metabolism

THE PROGNOSIS of patients with heart failure remains poor, although chronic treatment with angiotensin-converting enzyme (ACE) inhibitors (8, 37, 42) and, more recently, β -receptor blockers (4, 6, 44) may reduce mortality. The mechanisms of the protective effects of ACE inhibitors and β -receptor blockers are only partially understood and are, almost certainly, complex and multifactorial. One attractive hypothesis is that the failing heart is energy depleted (16, 19, 20, 30), and that the beneficial functional effects of ACE inhibitors and β -receptor blockers are accompanied and possibly accounted for, by a preservation of energy metabolism. Although a large number of experimental studies have

demonstrated the protective functional effects of ACE inhibitors and, to a lesser extent, of β -receptor blockers in heart failure models, only sporadic evidence exists on the energetic effects of these compounds in heart failure (24, 36, 45). The poor prognosis of patients with heart failure necessitates the search for novel therapeutic approaches, and the demonstration of a protective effect of established heart failure drugs such as ACE inhibitors or β -receptor blockers on energy metabolism may fuel the search for therapies targeted more specifically to cellular systems involved in the regulation of energy metabolism.

The purpose of this study was thus to define the geometric, functional, and energetic cardiac effects of chronic treatment with the β -receptor blocker bisoprolol and the ACE inhibitor captopril in a clinically highly relevant model of cardiac dysfunction, occurring postmyocardial infarction (MI) in the rat. Using a combination of nuclear magnetic resonance (NMR) spectroscopy, high-performance liquid chromatography (HPLC), and enzyme analysis, we define steady-state levels, turnover rates, and free energy change of high-energy phosphates as well as tissue activities (V_{max}) of creatine kinase (CK) isoenzymes.

MATERIALS AND METHODS

Animals and experimental MI. Infarcts or sham operations were performed in 12-wk-old Wistar rats kept in a 12:12-h light-dark cycle. Left coronary artery ligation (MI) was induced by a previously described technique (11, 35). A left thoracotomy was performed under ether anesthesia and positive pressure ventilation. The heart was rapidly exteriorized by applying gentle pressure on both sides of the thorax. The left coronary artery was ligated between the pulmonary outflow tract and the left atrium. The heart was then replaced into the thorax, lungs were inflated by increasing positive end-expiratory pressure, and the wound was closed immediately. Sham operation was performed using an identical procedure except that the suture was passed under the coronary artery without ligation. Mortality rate of infarcted rats for the first 24 h after the operation was 40–50%. Surviving rats were kept on commercial rat chow and water ad libitum. The investigation conformed with the "Guiding Principles for Research Involving Animals and Human Beings."

Bisoprolol and captopril treatment and experimental groups. Rats were randomly assigned to one of six groups: untreated sham (sham, $n = 9$), untreated MI (MI, $n = 8$), bisoprolol-treated sham (sham-Biso, $n = 13$), bisoprolol-treated MI (MI-Biso, $n = 6$), captopril-treated sham (sham-Capto, $n = 11$), and captopril-treated MI (MI-Capto, $n = 6$). After surgery, bisoprolol-treated groups received $60 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ bisoprolol with the drinking water. Captopril was added to the drinking water at 2 g/l. These concentrations were chosen because they were shown to exert a small but significant

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hemodynamic effect [10% reduction of blood pressure (captopril) or heart rate (bisoprolol)] (3, 24). Because bisoprolol has a slightly bitter taste, 5% glucose was added to the drinking water of all groups. Drinking water was freshly prepared every other day. Therapy was continued for 8 wk and was stopped 1 day before the isolated heart experiment.

Isolated rat heart preparation. Eight weeks after the left coronary artery ligation or sham operation, rats were anesthetized with the injection of 50 mg pentobarbital sodium intraperitoneally. A transverse laparotomy and left and right anterolateral thoracotomy were performed, and the heart was rapidly excised and immersed in ice-cold buffer. The aorta was dissected free and mounted onto a cannula attached to a perfusion apparatus, as previously described (2). Retrograde perfusion of the heart was begun in the Langendorff mode at a constant temperature of 37°C and at a constant coronary perfusion pressure of 100 mmHg. A small vent made out of polyethylene tubing was pierced through the apex of the left ventricle to allow drainage of flow from the Thebesian veins. For control perfusion, phosphate-free Krebs-Henseleit buffer was used containing (mM) 118 NaCl, 4.7 KCl, 1.75 CaCl₂, 1.2 MgSO₄, 0.5 ethylenediaminetetraacetate tetrasodium, 25.0 NaHCO₃, and 11.0 glucose. Equilibrating the buffer with 95% O₂-5% CO₂ yielded a pH of 7.4. Coronary flow was continuously measured by an ultrasonic flow probe (Transonic Systems, Ithaca, NY) built into the perfusate inflow tubing. As previously shown (2), the perfusion system allowed maintenance of hearts in a steady state for at least 90 min with changes of < 5% for all mechanical and metabolic parameters.

Cardiac performance measurements. A water-filled latex balloon was inserted into the left ventricle through an incision in the left atrial appendage, via the mitral valve, and secured by a ligature. The balloon was connected to a Statham P23 Db pressure transducer (Gould Instruments, Glen Burnie, MD) via a small-bore polyethylene tubing for continuous measurement of left ventricular pressure and heart rate on a four-channel recorder (Graphtec, Tokyo, Japan). Performance was estimated as the product of heart rate and left ventricular developed pressure (LVDP, mmHg/min). Frank-Starling curves were obtained by increasing the volume of the intraventricular balloon by 0.05-ml increments until LVDP reached a maximum.

³¹P NMR spectroscopy. The perfused hearts were placed into a 20-mm NMR sample tube and inserted into a probe seated in the bore of a superconducting superwide bore (150 mm), 7.05-Tesla magnet (Bruker, Rheinstetten, Germany) as previously described (30). Hearts were bathed in their own perfusate, which was pumped from the NMR tube at a level immediately above the heart. An Aspect 3000 computer (Bruker) was used in the pulsed Fourier transform mode to generate ³¹P NMR spectra at 121.50 MHz. A 14-channel Shimadzu Unit served to homogenize the magnetic field. Single ("one pulse") spectra were accumulated over 5-min periods, and averaging data from 152 free induction decays were obtained using a pulse time of 37.6 μs, a pulse angle of 45°, and an interpulse delay of 1.93 s. The resonance areas corresponding to ATP, phosphocreatine (PCr), and P_i, which are proportional to the number of phosphorus atoms of the respective compound, were measured by integration using the NMR1 software (TRIPOS, Munich, Germany). Relative saturation factors for each resonance were determined by comparing spectra to fully relaxed spectra obtained using a pulse angle of 45° and an interpulse delay of 15 s; correction factors were 1.12 ± 0.03 for PCr and 1.08 ± 0.05 for P_i (n = 15); spectra were corrected accordingly. Myocardial ATP content was found to be 28.3 ± 5.6 nmol/mg protein in sham and 28.0 ± 3.0

nmol/mg protein in MI hearts by HPLC (30); the myocardial contents of the other metabolites were calculated by multiplying the ratio of resonance area of metabolite to the [γ-P]ATP area by 28.3 nmol/mg protein for sham and by 28.0 nmol/mg protein for MI hearts. This assumes that neither bisoprolol nor captopril affected normal ATP content, demonstrated before for sham-operated and infarcted hearts (30), which is most likely the case. ATP could not be determined by HPLC in this study, because left ventricles were fixed in Formalin for infarct size measurements, and right ventricles were cut off and frozen allowing determination of total creatine and CK activity. ATP levels were not determined in the right ventricle because we cut off the right ventricle from the beating heart and froze it after several seconds, because freeze-clamping the beating heart was impossible when we wanted to determine infarct size. In our experience, ATP levels cannot reliably be determined when tissue is not directly freeze-clamped. Intracellular pH (pH_i) was measured by comparing the chemical shift between P_i and creatine phosphate with values obtained from a standard curve. The free cytosolic ADP concentration was calculated by using [ATP], [PCr], and [H⁺] measured in the intact beating heart by ³¹P-NMR spectroscopy, and total creatine was measured chemically in the right ventricular homogenates by assuming that CK is in equilibrium and by using a CK equilibrium constant of 1.66 × 10⁹ M⁻¹ (25, 43)

$$[\text{ADP}] = ([\text{ATP}][\text{Cr}]_{\text{free}})/([\text{PCr}][\text{H}^+]/1.66 \times 10^9)$$

The free energy change of ATP hydrolysis (ΔG) was calculated as

$$\Delta G \text{ (kJ/mol)} = \Delta G^\circ + RT \ln ([\text{ADP}][\text{P}_i]/[\text{ATP}])$$

where ΔG° (−30.5 kJ/mol) is the value of ΔG under standard conditions of molarity, temperature, pH, and [Mg²⁺] (14); R is the gas constant (8.3 J/mol K); and T is the temperature in Kelvin (K).

³¹P-NMR magnetization transfer measurements of CK kinetics. For magnetization transfer experiments, each broadband pulse was preceded by a low-power, narrow-band pulse at the resonance frequency of [γ-P]ATP for 0, 0.3, 0.6, 1.2, 2.4, or 3.6 s as previously described (29, 30). Separate studies showed that the narrow-band pulse directly attenuated the PCr magnetization by <5% when the carrier frequency was placed 2.5 ppm downfield from the resonance of PCr. For each of the six saturation transfer spectra, 64 scans were accumulated by repetitively cycling through the six different times of presaturation. Thus any metabolic deterioration occurring during the saturation transfer measurement was equally distributed among the spectra. A complete saturation transfer experiment was acquired in 32 min. Stability of the preparation was assessed by comparing one-pulse spectra obtained before and after each magnetization transfer experiment. Magnetization transfer measurements of the forward CK reaction phosphocreatine → [γ-P]ATP were analyzed according to the two-site chemical exchange model of Forsen and Hoffman (9), providing estimates of the pseudo first-order rate constant (k_{on}) and the intrinsic longitudinal relaxation time for PCr (T₁). Briefly, as the time of saturation at [γ-P]ATP, t, is increased from 0 to 3.6 s, the integrated signal intensity of the PCr resonance peak (M_t) decays from M₀ to M_∞ (defined as magnetization at zero and infinite saturation times, respectively) with a time constant τ₁ as

$$M_t = M_\infty + (M_0 - M_\infty)e^{-t/\tau_1}$$

where

$$1/\tau_1 = 1/T_1 + k_{on}$$

use in parenteral formulations. The degree of substitution of hydroxypropyl groups can vary.

18 Comments

Hydroxypropyl betadex has been investigated as an absorption/permeation enhancer in oral,¹⁵ transdermal,¹⁶ and nasal¹⁷ systems. It was found to be effective in increasing penetration in some studies, although the mechanism of action may be compound specific.

19 Specific References

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- 3 Aibers E, Müller BW. Cyclodextrin derivatives in pharmaceuticals. *Crit Rev Ther Drug Carrier Syst* 1995; 12: 311–337.
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20 General References

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21 Author

W Cook.

22 Date of Revision

27 February 2009.

Hydroxypropyl Cellulose

1 Nonproprietary Names

BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulose
USP-NF: Hydroxypropyl Cellulose

2 Synonyms

Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulosum; hypolose; *Klucel*; *Nisso HPC*; oxypropylated cellulose.

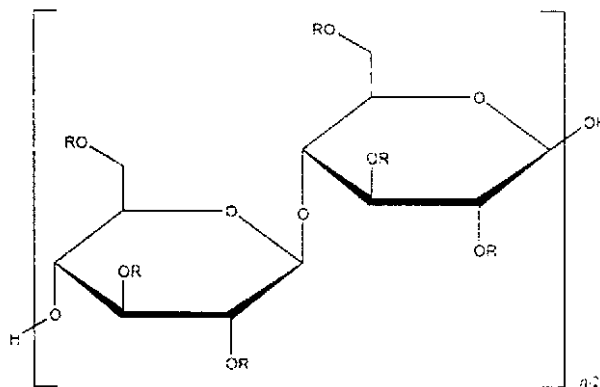
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula and Molecular Weight

The PhEur 6.0 and USP32–NF27 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000; see also Section 10.

5 Structural Formula



R is H or $[\text{CH}_2\text{CH}(\text{CH}_3)\text{O}]_m\text{H}$ where m is a common integral number of cellulose derivatives.

Hydroxypropyl cellulose is an ether of cellulose where some of the hydroxyl groups of the cellulose have been hydroxypropylated forming $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3$ groups. The average number of

hydroxyl groups in the glucose ring substituted is referred to as the degree of substitution (DS). Complete substitution would provide a DS of 3.0. Because the hydroxypropyl group added contains a hydroxyl group, this can also be etherified during preparation of hydroxypropyl cellulose. When this occurs, the number of moles of hydroxypropyl groups per glucose ring, or moles of substitution (MS), can be higher than 3. Hydroxypropyl cellulose must have an MS value of approximately 4 in order to have good solubility in water.

6 Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; see Table I.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder,¹¹ film-coating,¹² and extended-release-matrix former.¹³⁻¹⁵ Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.¹¹⁻¹³ Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.^{14,15} The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Blends of hydroxypropyl cellulose and other cellulosic polymers have been used to improve wet granulation characteristics and tableting characteristics, as well as to achieve better control and manipulation of the rate of drug release.¹²⁻¹⁵ As an alternative technology to wet granulation, dry granulation and direct compression of hydroxypropyl cellulose formulations have been reported to exhibit acceptable tableting and flow characteristics for application in extended-release matrix tablets.^{16,17} Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose together with an amount of methyl cellulose or ethanolic solutions have been used.¹⁸⁻²⁰ Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; see Hydroxypropyl Cellulose, Low-substituted.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.²¹⁻²³

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Table I: Typical uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

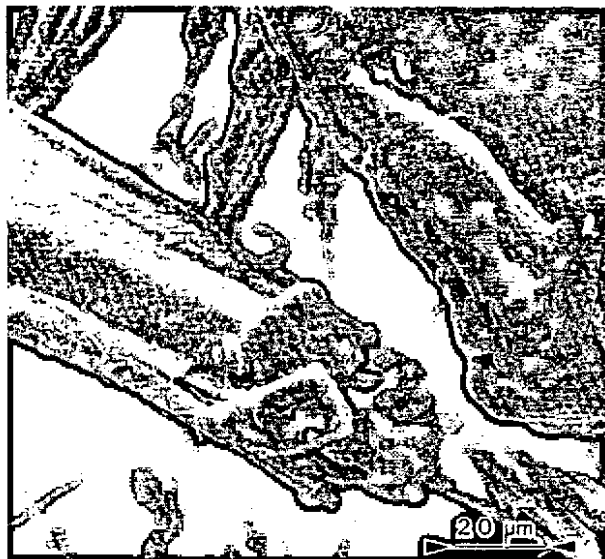
8 Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. See also Section 10.

SEM 1: Excipient: hydroxypropyl cellulose (Klucel); manufacturer: Ashland Aqualon Functional Ingredients; magnification: 600x.



SEM 2: Excipient: hydroxypropyl cellulose (Klucel); manufacturer: Ashland Aqualon Functional Ingredients; magnification: 600x.



9 Pharmacopeial Specifications

See Table II. See also Section 18.

10 Typical Properties

Acidity/alkalinity pH = 5.0–8.5 for a 1% w/w aqueous solution (as stated in PhEur 6.0).

Density (bulk) ≈0.5 g/cm³

Interfacial tension 12.5 mN/m for a 0.1% w/w aqueous solution compared with mineral oil.

Melting point Softens at 130 °C; chars at 260–275 °C.

Moisture content Hydroxypropyl cellulose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative

Table II: Pharmacopeial specifications for hydroxypropyl cellulose.

Test	JP XV	PhEur 6.0	USP32-NF27
Identification	—	—	—
Characters	—	—	—
Apparent viscosity	—	—	—
Appearance of solution	—	—	—
pH ^(a)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	≤ 5.0%	≤ 7.0%	≤ 5.0%
Residue on ignition	≤ 0.5%	—	≤ 0.2%
Sulfated ash	—	≤ 1.6%	—
Arsenic	≤ 2 ppm	—	—
Chlorides	≤ 0.142%	≤ 0.5%	—
Lead	—	—	≤ 0.001%
Heavy metals	≤ 20 ppm	≤ 20 ppm	≤ 20 µg/g
Silica	—	≤ 0.6%	—
Sulfate	≤ 0.048%	—	—
Assay of hydroxypropoxy groups	53.4–77.5%	—	≤ 80.5%

(a) pH: 1 g in 50 mL for JP XV; 1 g in 100 g for PhEur 6.0; 1 g in 100 mL for USP32-NF27.

Table III: Moisture content of Klucel (Aqualon).

Grade	Molecular weight	Moisture (%)
Klucel EF	≈ 80 000	0.59
Klucel LF	≈ 95 000	2.21
Klucel JF	≈ 140 000	1.44
Klucel GF	≈ 370 000	1.67
Klucel MF	≈ 850 000	1.52
Klucel HF	≈ 1 150 000	4.27

humidity and 12% w/w at 84% relative humidity. See Table III. See also Figure 1.

NIR spectra see Figure 2.

Particle size distribution

Klucel (regular grind), minimum 85% (minimum 80% for Klucel H grades) through a US #30 mesh (590 µm), and minimum 99% through a US #20 mesh (840 µm);

Klucel (fine-grind), minimum 99% through a US #60 mesh (250 µm), minimum 90% through a US #80 mesh (177 µm), and minimum 80% through a US #100 mesh (149 µm);

Nisso HPC-I (regular type); 99% through a US #40 mesh sieve (350 µm);

Nisso HPC-I (fine powder type); 99% through a US #100 mesh sieve (150 µm).

Refractive index $n_D^{25} = 1.3353$ for a 2% w/v aqueous solution.

Solubility

Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

Hydroxypropyl cellulose is freely soluble in water below 38 °C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45 °C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol (95%); methanol; propan-2-ol (95%); and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids that are borderline solvents, such as acetone; butyl acetate; cyclohexanol; dichloromethane; lactic acid; methyl acetate; methyl ethyl ketone; propan-2-ol (99%); and *tert*-butanol.

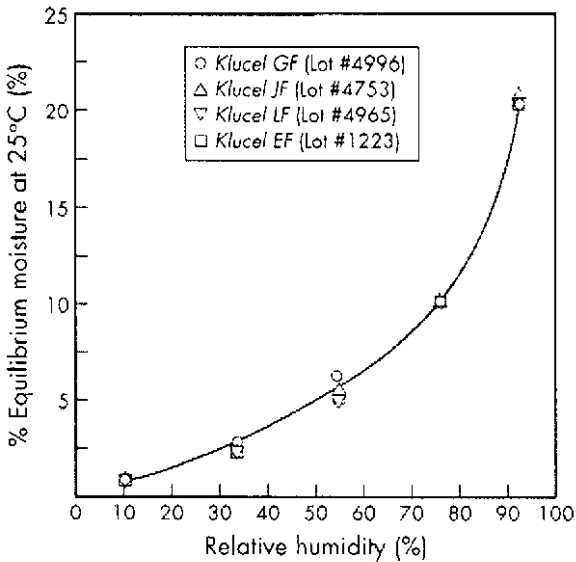


Figure 1: Equilibrium moisture content of various grades of hydroxypropyl cellulose (Klucel, Ashland Aqualon Functional Ingredients).

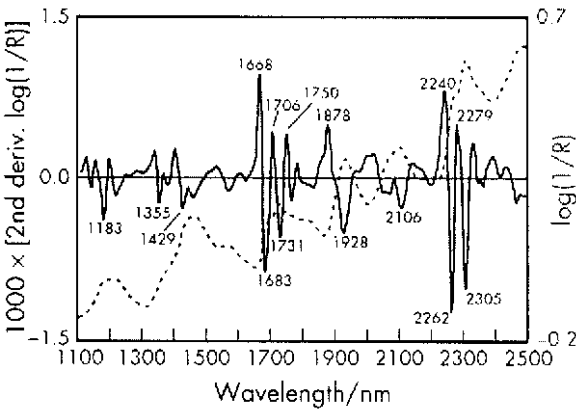


Figure 2: Near-infrared spectrum of hydroxypropyl cellulose measured by reflectance.

The higher-viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5–15%) of a cosolvent. For example, dichloromethane is a borderline solvent for Klucel HF and solutions have a granular texture, but a smooth solution may be produced by adding 10% methanol.

Hydroxypropyl cellulose is compatible with a number of high-molecular-weight, high-boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are acetylated mono-glycerides, glycerides, pine oil, polyethylene glycol, and polypropylene glycol.

Specific gravity 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20 °C.

Surface tension see Table IV.

Viscosity (dynamic) A wide range of viscosity types are commercially available; see Table V. Solutions should be prepared by gradually adding the hydroxypropyl cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. See also Section 11 for information on solution stability.

Table IV: Surface tension (mN/m) of aqueous solutions of Nisso HPC [Nippon Soda Co. Ltd.] at 20°C.

Grade	Surface tension (mN/m) at 20°C for aqueous solutions of stated concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Table V: Viscosity of aqueous solutions of Klucel (Ashland Aqualon Functional Ingredients) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions of stated concentration			
	1%	2%	5%	10%
Klucel HF	1500–3000	—	—	—
Klucel MF	—	4000–6500	—	—
Klucel GF	—	150–400	—	—
Klucel JF	—	—	150–400	—
Klucel LF	—	—	75–150	—
Klucel EF	—	—	—	200–600

11 Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration. At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur owing to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to decrease gradually until the viscosity drops suddenly at about 45°C owing to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.²⁰ However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may occur. Certain enzymes produced by microbial action will degrade hydroxypropyl cellulose in solution.²⁴ Therefore, for prolonged storage, an antimicrobial preservative should be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions have optimum stability when the pH is maintained at 6.0–8.0, and also when the solution is protected from light, heat, and the action of microorganisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

Table VI: Compatibility of hydroxypropyl cellulose (Nisso HPC) with inorganic salts in aqueous solutions.^(a)

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferricyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

(a) S, completely soluble; T, turbid white; I, insoluble

12 Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration; see Table VI. Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials.

The balance of the hydrophilic-lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system; see Table VII.

Table VII: Variation in precipitation temperature of hydroxypropyl cellulose (Klucel H) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% Klucel H	41
1% Klucel H + 1.0% sodium chloride	38
1% Klucel H + 5.0% sodium chloride	30
0.5% Klucel H + 10% sucrose	41
0.5% Klucel H + 30% sucrose	32
0.5% Klucel H + 40% sucrose	20
0.5% Klucel H + 50% sucrose	7

13 Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This

results in the formation of side chains containing more than 1 mole of combined propylene oxide.

14 Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.^{135,136} It is not absorbed from the gastrointestinal tract and is fully recovered in feces after oral administration in rats. It does not exhibit skin irritation or skin sensitization. However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare. However, it has been reported that a single patient developed contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.²⁷³

The WHO has specified an acceptable daily intake for hydroxypropyl cellulose of up to 1500 mg/kg body-weight.^{132,133} Excessive consumption of hydroxypropyl cellulose may have a laxative effect.

LD₅₀ (rat, IV): 0.25 g/kg^{132,133}

LD₅₀ (rat, oral): 10.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosions.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hypromellose.

18 Comments

Hydroxypropyl cellulose is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

It is also used in hot-melt extruded films for topical use. When it is produced with chlorpheniramine maleate, the matrix is stabilized, allowing film processing at lower temperatures.¹³⁰ Mucoadhesive hydroxypropyl cellulose microspheres have been prepared for powder inhalation preparations.¹³¹

A specification for hydroxypropyl cellulose is included in the Food Chemicals Codex (FCC).¹³²

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20 General References

21 Authors

SA Shah, D Thassu.

22 Date of Revision

8 October 2008.



Hypromellose

1 Nonproprietary Names

BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

2 Synonyms

Benical MHPC; F464; hydroxypropyl methylcellulose; HPMC; hypromellosum; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; MHPC; *Pharmacoat*; *Tyopur*; *Tylose MO*.

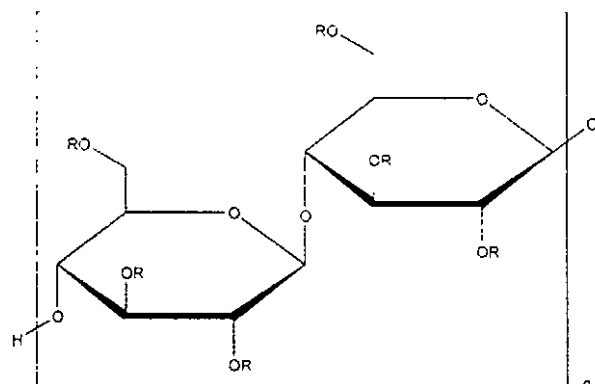
3 Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula and Molecular Weight

The PhEur 6.3 describes hypromellose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, mPa.s, of a 2% w/w aqueous solution at 20 °C. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name; e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH₂CH(OH)CH₃), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the various types of hypromellose; see Section 9. Molecular weight is approximately 10 000–1 500 000.

5 Structural Formula



where R is H, CH₃, or CH₂CH(OH)CH₃

6 Functional Category

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,⁽¹⁾ in film-coating,^(2–7) and as a matrix for use in extended-release tablet formulations.^(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.⁽¹³⁾

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while

higher-viscosity grades are used with organic solvents. Examples of film coating materials that are commercially available include *AnyCoat C*, *Spectracel*, *Pharmacoat*, and the *Methocel E Premium IV* series.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%.¹³

Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

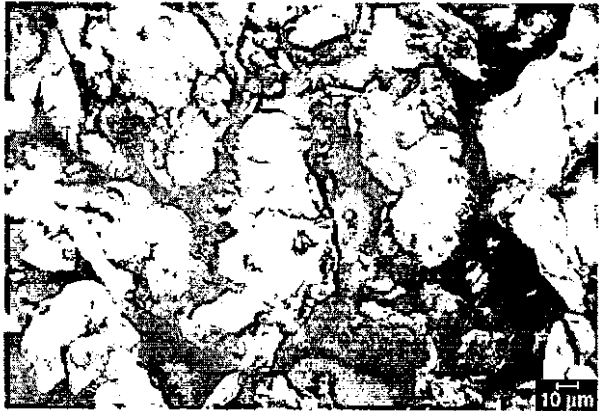
8 Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder. See also Section 10.

SEM 1: Excipient: *Methocel E5*; manufacturer: Dow Wolff Cellulosics; magnification: 200 $\times$; voltage: 3 kV



SEM 2: Excipient: *Methocel K4M*; manufacturer: Dow Wolff Cellulosics; magnification: 500 $\times$; voltage: 3 kV



9 Pharmacopeial Specifications

See Table 1.

Table 1: Pharmacopeial specifications for hypromellose.

Test	JP XV	PhEur 6.3	USP 32
Identification	—	—	—
Characters	—	—	—
Appearance of solution	—	—	—
pH (2% w/w solution)	5.0–8.0	5.0–8.0	5.0–8.0
Apparent viscosity	+	+ ^(a)	—
<600 mPa s	80–120%	80–120%	80–120%
≥600 mPa s	75–140%	75–140%	75–140%
Loss on drying	≤5.0%	≤5.0%	≤5.0%
Residue on ignition	≤1.5%	—	≤1.5%
Sulfated ash	—	≤1.5%	—
Heavy metals	≤20 ppm	≤20 ppm	≤20 ppm
Methoxy content	—	+ ^(a)	—
Type 1828	16.5–20.0%	16.5–20.0%	16.5–20.0%
Type 2208	19.0–24.0%	19.0–24.0%	19.0–24.0%
Type 2906	27.0–30.0%	27.0–30.0%	27.0–30.0%
Type 2910	28.0–30.0%	28.0–30.0%	28.0–30.0%
Hydroxypropoxy content	—	+ ^(a)	—
Type 1828	23.0–32.0%	23.0–32.0%	23.0–32.0%
Type 2208	4.0–12.0%	4.0–12.0%	4.0–12.0%
Type 2906	4.0–7.5%	4.0–7.5%	4.0–7.5%
Type 2910	7.0–12.0%	7.0–12.0%	7.0–12.0%

(a) May be a functionality related characteristic.

10 Typical Properties

Acidity/alkalinity pH = 5.0–8.0 for a 2% w/w aqueous solution.

Ash ≤1.5%

Autoignition temperature 360°C

Density (bulk) 0.341 g/cm³

Density (tapped) 0.557 g/cm³

Density (true) 1.326 g/cm³

Melting point Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Moisture content Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. See Figure 1.

NIR spectra see Figure 2.

Solubility Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol.¹⁴ See also Section 11.

Specific gravity 1.26

Viscosity (dynamic)

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions; see Table II.

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, and then the hypromellose should be added. The heat source can be removed once the hypromellose has been thoroughly dispersed into the hot water. Sufficient cold water should then be added to produce the required volume while continuing to stir.

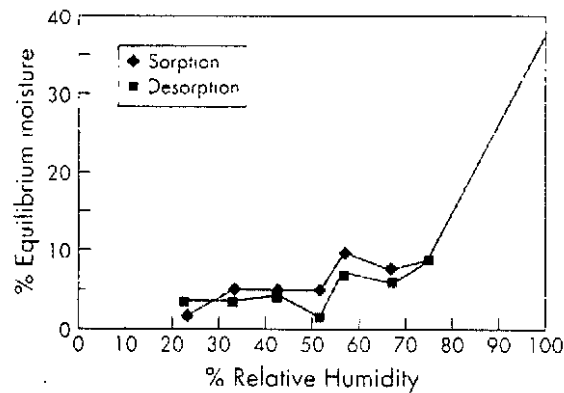


Figure 1: Absorption-desorption isotherm for hypromellose.

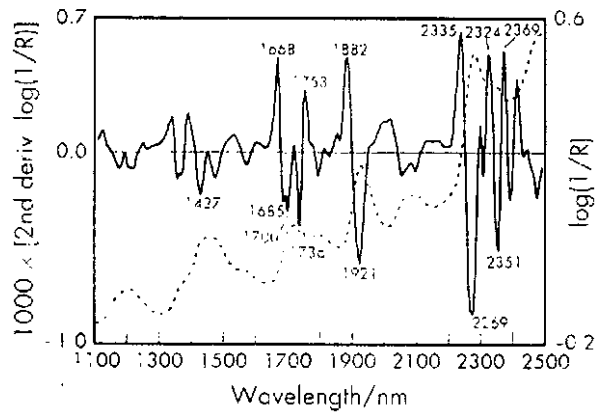


Figure 2: Near-infrared spectrum of hypromellose measured by reflectance

When aqueous/organic cosolvent mixtures are used for solution preparation, hypromellose should first be dispersed into the organic solvent at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the final volume. Examples of suitable water-miscible organic solvents include ethanol and glycols. A similar preparation procedure should be used when ethanol and dichloromethane constitute a completely organic cosolvent mixture.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gelation temperature is 50–90 °C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.⁽¹⁵⁾ However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative; when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Wolff Cellulosics) and Metolose (Shin-Etsu Chemical Co. Ltd.). Viscosities measured at 20°C.

Methocel and Metolose products	JP/PhEur/USP designation	Nominal viscosity (mPa s)
Methocel K3 Premium LV	2208	3
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E3 Premium LV	2910	3
Methocel E5 Premium LV	2910	5
Methocel E6 Premium LV	2910	6
Methocel E15 Premium LV	2910	15
Methocel E50 Premium LV	2910	50
Methocel E4M Premium	2910	4000
Methocel E10M Premium CR	2910	10 000
Methocel F50 Premium	2906	50
Methocel F4M Premium	2906	4000
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

13 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules. Hypromellose can then be exposed to anhydrous hydrogen chloride to induce depolymerization, thus producing low viscosity grades.

14 Safety

Hypromellose is widely used as an excipient in oral, ophthalmic, nasal, and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and non-irritating material, although excessive oral consumption may have a laxative effect.⁽¹⁶⁾ The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.⁽¹⁷⁾ In fact, high dosages of hypromellose are being investigated for treating various metabolic syndromes.^(18,19)

LD₅₀ (mouse, IP): 5 g/kg⁽²⁰⁾
LD₅₀ (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets;

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
JAIME EDUARDO DELGADO VILLEGAS

ASUNTO	Radicación	08 115 883
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	009094
	Folios	

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒ Cap. II ☐
No. Solicitud Internacional PCT/EP2007/003425			
Fecha de Presentación Internacional 19/Abril/2007			

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 comunica:

1. Documentos estudiados

Descripción:	Folios 27 a 38	29/Octubre/2008
Reivindicaciones:	Folios 39 a 40	29/Octubre/2008
Dibujos:	Folios 42 a 43	29/Octubre/2008
Prioridad:	DE 10 2006 020 604.5	02/Mayo/2006

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (art. 9 d 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Formulación de medicamento líquida para betabloqueantes" (modificado en el folio 55).

El problema planteado en esta solicitud consiste en la necesidad de diseñar formulaciones de fármacos betabloqueantes para uso veterinario con alta aceptación por parte del animal, buena capacidad de dosificación y buena estabilidad a largo plazo.

Para resolver este problema técnico la solicitud en estudio proporciona una formulación líquida de betabloqueantes que comprende espesantes, saborizantes, aromatizantes y conservantes.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 9/0; A 61 K 31/135; A 61 K 31/22

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de la reivindicación 11 no es patentable, de acuerdo con el Art 14.

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es clara porque define la formulación por su rápida biodisponibilidad, lo cual corresponde a un resultado a alcanzar y no define la formulación de manera clara, precisa e inequívoca, puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere reemplazarlo por las características esenciales que contribuyen a la obtención de este efecto, es decir, por los ingredientes y sus proporciones.

Adicionalmente, las reivindicaciones 1 a 8 no son claras ni concisas por cuanto los términos “betabloqueante soluble en agua”, “espesante soluble en agua”, “saborizantes y/o aromatizantes” y “formador de gel” definen los ingredientes por su función y no precisan inequívocamente los componentes dentro de la composición, definiendo opciones ilimitadas de la composición que no encuentran soporte en la descripción. Se sugiere al solicitante definir estos ingrediente de la composición por su nombre común, haciendo una generalización razonable de las realizaciones preferidas mostradas en el capítulo descriptivo de la solicitud.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: mayo 02 de 2006 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	US 4600708	Propanolol hydrochloride liquid formulations	15/Julio/1986
D2	Hügel, Stephanie, Am. J. Physiol. 277 (Heart Circ. Physiol. 46), H2167–H2175	Effects of ACE inhibition and b-receptor blockade on energy metabolism in rats postmyocardial infarction	1999

D1 http://gb.espacenet.com/search97cgi/s97_cgi.exe?Action=FormGen&Template=gb/en/advanced.htm divulga (Resumen) formulaciones líquidas de administración oral de clorhidrato de propanolol que contiene lecitina y/o aminoácidos que enmascaran las características de sabor.

D2 enseña (Pág. H2167 y H2168, folios 75 y 76) los efectos del tratamiento crónico con un betabloqueador (bisoprolol) y un inhibidor ACE (captopril).

7. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una formulación de medicamento líquida basada en agua para su administración por vía oral que contiene como máximo el 1% en peso de un betabloqueante en forma disuelta, presentando la formulación una rápida biodisponibilidad.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
formulación de medicamento líquida	formulación de medicamento líquida
basada en agua	basada en agua (abstract)
máximo el 1% en peso de un betabloqueante en forma disuelta	0.97% (ejemplo 1)

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual enseña una formulación de dosificación oral líquida de clorhidrato de propanolol (resumen) que contiene un componente enmascarador del sabor amargo del clorhidrato de propanolol (columna 1, líneas 26 – 30).

En consecuencia, la reivindicación 1 no es nueva según lo divulgado en el documento D1.

Nivel Inventivo (Art18 D486)

La reivindicación 3 consiste en una formulación de medicamento según las reivindicaciones precedentes que contiene bisoprolol como betabloqueante soluble en agua.

La reivindicación 5 consiste en una formulación de medicamento según las reivindicaciones precedentes, que contiene saborizantes y/o aromatizantes.

La reivindicación 7 consiste en una formulación de medicamento según la reivindicación 6 que contiene del 1 al 10% en peso de formador de gel.

La reivindicación 9 consiste en una formulación de medicamento según la reivindicación 8 que contiene como formador de gel hidroxipropilcelulosa.

La reivindicación 10 consiste en una formulación de medicamento según la reivindicación 8 que contiene como formador de gel hidroxipropilmetilcelulosa.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
formulación de medicamento líquida	formulación de medicamento líquida	Enseña que el bisoprolol es un fármaco betabloqueador (Pág. H2167, folio 75, Columna 2, párrafo 2) y que esta sustancia presenta un sabor amargo (Pág. H2168, folio 76, Columna 1, párrafo 1)
basada en agua	basada en agua (abstract)	
máximo el 1% en peso de un betabloqueante en forma disuelta	0.97% (ejemplo 1)	
El fármaco betabloqueador corresponde a bisoprolol (reivindicación 3)	El fármaco betabloqueador corresponde a clorhidrato de propanolol	
Una o varias sustancias saborizantes y/o aromatizantes (reivindicación 5)	saborizantes también pueden ser adicionados, como sabores artificiales de fresa o limón o sabores naturales de vainilla o limón (Columna 2, líneas 41 – 42)	
Formador de gel (1-10%) que corresponde a hidroxipropilcelulosa y hidroxipropilmetilcelulosa (reivindicaciones 7, 9,10)	incluyen modificadores de viscosidad, como el silicato de aluminio magnesio, que puede adicionarse en concentraciones entre 0.1 al 0.5% en peso de la composición (Columna 2, líneas 28 – 32)	

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en las reivindicaciones 3, 5, 7, 9 y 10 porque:

El documento D1 enseña una formulación de dosificación oral líquida de clorhidrato de propanolol (resumen) que contiene un componente enmascarador del sabor amargo del clorhidrato de propanolol (columna 1, líneas 26 – 30) en donde la formulación contiene aditivos que producen suspensiones estables y efectivas (Columna 2, líneas 8 – 10) que incluyen modificadores de viscosidad, como el silicato de aluminio magnesio, que puede adicionarse en concentraciones entre 0.1 al 0.5% en peso de la composición (Columna 2, líneas 28 – 32); enseña los conservantes que pueden ser adicionados, tales como parabenos, benzoato o mezclas de los mismos (Columna 2, líneas 32 – 34). Además, el documento señala los saborizantes que pueden ser adicionados, tales como sabores artificiales de fresa o limón o sabores naturales de vainilla o limón (Columna 2, líneas 41 – 42). El ejemplo 1 (columna 2, líneas 47 a columna 3, línea 5) muestra una solución acuosa líquida de 10gr de clorhidrato de propanolol ($(10\text{g}/1029\text{g}) \cdot 100 = 0.97\%$).

El documento D2 enseña que el bisoprolol es un fármaco betabloqueador (Pág. H2167, folio 75, Columna 2, párrafo 2) y que esta sustancia presenta un sabor amargo (Pág. H2168, folio 76, Columna 1, párrafo 1).

La diferencia entre la invención, definida en la reivindicación 1 y la formulación de D1 consiste en que la invención define la formulación para el bisoprolol como fármaco betabloqueante (reivindicación 3) y el uso de hidroxipropilcelulosa y hidroxipropilmetilcelulosa como formador de gel (reivindicaciones 9 y 10) en una proporción de 1 – 10% de estos componentes (reivindicación 7).

El efecto que logra el definir el bisoprolol como fármaco betabloqueador y la utilización de hidroxipropilcelulosa y hidroxipropilmetilcelulosa como formador de gel en una proporción de 1 – 10% dentro de la formulación es la obtención de la composición con sabor mejorado de bisoprolol.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "cómo modificar la formulación conocida en D1 para conseguir una formulación con sabor mejorado de bisoprolol?".

Sin embargo, la utilización de bisoprolol como fármaco betabloqueador y sus problemas de sabor amargo son enseñados por el documento D2 (Pág. H2167, folio 75, Columna 2, párrafo 2; Pág. H2168, folio 76, Columna 1, párrafo 1). Igualmente, es del conocimiento de una persona versada en la materia que la hidroxipropilcelulosa y hidroxipropilmetilcelulosa son utilizados como formadores de gel en una proporción del 1 al 10% (Handbook of pharmaceutical excipients, Folios 77 a 84)

Por tal motivo, la persona del oficio normalmente versada en la materia habría sido claramente motivada a reemplazar en la composición divulgada por D1 el clorhidrato de propanolol por bisoprolol, considerando que este es un fármaco betabloqueador con sabor amargo, según la enseñanza del documento D2, teniendo una expectativa razonable de camuflar características organolépticas del fármaco, como el sabor no deseable y llegando al objeto del capítulo reivindicatorio de la solicitud. Por lo cual se considera obvia.

Conclusión:

El capítulo reivindicatorio cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

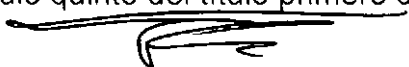
8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 4600708	1 – 10	Nivel Inventivo
D2	Hügel, Stephanie, Am. J. Physiol. 277 (Heart Circ. Physiol. 46), H2167-H2175	1 – 10	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 (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 01 JUN. 2012

Elaborado por: María del Pilar Obando Patiño
Revisado por: Consuelo Leguizamón Leguizamón 