

SUPERINDUSTRIA Y COMERCIO

Radicacion : 05050509 00000001 **Folios:** 64

Fecha (AMB) 2006-01-24 08:46:39

Tramite 011 PCT-PATENT 379 FASE NACI 400 OPOSICION

Dependencia 2020 DIVISION DE NUEVOS CREACIONES

7

☒ Patente de Invención
☐ Patente de Modelo de Utilidad
☐ Diseño Industrial
☐ Esquema de Trazado para Circuitos Integrados.
☐ Marcas de Productos o Servicios.

②

③ OPOSICIÓN PRESENTADA POR

SOLICITANTE	Nombre PROCAPS S.A. Dirección CALLE 80 No 78b-201 Nacionalidad o Domicilio COLOMBIA Lugar de Constitución BARRANQUILLA	IDENTIFICACIÓN CC ☐ NIT ☒ CE ☐ Otro ☐ Cual _____ Número <u>890 106 527-5</u>
	Teléfono 371 99 00 Fax 373 08 18 E mail _____	
REPRESENTANTE O APODERADO	Nombre RFINALDO PINILLA MORENO Dirección TRANVERSAL 13 A 119-95 OFICINA 104 Teléfono 213 12 13 Fax 612 19 79 E mail negocios@optimum-co.com	IDENTIFICACIÓN CC ☒ NT ☐ CE ☐ Otro ☐ Cual _____ Número <u>80425609</u> TP <u>91563</u>

④ FUNDAMENTOS DE LA OPOSICIÓN

Art 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causa	No cumple con los requisitos de patentabilidad
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Signo opositor

Justificación

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos"

⑤ Comprobante de pago No _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa
- ☒ Poderes si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☐ Documentos que acrediten el legítimo interés si fuere el caso
- ☒ Documento que acredita la existencia y representación legal de las partes cuando sean personas jurídicas

⑦

NOMBRE REINALDO PINILLA MORENO

FIRMA *Reinaldo Pinilla Moreno*

C.C 80425609

TP 91563 CSJ

COMPARECENCIA PERSONAL Y AUTENTICACION DE FIRMA
El Notario Treinta y Nueve (39) de Bogotá, da fe que el anterior escrito dirigido a Superintendencia de Industria y Comercio fue presentado personalmente por Reinaldo Pinilla Moreno quien exhibió la C.C No 80425609 de USG944 y TP No 91563 y manifestó que la firma y huella que aparecen en el presente documento son suyas, y que acepta el contenido del mismo.

FIRMA
Miguel Arturo Linero de Cambil
28 ENE 2008
MIGUEL ARTURO LINERO DE CAMBIL
NOTARIO

Notaria
39

OLIOPIA
SECRETARIA
NO DE CAMBIL
NOTARIO
2014



Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E S D

Referencia : Expediente N° 05 050 509

Asunto : Oposición a la solicitud de patente de Invención titulada "GRANULADOS DE MELOXICAM SOLUBLES EN AGUA."

Solicitante : BOEHRINGER INGELHEIM VETMEDICA.

Opositora PROCAPS S.A.

**Publicada en la Gaceta de la Propiedad Industrial
N° 557 del 31 de Octubre de 2005**

Yo **REINALDO PINILLA MORENO** abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura en mi condición de apoderado de la sociedad **PROCAPS S.A** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla Colombia atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada presento oposición a la concesión del registro de la patente de Invención titulada **"GRANULADOS DE MELOXICAM SOLUBLES EN AGUA"** solicitada por **BOEHRINGER INGELHEIM VETMEDICA** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada

Transversal 43- N° 11095 Of 104 Tel (571) 2 13 12 13 - 6 20 50 21 - Fax (571) 6 12 19 79
E-mail: negocios@optimum-co.com www.optimum-co.com
Bogotá Colombia



Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

1 INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley manifiesto el legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que pretende mi representada en materia de MELOXICAM en particular. Por lo tanto solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2 FUNDAMENTOS DE HECHOS

2.1 La solicitud objeto de la presente fue presentada el 24 de mayo de 2005 reivindicando prioridad bajo las solicitudes DE20021050081 2002-10-25 y fue publicada en Colombia en la Gaceta de la Propiedad Industrial N° 557 del 31 de octubre de 2005 página 419 N° publicación 680 cuya publicación internacional corresponde a la WO2004/037264 del 06/05/2004.

2.2 La solicitud colombiana 05 050 509 objeto de la presente oposición se refiere a granulados de meloxicam solubles en agua que contienen meloxicam, un aglutinante un azúcar o edulcorante un vehículo un formador de sales que forma la sal de meglumina sodio potasio o amonio de meloxicam eventualmente un aromatizante y eventualmente otros coadyuvantes donde el formador de sales es meglumina donde el aglutinante se elige del grupo consistente en hidroxipropilmetil-celulosa polivinil pirrolidona gelatina almidón y



polietilenglicoléter donde el azúcar o edulcorante se elige del grupo consistente en sacarina sódica aspartam y Sunett donde el aromatizante se elige del grupo consistente en vainilla aroma de miel aroma de manzana y contramarum, donde el vehículo se elige del grupo consistente en lactosa glucosa manitol xilitol sacarosa y sorbitol donde la proporción de meloxicam oscila entre 0.05% y 4% y donde contienen meglumina y meloxicam en una relación molar entre 9.8 y 12.8

2.3 En primera instancia se debe advertir que las reivindicaciones se refieren al uso o utilización según la legislación decisión 486 de la Comunidad Andina de Naciones Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento ()"* los usos no están contemplados como patentables Solo serán patentables los productos o procedimientos

2.4 De otra parte el artículo 14 de la Decisión 486 de la CAN consigna lo siguiente

"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial" Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud

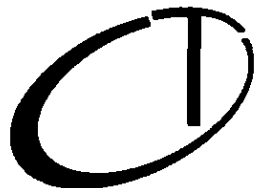
- D1 CA2326517 07-10-1999
- D2 US2002035107 2002-03-21

2.5 Ahora bien el documento D1 se refiere al uso de una sal del meloxicam de base inorgánica u orgánica por producir una dosis oral sólida Según esta invención específicamente en la página 24 líneas 22 a línea 30 se revela una formulación en cápsulas de granulos de meloxicam que comprenden meloxicam citrato sódico celulosa lactosa, polivinilpirrolidona soluble y cruzado dióxido de sílice y estereato

de magnesio. Así las cosas, con base en lo que dicta el documento D1, la presente formulación objeto de oposición no es Novedosa dado que la formulación propuesta en la presente solicitud objeto de oposición comprende similar al arte anterior revelado en el documento D1: granulados de meloxicam solubles en agua que contienen meloxicam, un aglutinante, un azúcar o edulcorante, un vehículo, un formador de sales que forma la sal de meglumina sodio, potasio o amonio de meloxicam, eventualmente un aromatizante y eventualmente otros coadyuvantes. Por lo tanto, a los ojos de este documento D1, la presente solicitud no es novedosa.

2.6 Por su parte, el documento D2 en la descripción y reivindicaciones particularmente en los ejemplos 1 a 5 revela una cantidad de meloxicam disueltos en una solución acuosa de meglumina, además de PEG-300, poloxamer, etanol, glicina, EDTA-Na, HCL y NaOH. Según este documento, las soluciones contienen meglumina y meloxicam en un ratio molar del grupo que consiste en 9:8 y 12:8, preferiblemente 10:8, según las reivindicaciones 3 y 4. Por lo tanto, la presente solicitud objeto de oposición, especialmente respecto a la relación molar, a los ojos de este documento D2, no es novedosa.

2.7. Adicionalmente, si combinamos este documento D2 con el documento D1, obviamente cualquier persona versada en la materia puede derivar una composición de granulados de meloxicam solubles en agua, que contienen meloxicam, un aglutinante, un azúcar o edulcorante, un vehículo, un formador de sales que forma la sal de meglumina sodio, potasio o amonio de meloxicam, eventualmente un aromatizante y eventualmente otros coadyuvantes (basados en el documento D1) donde la proporción de meloxicam puede oscilar entre 0.05% y 4%, y donde contienen meglumina y meloxicam en una relación molar entre 9:8 y 12:8 (según el documento D2).



2.8 En consecuencia y de acuerdo a lo descrito anteriormente se deriva que la solicitud colombiana 05050509 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección

2.9 Que por consiguiente respecto a la solicitud pretendida se tiene que

2.9.1 **CARECE DE NOVEDAD** Según la decisión 486 de la Comunidad Andina de Naciones Artículo 16 *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o en su caso de la prioridad reconocida."* A la fecha de prioridad, ya era conocido pues como se demostró era parte del arte anterior con base en el documento D1 y D2 la formulación de granulados de meloxicam solubles en agua sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2 **CARENCIA DE ALTURA INVENTIVA** Según la Decisión 486 de la Comunidad Andina de Naciones Artículo 18 *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad 2002-10-25, a partir de los documentos D1 y D2 en combinación es posible deducir la conformación de granulados de meloxicam solubles en agua según lo definido en las reivindicaciones de la presente solicitud

2.10 Dado lo anterior es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la

Comunidad Andina de Naciones Artículo 14.- "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." La solicitud pretendida no cumple con los requisitos de patentabilidad

2 11 Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486

2 12 Por todo lo anterior atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"GRANULADOS DE MELOXICAM SOLUBLES EN AGUA"** solicitada por **BOEHRINGER INGELHEIM VETMEDICA**. solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 557

3 PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes

- D1 CA2326517 07 10-1999
- D2 US2002035107, 2002-03-21

4 FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes

- 4 1 Numeral 1 del artículo 586 del Código de Comercio
- 4 2 Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena
- 4 3 En las demás normas concordantes

5 ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos

- D1 CA2326517 07 10-1999
- D2 US2002035107 2002-03-21

6 NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Transversal 13ª N° 119-95 Of 104 de esta ciudad de Bogotá.

Señor Superintendente


REINALDO PINILLA MORENO

C.C. 80'425 609 de Bogotá

T.P.A. 91563 del C.S. de la J.



PODER ESPECIAL

94

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **REINALDO PINILLA MORENO**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No 91563 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No 05 050 509, de título "GRANULADOS DE MELOXICAM SOLUBLES EN AGUA", publicada en la gaceta No 557 del 31 de Octubre de 2005

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley

Dado y Firmado en Barranquilla (Colombia) a los 10 días del mes de enero de 2006

PROCAPS S.A.

WALTER TANAKA TATEKAWA

C.C. N° 16 251 923 de Palmira

Representante Legal - *atris*

Acepto,

REINALDO PINILLA MORENO

C C. 80'425 609 de Bogotá

T P.A. 91563 del C.S de la J

COMPARECENCIA PERSONAL Y AUTENTICACION DE FIRMA

El Notario Treinta y Nueve (39) de Bogotá, da fe que el presente escrito dirigido a Superintendencia de Industria y Comercio fue presentado personalmente por Neirado Pardo Meres quien exhibió la C C No 26425609 de USE 725 y TP No 91863 y manifiesta que la firma y huella que aparecen en el presente documento son suyas, y que acepta el contenido del mismo.



[Signature]
FIRMA

23 ENE 2006
MIGUEL ARTURO LINERO DE CAMBIL



NOTA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO
La suscrita Notaria Certifica que este escrito fué

presentado personalmente por Walter Faruk Latorre

Identificado con 16 251 923 -

Expedida en Palmar

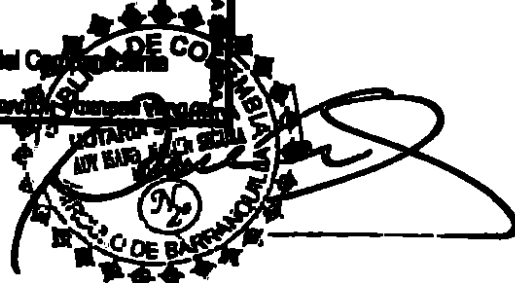
Quien declaró que su contenido es cierto y que la firma puesta en el es suya

Firma [Signature]



16 ENE 2006

Huella del Circulante



[Signature]

12
95

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 800176089-2

RECIBO OFICIAL DE CAJA : 06 5,021
FECHA ENERO 24 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
LAB PROCAPS	CONSIGNACION	BANCO POPULAR	050 00110-6	34008881	18/11/2005	940,000 00

***** C O N C E P T O *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005 01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	246,000 00
		TOTAL :	\$ 246,000 00

SOM DOSCIENTOS CUARENTA Y SEIS MIL PESOS

RESPONSABLE 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____



***** Pag 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE
DOCUMENTOS
PROCAPS S A -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA

C E R T I F I C A

Que por Escritura Pública No 1 190 del 22 de Julio de 1976
otorgada en la Notaria Tercera de Barranquilla inscrito(as) en
esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No 6 070
del libro respectivo fue constituida la sociedad-----
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA" -----

C E R T I F I C A

Que por Escritura Pública No 1 307 del 28 de Junio de 1979
otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en
esta Cámara de Comercio el 23 de Julio de 1979 bajo el No 10 039
del libro respectivo la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S A " PROCAPS S A " -----

C E R T I F I C A

Que por Escritura Pública No 3 810 del 31 de Dic/bre de 1980
otorgada en la Notaria Primera de Barranquilla, inscrito(as) en
esta Cámara de Comercio el 30 de Enero de 1981 bajo el No 12 705
del libro respectivo la sociedad antes mencionada-----
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA" -----

C E R T I F I C A

Que por Escritura Pública No 3 755 del 10 de Nov/bre de 1983,
otorgada en la Notaria Unica de Soledad, inscrito(as) en esta
Cámara de Comercio el 22 de Nov/bre de 1983 bajo el No 17 922 del
libro respectivo la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S A "PROCAPS S A " -----

C E R T I F I C A

Que por Escritura Pública No 3 615 del 06 de Dic/bre de 1996
otorgada en la Notaria 2a de Barranquilla inscrito(as) en esta
Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No 67 218 del
libro respectivo la sociedad antes mencionada-----
cambio de raz n social, por la denominacion LABORATORIOS PROCAPS S A

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----

C E R T I F I C A

Que por Escritura Pública No 3 775 del 18 de Dic/bre de 1996 otorgada en la Notaria 2a de Barranquilla inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No 67 704 del libro respectivo la sociedad antes mencionada----- cambio de razon social, por la denominacion PROCAPS S A -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados

Numero	aaaa/mm/dd	Notaria	No	Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a de Barranquilla	9	452	1979/01/24
992	1981/04/30	Notaria 1a de Barranquilla	13	112	1981/05/06
1 464	1982/08/27	Notaria Unica de Soledad	15	533	1982/09/08
2 744	1983/08/18	Notaria Unica de Soledad	17	416	1983/08/26
3 826	1984/07/16	Notaria Unica de Soledad	19	554	1984/07/27
3 835	1985/08/26	Notaria Unica de Soledad	22	230	1985/09/04
2 260	1986/09/10	Notaria Unica de Soledad	24	995	1986/09/15
1 849	1989/07/11	Notaria 2a de Barranquilla	33	909	1989/07/13
444	1990/02/21	Notaria 2a de Barranquilla	36	101	1990/03/16
3 090	1991/12/17	Notaria 2a de Barranquilla	43	993	1992/01/28
269	1993/02/01	Notaria 2a de Barranquilla	48	428	1993/02/16
2 342	1993/07/28	Notaria 2a de Barranquilla	50	582	1993/08/10
3 652	1993/11/09	Notaria 2a de Barranquilla	51	798	1993/11/22
3 615	1996/12/06	Notaria 2a de Barranquilla	67	218	1996/12/20
89	1997/01/16	Notaria 2a de Barranquilla	67	704	1997/01/23
2 070	1997/07/17	Notaria 2a de Barranquilla	70	627	1997/07/31
2 281	1997/08/04	Notaria 2a de Barranquilla	70	813	1997/08/14
765	1999/04/22	Notaria 3a de Barranquilla	80	628	1999/04/23
459	2001/02/21	Notaria 2a de Barranquilla	91	502	2001/02/23
2 608	2001/10/05	Notaria 2a de Barranquilla	95	771	2001/11/08
1 730	2004/07/29	Notaria 2 de Barranquilla	112	999	2004/08/26
416	2005/03/03	Notaria 2 de Barranquilla	116	364	2005/03/10
1 613	2005/07/28	Notaria 2 de Barranquilla	119	322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones

DENOMINACION O RAZON SOCIAL

PROCAPS S A -----

SIGLA PROCAPS

DOMICILIO PRINCIPAL Barranquilla

NIT No 890 106 527-5

MATRICULA MERCANTIL 24 802

C E R T I F I C A

Direccion para notificaciones judiciales

CL 80 No 78 B - 201

De la ciudad de Barranquilla

***** C O N T I N U A *****



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE
DOCUMENTOS
PROCAPS S A -----

C E R T I F I C A

DURACION El término de duración de la sociedad se fijó hasta el
18 de Agosto de 2073

C E R T I F I C A

OBJETO SOCIAL El objeto principal de la sociedad sera a)-La fabri-
cacion de capsulas y otros productos similares a partir de materia-
les tales como gelatinas u otros de distinta naturaleza, que puedan
ser utilizados como envases o recipientes de productos y sustancias
quimicas, farmaceuticas y cosmeticas para uso y consumo humano y
veterinario b)-La investigacion, desarrollo y fabricacion de toda
clase de productos y sustancias quimicas, farmaceuticas y cosmeticas
para uso y consumo humano animal y vegetal c)-La compra y venta de
materias primas, insumos y productos intermedios necesarios para los
procesos de fabricacion de sustancias quimicas farmaceuticas,alimen-
ticias y cosmeticas asi como la comercializacion interna y externa
de los productos terminados, d) La compra, venta, importacion ex-
portacion y distribucion de toda clase de elementos instru-
mentales y equipos medicos,quirurgicos odontologicos y hospitalarios
para la salud humana y animal e)La compra venta exportacion y dis-
tribucion de dulces confites, galletas y todo tipo de
golosinas o alimentos para el consumo humano f) Actuar como re-
presentante o agente de personas naturales y juridicas nacio-
nacionales y extranjeras en la realizacion de operaciones o tran-
sacciones relacionadas con la industria farmaceutica y en especial
con cualquiera de las actividades descritas en los literales a),
b), c) d) y e) antes descritos, g) Prestar los servicios de
ases ria y consultoria en las areas administrativas, de mer-
cadeo analisis clinico asistencia tecnica, investigacion costos y
produccion exportaciones importaciones, ventas relacionadas con
iguales o similares actividades a las que constituyen el objeto de
PROCAPS S A asi como los de publicidad y promocion de productos
quimicos cosmeticos y farmaceuticos para uso humano animal o in-
dustrial h)-Adquirir operar administrar y explotar a cualquier
titulo, empresa o establecimientos dedicados a la investigacion, de-
sarrollo fabricacion o comercializacion de productos quimicos, far-
maceuticos hospitalarios o cosmeticos En desarrollo de su objeto
principal, la sociedad podra tomar interes social como accionista
socio o fundador de empresas que tengan igual o similar objeto, c m-
prar vender importar y exportar maquinarias, insumos y repuestos
requeridos para el desarrollo de sus actividades tomar dinero en
prestamo financiar y garantizar las operaciones comerciales que ce-
lebre con terceros relativas a su objeto, celebrar y ejecutar todo

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----
tipo de actos y contratos necesarios para desarrollar sus operaciones girar aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar vender y constituir gravámenes sobre bienes muebles e inmuebles designar representantes o apoderados en el pais y en el exterior y en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza -----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2 000 000 000 *****	2 000 000 *****	1 000
Suscrito		
\$*****1 220 000 000 *****	1 220 000 *****	1 000
Pagado		
\$*****1 220 000 000 *****	1 220 000 *****	1 000

C E R T I F I C A

ADMINISTRACION La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas a la Junta Directiva al Presidente al Vicepresidente y a un Gerente General Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250 000) liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios se requerira que la operacion sea aprobada con el vot de por lo menos 2/3 partes de los integrantes de la Junta Directiva La sociedad tendra un Presidente quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social de conformidad con lo previsto en las leyes y en los presentes estatutos Constituir apoderados judiciales y extrajudiciales recibir notificaciones absolver interrogatorios de parte confesar obligaciones de la sociedad transigir, disistir y allanar a la sociedad en cualquier asunt judicial Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250 000) liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto Las demas funciones que le correspondan como Representante Legal por disposicion de la ley de estos estatutos o de la Junta Directiva El Presidente tendra un

***** C O N T I N U A *****



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suplente, designado por la Junta Directiva quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente El vicepresidente tendra las siguientes facultades entre otras Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social de conformidad con lo previsto en las leyes y en los presentes estatutos Constituir apoderados judiciales y extrajudiciales recibir notificaciones, absolver interrogatorios de parte confesar obligaciones de la sociedad transigir desistir y allanar a la sociedad en cualquier asunto judicial Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150 000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad inclusive de naturaleza muebles acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de los anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente Las demas funciones que le corresponda como Representante legal por disposicion de la ley de estos estatutos o de la Junta Directiva El Vicepresidente tendra (1) suplente designado por la Junta Directiva quien lo reemplazara conjunta o separadamente en sus faltas temporales absolutas o meramente accidentales con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular El Gerente General tendra las siguientes facultades entre otras Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social de conformidad con lo previsto en las leyes y en los presentes estatutos Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

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al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50 000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad inclusive de naturaleza mueble acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente -----

C E R T I F I C A

Que según Acta No 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad PROCAPS S A -----
cuya parte pertinente se inscribió en esta Cámara de Comercio el 15 de Agosto de 1997 bajo el No 70 838 del libro respectivo y según Acta No 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad PROCAPS S A -----
cuya parte pertinente se inscribió en esta Cámara de Comercio el 29 de Mayo de 2000 bajo el No 87 250 del libro respectivo, fueron hechos los siguientes nombramientos

CLASE JUNTA DIRECTIVA

Principales

1	Minski Gontovnik Ruben	CC *****7 463 982
2	Minski Gontovnik Meyer	CC *****7 461 324
3	Minski Gontovnik Jose	CC *****8 671 834

Suplentes

1	Minski Zilberblum Elliot	CC *****72 219 541
2	Minski Deitel Daniel	*****
3	Minski Sharon	PA *990 212 082 805

C E R T I F I C A

Que según Acta No 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio el 15 de Agosto de 1997 bajo el No 70 838 del libro respectivo fueron hechos los siguientes nombramientos

Cargo/Nombre	Identificación
Presidente	
Minski Gontovnik Ruben	CC *****7 463 982
Suplente del Presidente	
Minski Minski Abraham	CC *****802 575
Vicepresidente	
Minski Gontovnik Meyer	CC *****7 461 324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC *****8 671 834

***** C O N T I N U A *****



***** Pag 4
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE
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PROCAPS S A -----

C E R T I F I C A

Que según Acta No 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No 91 273 del libro respectivo, fueron hechos los siguientes nombramientos

Cargo/Nombre	Identificación
Gerente General Uribe Ochoa Guillermo Luis	CC *****70 073 754

C E R T I F I C A

Que según Acta No 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio el 09 de Sep/bre de 2004 bajo el No 113 263 del libro respectivo fueron hechos los siguientes nombramientos

Cargo/Nombre	Identificación
Suplente del Gerente, Tanaka Walter	CC *****16 251 923

C E R T I F I C A

Que según Acta No 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No 82 226 del libro respectivo fueron hechos los siguientes nombramientos

Cargo/Nombre	Identificación
Revisor Fiscal Ppal Vargas Pertuz Ana Isabel	CC *****32 696 645

C E R T I F I C A

Que según Acta No 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio el 29 de Mayo de 2000 bajo el No 87 250 del libro respectivo fueron hechos los siguientes nombramientos

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal Lozada Villareal Milena	CC *****32 748 111

C E R T I F I C A

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----

Que por escritura publica No 2 608 del 5 de Octubre del 2 001 otorgada en la Notaria 2a de Barranquilla inscrita en esta Camara de Comercio el 8 de Noviembre del 2 001 bajo los Nos 95 771 2 056 2 057 2 058 2 059 2 060, 2 061 2 062 y 2 064 del libro respectivo se reforma totalmente el articulo 65 contenido en la escritura publica No 3 705 de Noviembre 6 de 1 998 de la Notaria Segunda del Circuito de Barranquilla y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad 1 -Se confiere Poder Especial Amplio y Suficiente a los senores WALTER TANAKA TATEKAWA C C No 16 251 923 WILLIAM ALBERTO BARROS CERRA C C No 8 715 941 para que cada uno en forma independiente en nombre y representacion de PROCAPS S A , suscriba todas las declaraciones tributarias aduaneras y cambiarias a que este obligada la sociedad asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias aduaneras o cambiarias en los ordenes Distrital Departamental y Nacional 2 -Se confiere Poder Especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales hasta por la suma de US\$800 000 oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA) liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion GUPO A GUILLERMO LUIS URIBE OCHO C C No 70 073 754 LINO LAZALA SILVA VARGAS C C No 19 260 410 JAIRO MOLINA MEJIA C C No 8 706 380 CLAUDIA TANGARIFE CASTILLO C C No 41 660 -293 BRUPO B WALTER TANAKA TATEKAWA C C No 16 251 923 HENRY CARO DIAZ C C No 19 395 298 CARMEN ALICIA FLOREZ C C No 22 434 044 CARMEN ALICIA HERRERA DIAZGRANADOS C C No 22 377 540 Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B, 3 -Se otorga Poder General Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C C No 33 138 497 a la Doctora MARCELA CARVAJALINO PAGANO C C No 22 579 748 y al Doctor DANIEL MORENO VILLALBA C C No 19 113 210 para que cada uno representen a PROCAPS S A , ante todo tipo de autoridades administrativas y judiciales en asuntos de naturaleza cambiaria y fiscal tales como Contestar e interponer demandas y requerimientos comparecer en juicios pedir la practica de pruebas recibir notificaciones interponer recursos y ejercer acciones contencioso administrativas y de tutela transigir conciliar recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato Para la celebracion de cualquier acuerdo conciliatorio o transaccional judicial o extrajudicial cualquiera que sea su cuantia los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos firmar notificarse y realizar todo acto necesario para cumplir con el mandato encomendado -----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No 1 786

***** C O N T I N U A *****



***** Pag 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
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PROCAPS S A -----

del libro respectivo consta que RUBEN MINSKI GONTOVNIK C C No 7 463 982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C C No 32 732 070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S A en el giro normal de sus negocios y operaciones sociales --

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2 002, inscrito en esta Camara de Comercio el 15 de enero del 2 003 bajo el No 2 290 del libro respectivo el señor RUBEN MINSKI GONTOVNIK C C No 7 463 982 en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S A, mediante el presente documento otorgo PODER ESPECIAL al Sr MARLON TATIS PAREDES C C No 72 176 874 para que en representacion de PROCAPS S A suscriba declaraciones reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces En consecuencia el Sr MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S A declaraciones reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces -----

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2 004 bajo el No 2 753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C C 7 463 982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S A confiere poder especial amplio y suficiente a ANTONIO VARELA DIAZ, C C No 72 004 669 de Barranquilla para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S A a suscribir en el giro normal de sus negocios y operaciones sociales Por lo anterior, el señor ANTONIO VARELA DIAZ queda facultado para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado -

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----

esta Camara de Comercio el 28 de Marzo de 2 005 bajo el No 2 820 del libro respectivo consta que WALTER TANAKA TATEKAWA C C 16 251-923 de Palmira quien actua como representante legal de la sociedad PROCAPS S A otorga Poder Especial Amplio y Suficiente al senor MARLON TATIS PAREDES C C No 72 176 874 para que en representacion de PROCAPS S A , suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital departamental y nacional -----

C E R T I F I C A

Que por Escritura Publica No 1 613 del 28 de Junio del 2 005 otorgada en la Notaria Segunda de Barranquilla inscrita en esta Camara de Comercio el 18 de agosto del 2 005 bajo el No 2 913 del libro respectivo consta que RUBEN MINSKI GONTOVNIK C C No 7 463 928 en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S A confiere poder especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministro de mercancias y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800 000) liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion GRUPO A MIRIAM RODRIGUEZ DIAZ C C No 41 473 569 GRUPO B NELSON SUAREZ CHAVEZ C C No 79 417 971 -----

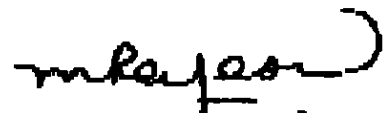
C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma disolución liquidación o nombramientos de representantes legales de la expresada sociedad

C E R T I F I C A

Que su última Renovación fue el 23 de Marzo de 2005

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula la de contratos sujetos a registro en Certificados Especiales



(19)  Canadian
Intellectual Property
Office

An Agency of
Industry Canada

Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

(11) **CA 2 326 517**

(13) **A1**

(40) 07 10 1999

(43) 07 10 1999

(12)

(21) 2 326 517

(51) Int. Cl. 5 **A61K 31/54 A61K 9/20**

(22) 23.03 1998

(85) 28.09 2000

(86) PCT/EP99/01849

(87) WO99/49867

(30) 98105689.2 EP 27 03 1998

(72)

SAGMULLER, PAUL (DE)
BOCK, THOMAS (DE)
SIEGER, PETER (DE)
TURCK, DIETRICH (DE)

(71)

BOEHRINGER INGELHEIM PHARMA KG
Binger Strasse 173
D-65216, INGELHEIM AM RHEIN XX (DE)

(74)

FETHERSTONHAUGH & CO

(54) NOUVELLES FORMES GALENIQUES DE MELOXICAME A ADMINISTRER PAR VOIE ORALE

(54) NOVEL GALENIC FORMULATIONS OF MELOXICAM FOR ORAL ADMINISTRATION

(57)

The invention relates to the use of a meloxicam salt of an inorganic or organic base for producing an orally administered solid drug formulation for treating pain. The active agent is rapidly released from the formulation and absorbed. The invention also relates to the corresponding drug formulations, which are produced by direct tableting and to the production method.



(72) BOCK THOMAS, DE
(72) SAGMULLER, PAUL DE
(72) SIEGER, PETER, DE
(72) TURCK DIETRICH DE
(71) BOEHRINGER INGELHEIM PHARM A KG DE
(51) Int Cl⁶ A61K 31/54 A61K 9/20
(30) 1998/03/27 (98105569 2) EP
(54) NOUVELLES FORMES GALENIQUES DE MELOXICAME A
ADMINISTRER PAR VOIE ORALE
(54) NOVEL GALENIC FORMULATIONS OF MELOXICAM FOR
ORAL ADMINISTRATION

(57) L'invention concerne l'utilisation d'un sel de meloxicam d'une base inorganique ou organique pour préparer une forme galénique solide à administrer par voie orale, d'où le principe actif est libéré et absorbé rapidement. Ces formes galéniques s'utilisent dans le traitement de la douleur. L'invention concerne en outre, des formes galéniques correspondantes obtenues par formation directe de comprimés, ainsi que le procédé permettant de les préparer.

(57) The invention relates to the use of a meloxicam salt of an inorganic or organic base for producing an orally administered, solid drug formulation for treating pain. The active agent is rapidly released from the formulation and absorbed. The invention also relates to the corresponding drug formulations which are produced by direct tableting, and to the production method.



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Abstract

The invention relates to the use of a meloxicam salt of an
5 inorganic or organic base for preparing an orally
administered, solid pharmaceutical preparation from which
the active substance is rapidly released and absorbed for
pain therapy corresponding pharmaceutical preparations
made by direct tableting and the process for preparing
10 them

Boehringer Ingelheim Pharma KG
D-55216 Ingelheim

Case 5/1233-Ro
Foreign filing text

5 New galenic preparations of meloxicam for oral
administration

The invention relates to new galenic preparations of the
active substance meloxicam which is one of the NSAIDs
(nonsteroidal-anti-inflammatory drugs) for oral
10 administration and processes for preparing them

The drugs used for the treatment of rheumatic diseases
often have antiphlogistic as well as analgesic properties
For this reason they are used not only to treat chronic
15 rheumatic diseases but also for acute rheumatic attacks
and for acute pain treatment

Many of these pharmaceutical compositions have only
limited solubility and for this reason are absorbed only
20 slowly by the body In the treatment of acute pain, a
rapid influx of active substance is essential to ensure
that the activity sets in rapidly It is therefore often
necessary to increase the speed of dissolution and
solubility of the active substances in question

25 For known drugs in this field, different approaches have
been adopted e g ibuprofen and diclofenac are used in
the form of their salts or piroxicam is used in the form
of β -cyclodextran inclusion compounds However when
30 administered by oral route these active substances do not
always exhibit a sufficient plasma concentration for rapid
effect within a short time The pharmacokinetic
differences of ibuprofen-lysinate compared with
ibuprofenic acid are described for example in Int J
35 Clin Pharmacol Ther Toxicol Vol 27 No 7 324
328 (1989) It says that the average peak-plasma level

measured on 8 fasting test subjects in the case of
ibuprofen-lysinate (1000 mg, film-coated tablet) was
achieved on average 0.55 h after administration and was
69.1 µg/ml, whereas the corresponding values for
5 ibuprofenic acid (600 mg, sugar-coated tablet) are given
as 0.89 h and 50.8 µg/ml. In non-fasting test subjects the
differences lose statistical significance according to the
authors and amount to 50.3 µg/ml ibuprofen-lysinate after
1.18 h and 44.6 µg/ml for ibuprofenic acid after 1.55 h
10
DE 37 00 172 explains that numerous NSAIDs do not
dissolve easily in water and are therefore not really
suitable for preparing parenteral formulations. To
overcome this problem the use of N-(methyl)-glucamine and
15 glucamine salts of a number of NSAIDs, including inter
alia Isoxicam, Tenoxicam and Piroxicam has been proposed.
A parenteral Piroxicam-N-(methyl)-glucamine formulation is
described as Example 4. It is also stated that these salts
can also be administered in oral, rectal or topical
20 formulations but the published application contains no
information on the absorption of oral formulations. The
problem described therein, namely the preparation of a
parenteral aqueous formulation of a comparatively
insoluble active substance, differs substantially from the
25 objective of the present invention. As explained
hereinafter, this consists in providing an orally
administered solid pharmaceutical preparation of meloxicam
which produces effective plasma levels soon after
administration. In addition the starting point of the
30 present invention was considerably more difficult as free
meloxicam is less water-soluble, by a factor of about 10,
than free piroxicam over a wide pH range (European Journal
of Pharmaceutical Science 4 (1996) 175-187 particularly
Fig. 10 on page 184)
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Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a novel antirheumatic which is distinguished by the fact that it is well tolerated by the stomach at the doses necessary for therapy. The active substance and its sodium salt - as well as its N-methyl-D-glucamine salt (meglumin salt) are described in EP-A-0 002 482. The anti-inflammatory and pain-relieving properties of meloxicam also make this active substance very interesting for use in pain therapy. However, the active substance has very low solubility in the acid range which prevails in the upper part of the gastro-intestinal channel. It is therefore absorbed with a time delay after administration. Maximum plasma levels are reached within 2 - 8 hours, depending on the formulation. However, the activity is long-lasting and highly effective. As a rule, therefore, a single dose each day is sufficient. In order to open up this active substance, which is suitable for pain therapy, for treating acute conditions as well, it is necessary to ensure rapid absorption and at the same time a rapid onset of activity.

The aim of the present invention was to prepare an orally administered, solid pharmaceutical preparation of meloxicam from which the active substance is released and absorbed rapidly so that a plasma level suitable for treating acute pain can be achieved sufficiently rapidly. The following profile of requirements can be defined in connection with this:

The maximum plasma level C_{max} should be higher than after the administration of an equal dose of a conventional meloxicam capsule formulation and should be achieved very much sooner. A high enough effective plasma level should then be maintained for a certain length of time. In particular, C_{max} should be reached at the latest two hours

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- 4 -

after the administration of a single dose and should be at
a dosage of 7.5 mg in the range from 650 to 1000 ng/ml
Ideally C_{max} at this dosage should correspond to about
twice the maximum plasma level which is achieved with the
5 conventional 7.5 mg capsule formulation and should
therefore be in the range from 800 to 900 ng/mL. After the
maximum plasma level is exceeded, a plasma level of 500 to
700 ng/ml should be maintained for 1 to 3 hours but
ideally a plasma level of 550 to 650 ng/ml which
10 corresponds to the steady state average plasma levels of
about 600 ng/ml after the administration of the
conventional 7.5 mg capsules. Moreover, the total
absorption of the formulation according to the invention
and the conventional capsule formulation with the same
15 dose should be equivalent.

Meloxicam is capable of forming salts with inorganic
bases, e.g. the sodium, potassium or ammonium salt and
20 also with organic bases, e.g. the meglumin salt, the Tris
salt (Tris-(hydroxymethyl)aminomethane) or salts with
basic amino acids such as L-lysine or L-arginine. In
connection with the objective of the invention the
solubilities of the active substance and its salts are of
25 interest.

Table 1 Saturation solubility of meloxicam and its salts in various dissolving media

Medium	Solubility at ambient temperature [mg/100 ml]			
	Meloxicam	Sodium salt	ammonium salt	meglumin salt
0.1 N hydrochloric acid (pH 1)	0.09	0.05	0.04	0.1
Buffer pH 4	0.05	0.02	0.02	0.04
Water (pH 7)	0.2	785	230	860
Buffer pH 7.4	About 100	635	285	1290
Buffer pH 10	231	1215	440	2315
0.1 N sodium hydroxide solution (pH 13)	2570	1215	1960	2900

5

The data in Table 1 show the following

Both meloxicam and meloxicam salts are only poorly soluble in aqueous systems at pH values ≤ 4 , with no apparent significant differences in the solubility of the different compounds. As the pH increases to between 4 and 10 the solubility of the meloxicam salts increases particularly the sodium and meglumin salt, significantly more than that of the free meloxicam and at very high pH values the effect of the increased solubility levels out. The free meloxicam exhibits a substantial increase in solubility only at pH levels above 7. At pH 13 meloxicam and its salts no longer exhibit any substantial differences in solubility. Accordingly, elevated dissolution rates can theoretically be expected for

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meloxicam salts at pH values above 4, and for free meloxicam only at pH values above 7

It is known that the pH value of gastric juices can vary
5 between 1 and 6 in fasting patients and is usually between 3 and 5 in non-fasting patients

Since meloxicam salts with bases in the acidic pH range which prevails in the stomach have very low solubility
10 one might expect that a solid meloxicam salt in this environment would dissolve only very slowly and thus be available for resorption or that a corresponding meloxicam salt already dissolved would be precipitated in this environment. An essential difference in resorption
15 characteristics would not be expected between meloxicam and its salts under these conditions on the basis of the solubility data. On the other hand one would expect salts of meloxicam with bases in a less acidic medium of the small intestine to dissolve faster and to a greater degree
20 than free meloxicam and be absorbed there correspondingly faster than the free meloxicam. The release and resorption of the active substance only in the small intestine whilst the active substance might be protected by a gastric juice-resistant coating during its passage through
25 the stomach is not however suitable as a solution to the problem of the invention. The passage through the stomach after a pharmaceutical preparation has been administered takes too long with the result that acute pain is not treated rapidly enough. Moreover the time taken for the
30 effect to set in would depend to a considerable extent on what had been eaten and would thus be subject to individual fluctuations

When choosing a suitable form of active substance for
35 developing a formulation capable of solving the problem of the invention it is necessary to take account not only of

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the pH-dependent solubilities but also other physicochemical properties of meloxicam and its salts. Polymorphism of the active component possibly the presence of various crystalline, variously solvated or amorphous modifications can have a considerable influence on the chemical, biological and pharmaceutical properties of a drug. The meloxicam meglumin salt shows a strong tendency to form various polymorphic forms and crystallises out of various organic solvents e.g. acetone, methanol, ethanol, ethanol/water (8/2 v/v) and isopropanol, in various crystalline modifications which contain 4-5% water of hydration as can be shown by microscopic, IR-spectroscopic and thermal analysis as well as X-ray powder diffractometry. Figure 1 shows an overview of the polymorphism present. Moreover, the meloxicam-meglumin salt displays only a slight tendency to spontaneous crystallisation.

The crystalline monohydrate modification of the meloxicam-meglumin salt is hygroscopic, whereas the meloxicam-sodium salt has no hygroscopic properties. Under ambient conditions the monohydrate of the meloxicam-meglumin salt is the stable modification, but at a relative humidity of over 75% a dihydrate is formed. The enclosed water can only be eliminated from the dihydrate under conditions of very great dryness. However, after dehydration, no stable anhydrous modification is obtained, but the anhydrous form very rapidly absorbs water to form the monohydrate form which is stable under ambient conditions. The water absorption/desorption characteristics of meloxicam-meglumin exhibit a hysteresis effect. By intensive drying over a fairly long period the anhydrous form changes more and more into an amorphous form, and after 24 h at 100 °C the material is totally amorphous.

35

In particular, the polymorphism and hygroscopic nature of the meloxicam-meglumin salt led us to expect considerable problems for the use of this form of active substance in a pharmaceutical formulation as only a uniform, stable
5 modification capable of being manufactured reproducibly can be used

The meloxicam-meglumin salt which is primarily obtained according to Example 3 of EP-A-0 002 482 is anhydrous and
10 amorphous (drying at 80° over phosphorus pentoxide) This modification is certainly suitable for the preparation of parenteral formulations but not for the preparation of solid pharmaceutical preparations as this form does not satisfy the criteria specified above but changes into a
15 hydrated form when stored under normal ambient conditions

Surprisingly, it has been found that meloxicam from the salts formed with bases becomes available for absorption substantially faster after administration and in greater
20 quantities than neutral meloxicam in spite of the low solubility at low pH levels which correspond to the environment of the stomach The rise in the plasma levels after oral administration of the salts of meloxicam takes place considerably faster than when pure meloxicam is
25 used The high degree and rapidity of the rise in plasma levels which can be achieved with meloxicam salts particularly the meloxicam-meglumin salt could not have been expected by anyone skilled in the art taking into account the properties of the NSAID salts known from the
30 prior art The increased solubility obtained by using a meloxicam salt surprisingly occurs *in vivo* even at low pH values This makes it possible for large amounts of the active substance to be dissolved even immediately after administration and thus become available for absorption by
35 the body

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Example 7 together with Figure 4 shows that after oral administration of a meloxicam salt formulation the plasma level rises considerably faster than after the administration of a conventional capsule formulation of the neutral active substance. Just 15 min after administration of the meloxicam-meglumin salt formulation according to the invention, a plasma level of 286 ng/ml is achieved, which virtually corresponds to the minimum plasma concentration in the steady-state whilst 30 min after administration of the comparative formulation still no appreciable plasma level (42 ng/ml) can be detected. Moreover with the formulation according to the invention after barely 2 hours a maximum plasma level of 812 ng/ml is obtained which is twice as great as the minimum steady-state plasma level achieved with the comparative formulation (the maximum plasma level was determined on the basis of variability in time not from the average curve in Fig 4, but from the underlying individual curves). Thus, a rapid onset of activity as well as a particularly high activity can be expected in the first 2-3 hours after taking a formulation according to the invention particularly a meloxicam-meglumin salt formulation which is important for relieving acute pain. With the comparative formulation on the other hand no marked plasma level peak is achieved but rather the plasma level rises more or less continuously until it reaches a plateau in the steady state.

The $AUC_{0-\infty}$ (AUC area under the plasma concentration-time curve, 0- ∞ from time 0 of the administration to infinity measurement of resorption) of the conventional capsule formulation according to Figure 4 is 14.1 $\mu\text{g h/mL}$, that of the meloxicam-meglumin salt formulation is 15.0 $\mu\text{g h/mL}$ the two are to be regarded as equivalent with regard to this parameter.

Other approaches to solving the problem of the present invention, e g the formation of inclusion compounds of meloxicam with β -cyclodextrin did not produce

5 sufficiently high plasma concentrations within a short period Similarly compression of a mixture of the two individual components meloxicam and meglumin did not solve the problem of the present invention

10 The invention therefore relates to the use of a meloxicam salt of an inorganic or organic base for preparing an orally administered solid drug preparation from which the active substance is rapidly released and absorbed for pain therapy particularly for treating acute rheumatic
15 attacks and for fighting acute pain Suitable salts include for example, the sodium, potassium or ammonium salt the meglumin salt the Tris salt or the salt of a basic amino acid such as L-lysine or L-arginine The meloxicam-meglumin salt and the meloxicam sodium salt are
20 preferred the meloxicam-meglumin salt is particularly preferred e g the meloxicam-meglumin salt dihydrate or especially the meloxicam-meglumin salt monohydrate

In order to ensure rapid release of active substance after
25 oral administration, it is also advantageous if the pharmaceutical preparation has a very short decomposition time since as a rule the release of active substance can only proceed to a greater extent after breakdown It has been found that a sufficiently short breakdown time can be
30 achieved if the active substance is made into tablets directly with suitable excipients such as lactose, dicalcium phosphate cellulose and suitable breakdown adjuvants such as crosslinked polyvinylpyrrolidone or sodium starch
i e the corresponding powder mixtures are compressed
35 directly into tablets without any intermediate granulation of the powder before compression as would normally be

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carried out This has the advantage of being a simpler and cheaper method of production

The invention thus also relates to an orally administered
5 solid pharmaceutical form of meloxicam from which the active substance is rapidly released and absorbed for the treatment of pain, particularly for treating acute rheumatic attacks and for relieving acute pain characterised in that meloxicam is present in the form of
10 a salt with an inorganic or organic base, optionally together with conventional excipients and/or carriers in a rapidly decomposing tablet produced by direct tableting

15 Suitable salts with an inorganic base include for example the sodium, potassium or ammonium salt of meloxicam Examples of salts with organic bases include the meglumin salt the Tris salt or a salt of meloxicam with a basic amino acid such as L-lysine or L-arginine Salts which
20 have proved particularly advantageous for the purposes of the present invention are the meglumin and sodium salt of meloxicam, the meloxicam-meglumin salt being particularly preferred e g the meloxicam-meglumin salt dihydrate or more particularly the meloxicam-meglumin salt monohydrate

25 Examples of excipients or carriers include microcrystalline cellulose, lactose, crosslinked polyvinylpyrrolidone magnesium stearate, dicalcium phosphate and various starches

30 Thirdly the invention relates to a process for preparing an orally administered solid pharmaceutical preparation of meloxicam, which has a short decomposition time and from which the active substance is released and absorbed
35 rapidly for pain therapy particularly for treating acute rheumatic attacks and for relieving acute pain,

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characterised in that an optionally pulverised meloxicam salt of an inorganic or organic base is intimately mixed with suitable pulverised excipients and/or carriers and compressed directly into tablets with no granulation of the powder before the compressing. The abovementioned meloxicam salts might be used for example the meglumin and the sodium salt of meloxicam being preferred. The meloxicam-meglumin salt is particularly preferred, for example the meloxicam-meglumin salt dihydrate or more particularly the meloxicam-meglumin salt monohydrate.

As already mentioned hereinbefore the polymorphism and hygroscopy of the meloxicam-meglumin salt particularly led one to expect considerable difficulties in using the active substance in this form to achieve the objective of the invention since only a reproducibly manufactured, uniform and stable modification can be used in a pharmaceutical formulation. Surprisingly, this condition can be met with the meloxicam-meglumin salt if during crystallisation of the salt from a mixture of a water-miscible organic solvent and water, seed crystals consisting of crystalline meloxicam-meglumin salt monohydrate, preferably seed crystals of a meloxicam-meglumin salt monohydrate form previously crystallised from acetone/water, are added to the mixture. A product is then obtained reproducibly and uniformly which corresponds to the crystalline form of the seed crystals used.

From the crystalline meloxicam-meglumin salt monohydrate thus obtained the crystalline meloxicam-meglumin salt dihydrate can be obtained by treating the monohydrate at high humidity.

As a result of the slight tendency to spontaneous crystallisation and the strong tendency to form different

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polymorphic forms it is advisable to seed the solution with crystals of the desired monohydrate form in the last step of the production of the solid meloxicam-meglumin salt for pharmaceutical use. If desired the dihydrate form can then be obtained from the monohydrate form as mentioned above. The synthesis plan is shown in Figure 2

Fourthly the invention thus relates to the crystalline meloxicam-meglumin salt monohydrate a process for preparing it, wherein meloxicam and meglumin are heated in a mixture of a water-miscible organic solvent and water and meloxicam-meglumin salt monohydrate seed crystals are added to the mixture for crystallisation, and an orally administered solid pharmaceutical preparation containing meloxicam in the form of the crystalline meloxicam-meglumin salt monohydrate

Examples of organic solvents include acetone, methanol ethanol n-propanol, 1-propanol, tetrahydrofuran or dioxane, preferably acetone ethanol tetrahydrofuran and dioxane. Acetone and ethanol are particularly preferred, especially acetone

In the mixture, organic solvent and water may be used in a ratio by volume of 10:1 to 100:1 preferably in a ratio of 20:1 to 50:1 or most preferably in a ratio of 35:1 to 45:1 a ratio of about 40:1 being particularly suitable when acetone is used

Meloxicam and meglumin may for example be used in a molar ratio of 1:1.5 to 1:5.1 preferably in a molar ratio of 1:1.2 to 1:2.1 but particularly in an equimolar ratio

Appropriately, the mixture may be heated with the addition of activated charcoal which is removed again before the addition of the seed crystals

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The amount of seed crystals added depends on the solvent system used and the quantity of mixture. For example, to a batch A = 12.5 kg meloxicam, mixture B = 5 to 50 g of meloxicam-meglumin salt monohydrate seed crystals (ratio by weight of A : B = 125 : 0.05 - 0.5) are added whilst if the solvent acetone/water is used the amount added is from 5 to 30 g, but particularly with a ratio of acetone/water = 40 : 1 it is particularly appropriate to add 10 to 15 g of seed crystals. It is readily possible for the skilled man to determine the proper quantity of seed crystals for a given batch size and a given solvent system.

After the addition of the seed crystals the mixture is cooled to 10 to 30 °C, but preferably to a temperature of about 20 °C. Preferably, the mixture is then refluxed again and then slowly cooled to a temperature 10 and 30°C, preferably 15 to 25°C, but most usefully about 20 °C. A fine crystalline crystal suspension of the desired meloxicam-meglumin salt monohydrate is obtained which is worked up in the usual way. The powder X-ray reflexes of the particularly preferred meloxicam meglumin salt monohydrate modification are contained in Table 2 which follows.

A fifth object of the invention is crystalline meloxicam-meglumin salt dihydrate, a process for preparing it in which crystalline meloxicam-meglumin salt monohydrate is treated at high humidity, and an orally administered solid pharmaceutical form containing meloxicam in the form of the crystalline meloxicam-meglumin salt dihydrate.

The treatment is carried out by storage for at least one day, preferably at least five days, at a high relative humidity. The relative humidity should be at least 75 %.

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preferably at least 85 % The powder X-ray reflexes of the particularly preferred meloxicam meglumin salt dihydrate modification are shown in Table 3 which follows

5 A sixth object of the invention is a process for preparing an orally administered solid pharmaceutical preparation containing meloxicam in the form of the meloxicam-meglumin salt monohydrate which has a short decomposition time and from which the active substance is rapidly released and
10 absorbed, for pain therapy particularly for treating acute rheumatic attacks and for relieving acute pain, in which meloxicam and meglumin are heated in a mixture of a water-miscible organic solvent and water meloxicam-meglumin salt monohydrate seed crystals are added to the
15 mixture for crystallisation then crystalline meloxicam-meglumin salt monohydrate is isolated in the usual way and powdered if desired and subsequently the meloxicam-meglumin salt monohydrate is intimately mixed with suitable powdered excipients and/or carriers and
20 compressed directly into tablets with no granulation of the powder

A seventh object of the invention is a process for preparing an orally administered solid pharmaceutical
25 preparation containing meloxicam in the form of the meloxicam-meglumin salt dihydrate which has a short decomposition time and from which the active substance is rapidly released and absorbed, for pain therapy, particularly for treating acute rheumatic attacks and for
30 relieving acute pain, in which crystalline meloxicam-meglumin salt monohydrate is treated at high relative humidity the meloxicam-meglumin salt dihydrate thus obtained is powdered if desired, and then intimately mixed with suitable powdered excipients and/or carriers
35 and compressed directly into tablets without granulation of the powder

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The following Examples are intended to illustrate the invention more fully

5 Example 1 Meloxicam meglumin salt monohydrate

12.5 kg (35.57 mol) meloxicam and 6.9 kg (35.57 mol) meglumin are added successively, with stirring to a mixture of 275 l of acetone and 7 l of water in a suitable
10 reactor I then 1 kg of industrial-grade activated charcoal are added. The reaction mixture is heated and refluxed for 30 minutes. Then the mixture is forced through a pressure filter into a second reactor II. Reactor I and the pressure filter are washed out with 10 l
15 of acetone. The mixture is combined with 10 - 15 g meloxicam meglumin salt monohydrate seed crystals, cooled to 20 °C and stirred for 2 hours at this temperature. Then the mixture is heated, refluxed for 15 minutes and then slowly cooled to 20°C during which time a fine
20 crystalline crystal suspension is formed. This is stirred for 15 hours at 20°C. The crystal suspension is then centrifuged and subsequently spun dry. The centrifugal pellet is washed with 35 l of acetone and again spun dry. The product is dried in the drying cupboard at 20 - 35 °C
25 with fresh air for about 24 hours. Yield 90.1 % of theory. pale yellow crystalline powder, needle-like crystals, melting point 120 °C.

The crystalline meloxicam meglumin salt monohydrate thus
30 obtained was investigated by IR-spectroscopy, by X-Ray Powder Diffraction and by thermal analysis (Thermogravimetry = TG, Differential Scanning Calorimetry = DSC).

35 1.1 IR spectroscopy

Apparatus Nicolet FTIR Spectrometer Magna - IR
550
Software Nicolet Software Packet OMNIC Version
1 20
5 Technique Transmittance,
KBr pellets (2.5 μ mol substance/300 mg
KBr),
N₂ rinse (flow 15 l N₂/min)

10 The FTIR spectrum is shown in Figure 5
Compared with the FTIR spectrum of the dihydrate form
there is a significant difference in the cleaved band at
about 1300 cm⁻¹ in the spectrum of the monohydrate form
otherwise the spectra are very similar

15
1 2 X-ray powder diffraction

Apparatus Philips X-Ray Powder Diffractometer
CuK α radiation, λ = 1.5418 Å, 35 mA 35 kV
20 Software Software package GUPFI 4.06 for data
interpretation
Software package ORIGIN for data
presentation
Parameters Range 3 - 50 ° 2 θ
25 Step scan 0.01° 2 θ step width 2 sec
counting time for each step

Table 2 Powder X-Ray Reflexes and their intensities
30 (standardised),
meloxicam meglumin salt monohydrate

2 θ $\rightarrow$ [°]	d $_{hkl}$ [Å]	Intensity I/I ₀
6.50	13.6	32
11.26	7.85	9

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13 03	6 79	78
13 42	6 59	61
14 92	5 93	90
15 91	5 57	10
16 66	5 32	7
17 84	4 97	20
18 38	4 82	20
18 58	4 77	47
19 24	4 61	25
20 29	4 37	5
20 47	4 34	16
21 97	4 04	13
22 72	3 91	3
23 18	3 84	7
23 34	3 81	4
23 49	3 78	4
23 79	3 74	8
23 97	3 71	6
25 45	3 50	13
25 83	3 45	100
26 30	3 39	14
26 95	3 31	6
27 25	3 27	4
27 89	3 20	3
28 55	3 12	3
29 09	3 07	7
29 53	3 02	10
30 18	2 96	8
31 19	2 87	4
36 01	2 49	9
36 16	2 48	8
37 73	2 38	8
38 64	2 33	6
39 78	2 26	8

The X-ray powder diffraction pattern is shown in Figure 6

1 3 Thermal Analysis

- 5 TG Apparatus Mettler Microbalance M3 Temperature-
controller TC15
Software Mettler Software package STAR
Technique γ -Al₂O₃ melting pot heating rate 10
K/min, N₂ atmosphere
- 10 DSC Apparatus Mettler DSC-20, temperature controller
TC15
Software Mettler Software package STAR
Technique open Al melting pot heating rate 3 and 10
K/min, N₂ atmosphere

15

A clear correlation can be found between the endothermic peak observed in the DSC diagram and the dehydration or melting processes Dehydration and melting are clearly separate processes

- 20 The DSC diagram is shown in Figure 8

Example 2 Meloxicam meglumin salt dihydrate

- 25 Crystalline meloxicam meglumin salt dihydrate is obtained by storing the crystalline meloxicam meglumin salt monohydrate obtained in Example 1 for five days over saturated potassium chloride solution at a relative humidity of 86 % and a temperature of 20 °C

- 30 The crystalline meloxicam meglumin salt dihydrate thus obtained was investigated by IR spectroscopy by X-Ray Powder Diffraction and by thermal analysis (thermogravimetry = TG, Differential Scanning Calorimetry = DSC) The apparatus software and parameters mentioned
- 35 in Example 1 were used

2 1 IR spectroscopy

The FTIR spectrum is shown in

Figure 5

2 2 X-Ray Powder diffraction

Table 3 Powder X-Ray Reflexes and their intensities

5 (standardised)

meloxicam meglumin salt dihydrate

$2\theta_{\text{exp}}$ [°]	d_{exp} [Å]	Intensity I/I_0
5 99	14 8	13
6 95	12 7	13
7 36	12 0	41
7 82	11 3	22
8 25	10 7	18
8 47	10 4	38
10 32	8 6	32
10 85	8 2	18
11 86	7 46	29
12 61	7 01	26
13 46	6 58	49
13 81	6,41	19
14 29	6 20	37
14 48	6 11	42
14 97	5 92	53
15 28	5 80	96
16 88	5 25	65
17 39	5 10	39
17 78	4 99	42
18 41	4 81	25
19 08	4 65	50
19 55	4 54	14
20 10	4 41	28
21 12	4 20	24
21 70	4 09	19
21 95	4 05	25
22 80	3 90	26

25 65	3 47	100
26 02	3 42	43
27 04	3 30	35
27 37	3 26	26
28 29	3 15	19
28 92	3 09	14
30 43	2 94	13

The X-ray powder diffraction pattern is shown in Figure 6

2 3 Thermal Analysis

5

Clear correlation of the endothermic peak observed in the DSC diagram is not possible since dehydration and melting processes overlap

The TG/DSC diagrams obtained are shown in Figures 8 and 9

- 10 The DSC diagram of the dihydrate form is very characteristic with a broad and structured endothermic peak between ambient temperature and 130 °C Five clear minima are visible at about 45, 65, 85 115 and 125 °C The comparison with the DSC diagram of the monohydrate
- 15 form in Figure 8 clearly shows the differences between these two hydrate forms All they have in common s the endothermic peaks at about 85-90 °C (dehydration step) and at about 125 °C (melting process)

20 Example 3 Anhydrous meloxicam meglumin salt

Meloxicam meglumin salt monohydrate can be converted into an anhydrous form by dehydration The relevant parameters of the dehydration process are the temperature and

- 25 duration of dehydration the influence of which were observed by X-ray powder diffraction The longer the dehydration process lasts, the less crystalline is the resulting material After 24 hours at 100 °C the meloxicam meglumin salt is anhydrous and totally amorphous, whereas

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after one hour at 80 °C no change can be detected in the monohydrate used. The X-ray powder diffraction diagrams obtained after 1 hour at 80 °C, 15 hours at 70 °C, 20 hours at 80 °C and 24 hours at 100 °C are shown in Figure

5 7

Example 4 Meloxicam meglumin salt (monohydrate) tablets directly compressed

10 Recipe for meloxicam meglumin salt tablets

	meloxicam meglumin salt	
	calculated as meloxicam	7.5 mg
	microcrystalline cellulose	205.5 mg
15	lactose	205.5 mg
	polyvinylpyrrolidone	
	(crosslinked)	22.5 mg
	magnesium stearate	4.5 mg

20 Preparation

The active substance (ground or not ground) is intimately mixed with the excipients specified in the recipe and compressed directly to form tablets

25 Example 5 Meloxicam sodium salt tablets compressed directly

Recipe for meloxicam sodium salt tablets

30	meloxicam sodium salt	
	calculated as meloxicam	7.5 mg
	microcrystalline cellulose	209.5 mg
	lactose	205.5 mg
	polyvinylpyrrolidone	
35	(crosslinked)	22.5 mg
	magnesium stearate	4.5 mg

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Preparation

The active substance (ground or not ground) prepared for example according to the data in EP-A-0 002 482 is
5 intimately mixed with the excipients specified in the recipe and compressed directly to form tablets

Example 6 in vitro release

10 meloxicam (neutral)/directly compressed versus
meloxicam (neutral)/granulated/compressed

When the release profiles of two tablets are compared with each other, one formulation having been produced by compressing a powder mixture whilst the other has been
15 prepared by compressing previously granulated powder it is apparent that the meloxicam is released more quickly from the tablet prepared by compressing of the powder mixture (Figure 3) The release was measured over the investigation period by spectral-photometric determination
20 of the active substance at its extinction peak

Recipe for meloxicam tablets (directly compressed from powder)

25	meloxicam	7 5 mg
	microcrystalline cellulose	210 0 mg
	lactose	205 0 mg
	polyvinylpyrrolidone	
	(crosslinked)	22 5 mg
30	magnesium stearate	4 5 mg

Recipe for meloxicam tablets (compressed from granules)

35	meloxicam	7 5 mg
	microcrystalline cellulose	210 0 mg
	lactose	205 0 mg
	polyvinylpyrrolidone	

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(crosslinked)	22 5 mg
magnesium stearate	4 5 mg

Example 7 Human trials for verifying the advantages
 5 of the pharmaceutical composition according to the
 invention over a conventional preparation

The following formulations were tested on 18 test subjects
 in a single dose in a cross-over trial

10

Recipe for meloxicam meglumin salt tablets (directly
 compressed)

	meloxicam meglumin salt	
15	calculated as meloxicam	7 5 mg
	microcrystalline cellulose	205 5 mg
	lactose	205 5 mg
	polyvinylpyrrolidone	
	(crosslinked)	22 5 mg
20	magnesium stearate	4 5 mg

Recipe for meloxicam (granulated) capsules

	meloxicam	7 5 mg
	sodium citrate	15 0 mg
25	microcrystalline cellulose	102 0 mg
	lactose	23 5 mg
	polyvinylpyrrolidone (soluble)	10 5 mg
	silicon dioxide (highly dispersed)	3 5 mg
	polyvinylpyrrolidone (crosslinked)	16 3 mg
30	magnesium stearate	1 7 mg

Figure 4 shows the averages of the plasma levels obtained
 It is apparent that the differences found in the
 dissolution processes *in vitro* are also seen in the blood
 35 levels in humans after oral administration When the
 rapidly released form with the salt of meloxicam was used

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the plasma levels rose faster, leading to an increase in the maximum plasma levels and a shortening of the time taken to achieve these levels

- 5 With an onset of activity correlated to the plasma level a formulation of this kind will give a faster acting analgesic effect

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Patent Claims

- 1 Use of a meloxicam salt of an inorganic or organic
5 base preferably the sodium, potassium or ammonium salt
 the meglumin salt the Tris salt or the salt of a basic
 amino acid, for preparing an orally administered solid
 pharmaceutical form from which the active substance is
 rapidly released and absorbed, for pain therapy
- 10 2 Use according to claim 1, characterised in that the
 meloxicam salt is the sodium or meglumin salt
- 15 3 Orally administered solid pharmaceutical form of
 meloxicam, from which the active substance is rapidly
 released and absorbed, for pain therapy, characterised in
 that meloxicam is present in the form of a salt with an
 inorganic or organic base, preferably the sodium
 potassium or ammonium salt the meglumin salt, the Tris
20 salt or the salt of a basic amino acid optionally
 together with conventional excipients and/or carriers, in
 a rapidly decomposing tablet produced by direct
 tableting
- 25 4 Pharmaceutical form according to claim 3, characterised
 in that the meloxicam salt is the sodium or meglumin salt
- 30 5 Process for preparing an orally administered solid
 pharmaceutical preparation of meloxicam, which has a short
 decomposition time and from which the active substance is
 released and absorbed rapidly for pain therapy,
 characterised in that an optionally pulverised meloxicam
 salt of an inorganic or organic base preferably the
 sodium potassium or ammonium salt the meglumin salt, the
35 Tris salt or the salt of a basic amino acid is intimately
 mixed with conventional powdered excipients and/or

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carriers and compressed directly into tablets with no granulation of the powder

6 Process according to claim 5 characterised in that
5 the meloxicam salt is the sodium or meglumin salt

7 Crystalline meloxicam meglumin salt monohydrate and
crystalline meloxicam meglumin salt dihydrate

10 8 Process for preparing the crystalline meloxicam-
meglumin salt monohydrate characterised in that meloxicam
and meglumin are heated in a mixture of a water-miscible
organic solvent, preferably acetone methanol ethanol n-
propanol I-propanol tetrahydrofuran or dioxane and
15 water, and meloxicam-meglumin salt monohydrate seed
crystals are added to the mixture for crystallisation

9 Process according to claim 8 characterised in that
acetone or ethanol is used as the organic solvent
20

10 Process according to claim 9 characterised in that
in the mixture organic solvent and water are used in a
ratio by volume of 10 1 to 100 1, preferably 20 1 to 50 1
or most preferably in a ratio of 35 1 to 45 1
25

11 Process according to claim 8, characterised in that
meloxicam and meglumin are used in a molar ratio of 1 1 5
to 1 5 1 preferably in a molar ratio of 1 1 2 to 1 2 1

30 12 Process according to claim 8, characterised in that in
a mixture of A = 12 5 kg meloxicam, mixture B = 5 to 50 g
of meloxicam-meglumin salt monohydrate seed crystals are
added or in a different quantity of mixture seed
crystals are added in a corresponding ratio by weight of
35 A B = 125 0 05 - 0 5

48
131

- 28 -

13 Process for preparing crystalline meloxicam-meglumin
salt dihydrate characterised in that crystalline
meloxicam-meglumin salt monohydrate is treated at high
humidity preferably by storing it for at least one day at
5 a relative humidity of at least 75 %

14 Process for process for preparing an orally
administered solid pharmaceutical preparation containing
meloxicam in the form of the meloxicam-meglumin salt
10 monohydrate, which has a short decomposition time and from
which the active substance is rapidly released and
absorbed, for pain therapy, characterised in that
meloxicam and meglumin are heated in a mixture of a water-
miscible organic solvent and water meloxicam-meglumin
15 salt monohydrate seed crystals are added to the mixture
for crystallisation, then crystalline meloxicam-meglumin
salt monohydrate is isolated in the usual way and powdered
if desired and subsequently the meloxicam meglumin salt
monohydrate is intimately mixed with conventional powdered
20 excipients and/or carriers and compressed directly into
tablets with no granulation of the powder

15 Process for preparing an orally administered solid
25 pharmaceutical preparation containing meloxicam in the
form of the meloxicam-meglumin salt dihydrate, which has a
short decomposition time and from which the active
substance is rapidly released and absorbed for pain
therapy characterised in that crystalline meloxicam-
30 meglumin salt monohydrate is treated at high relative
humidity the meloxicam-meglumin salt dihydrate thus
obtained is powdered if desired and then intimately
mixed with suitable powdered excipients and/or carriers
and compressed directly into tablets without granulation
35 of the powder

49
132

- 29 -

16 Orally administered solid pharmaceutical form containing meloxicam in the form of the crystalline meloxicam meglumin salt monohydrate

5 17 Orally administered solid pharmaceutical form containing meloxicam in the form of the crystalline meloxicam meglumin salt dihydrate

Figure 1 polymorphism of the meloxicam-meglumin salt (UHAC 62 MU)

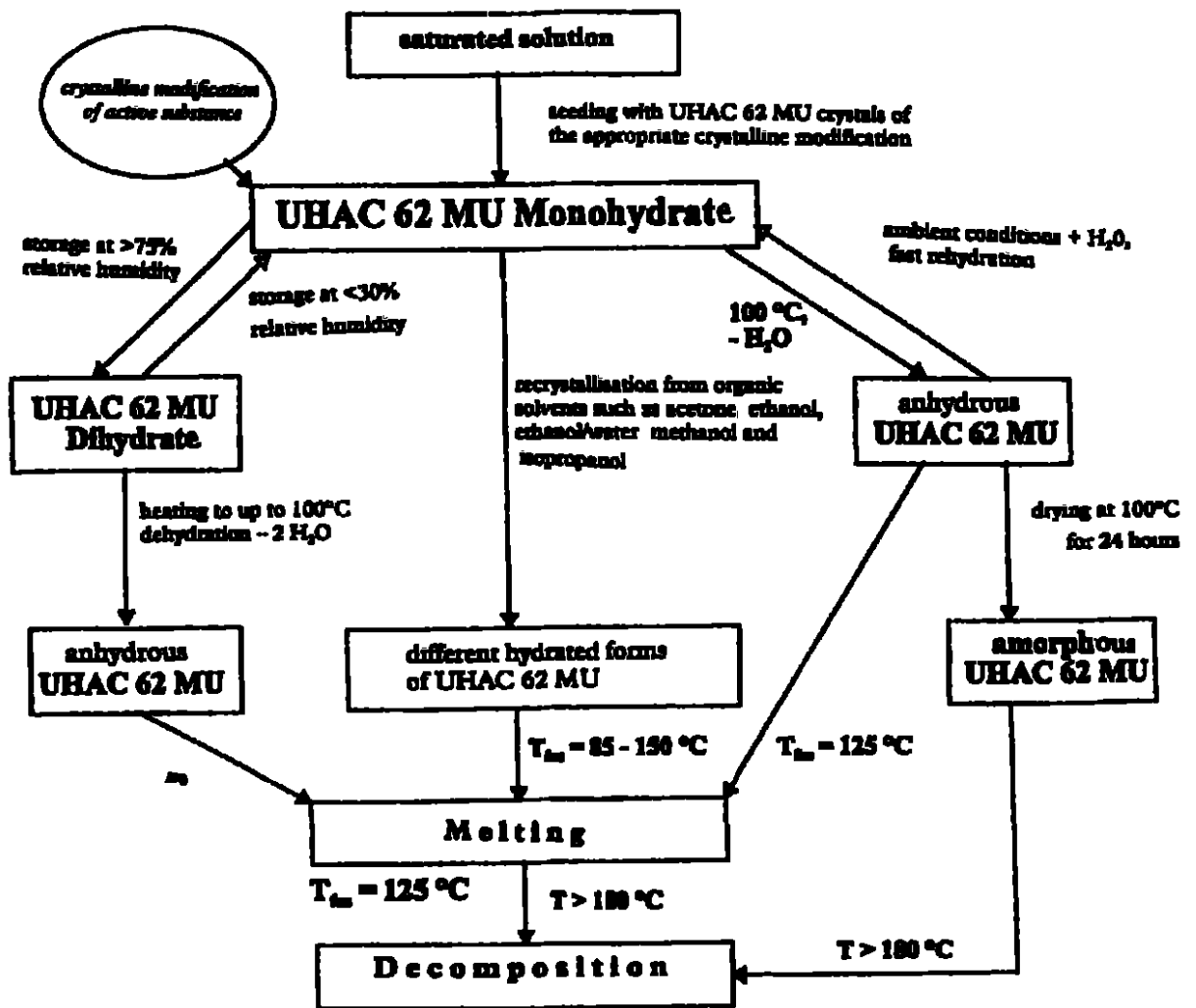


Figure 2 Plan of synthesis for meloxicam-meglumin salt (UHAC 62 MU)

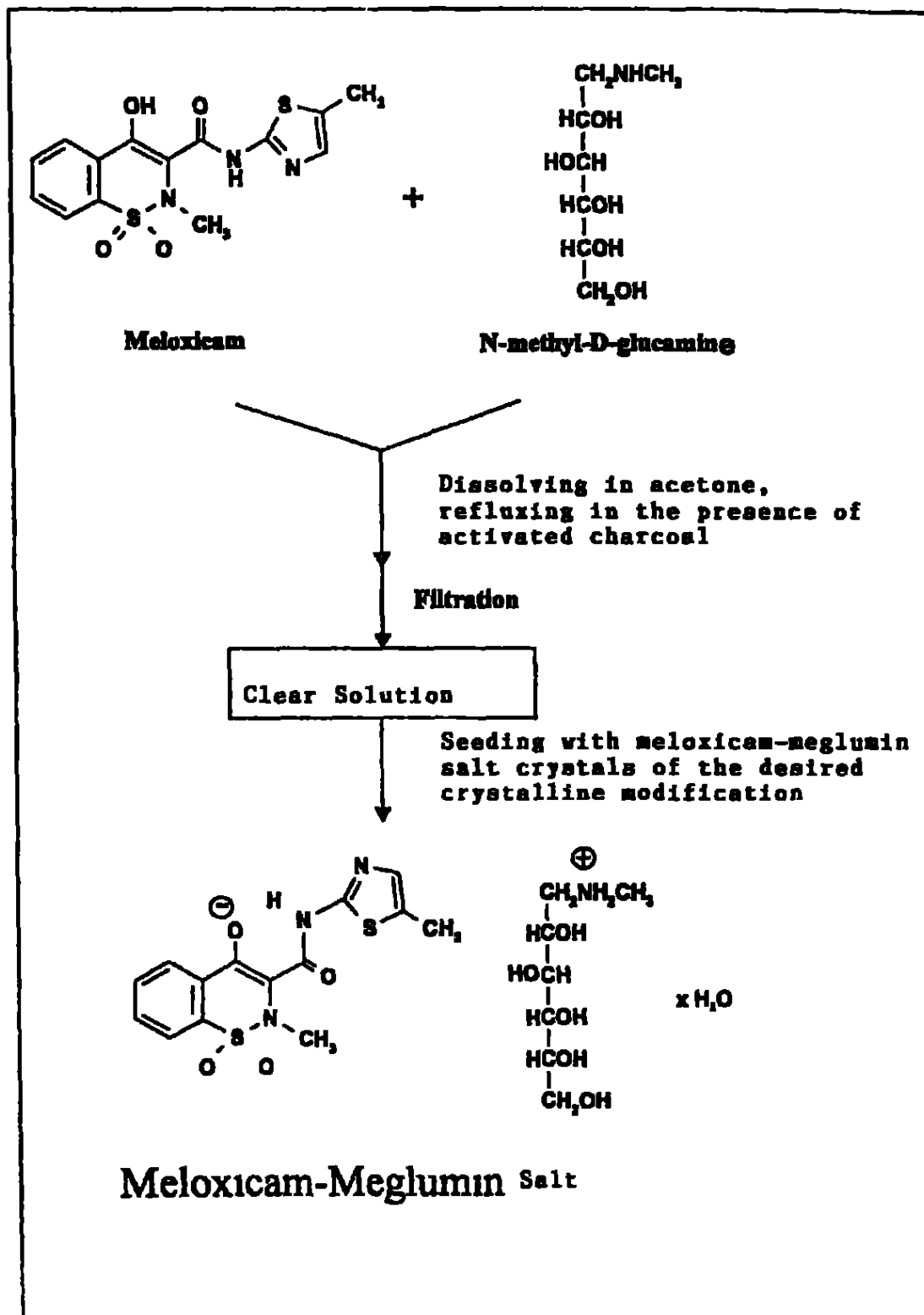


Figure 3 Release profiles of a directly compressed meloxicam tablet and a meloxicam tablet formulation prepared from a granulate, at pH 7.5 (averages from three measurements)

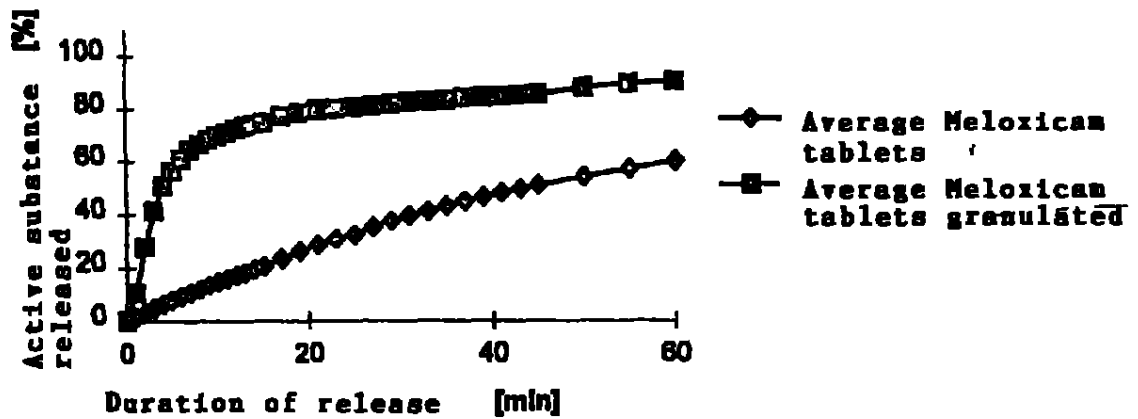


Figure 4 Plasma levels of a tablet and capsule formulation in 18 test subjects in cross-over trials (geometric mean)

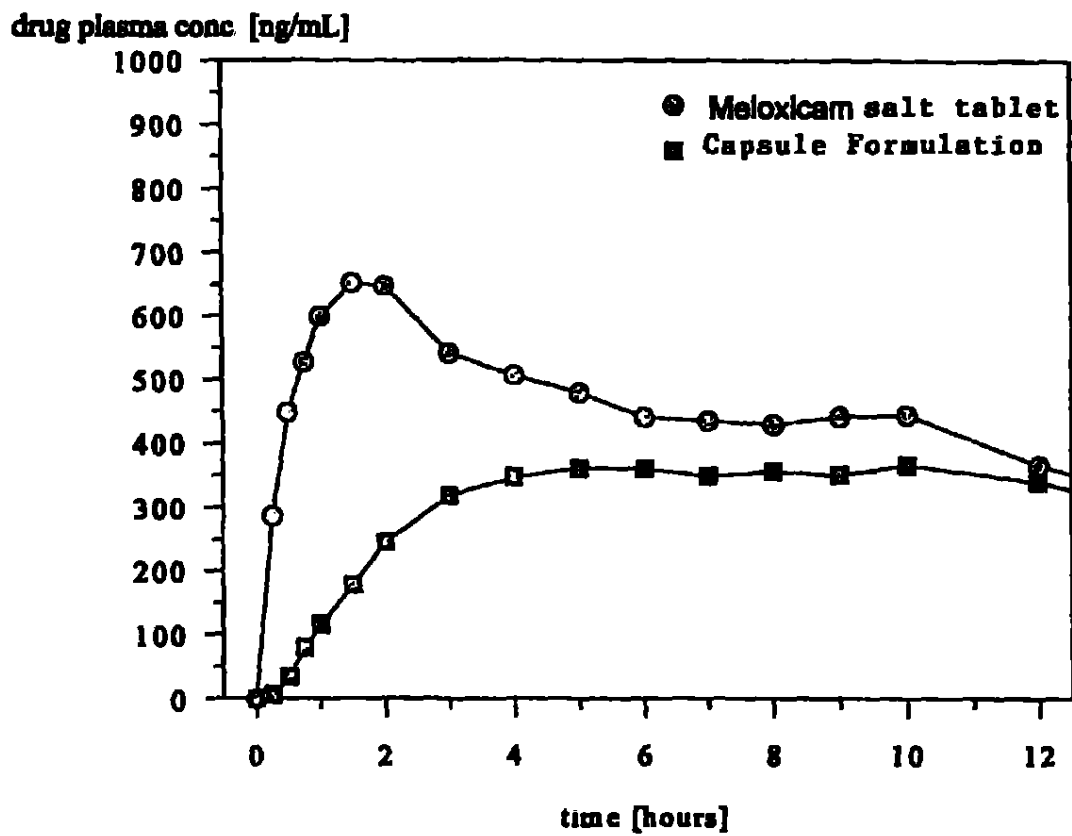
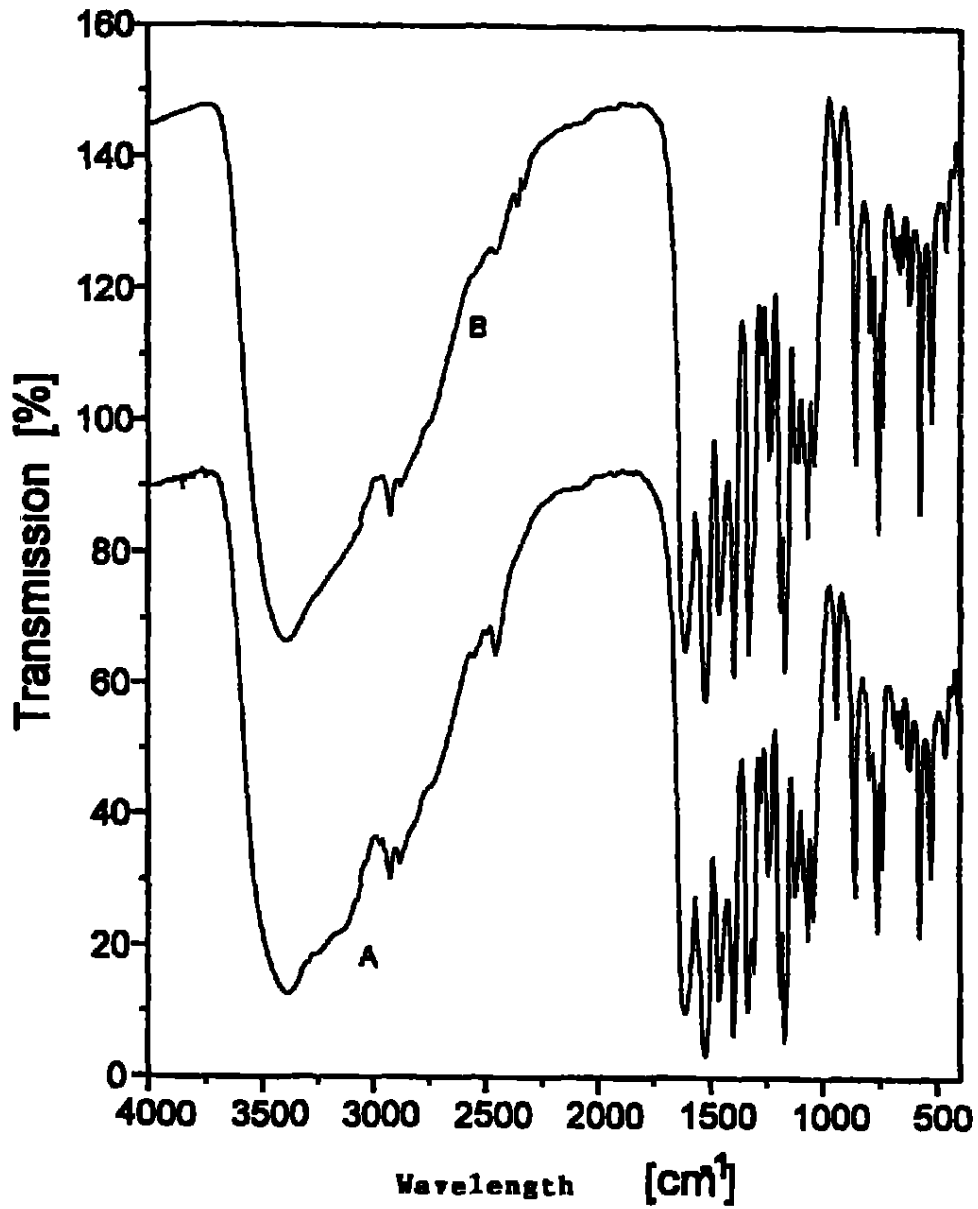


Figure 5 Solid FTIR spectra of meloxicam meglumin salt monohydrate (A) and meloxicam meglumin salt dihydrate (B)



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Figure 6 X-Ray Powder Diffraction, meloxicam meglumin salt monohydrate (A) and meloxicam meglumin salt dihydrate (B)

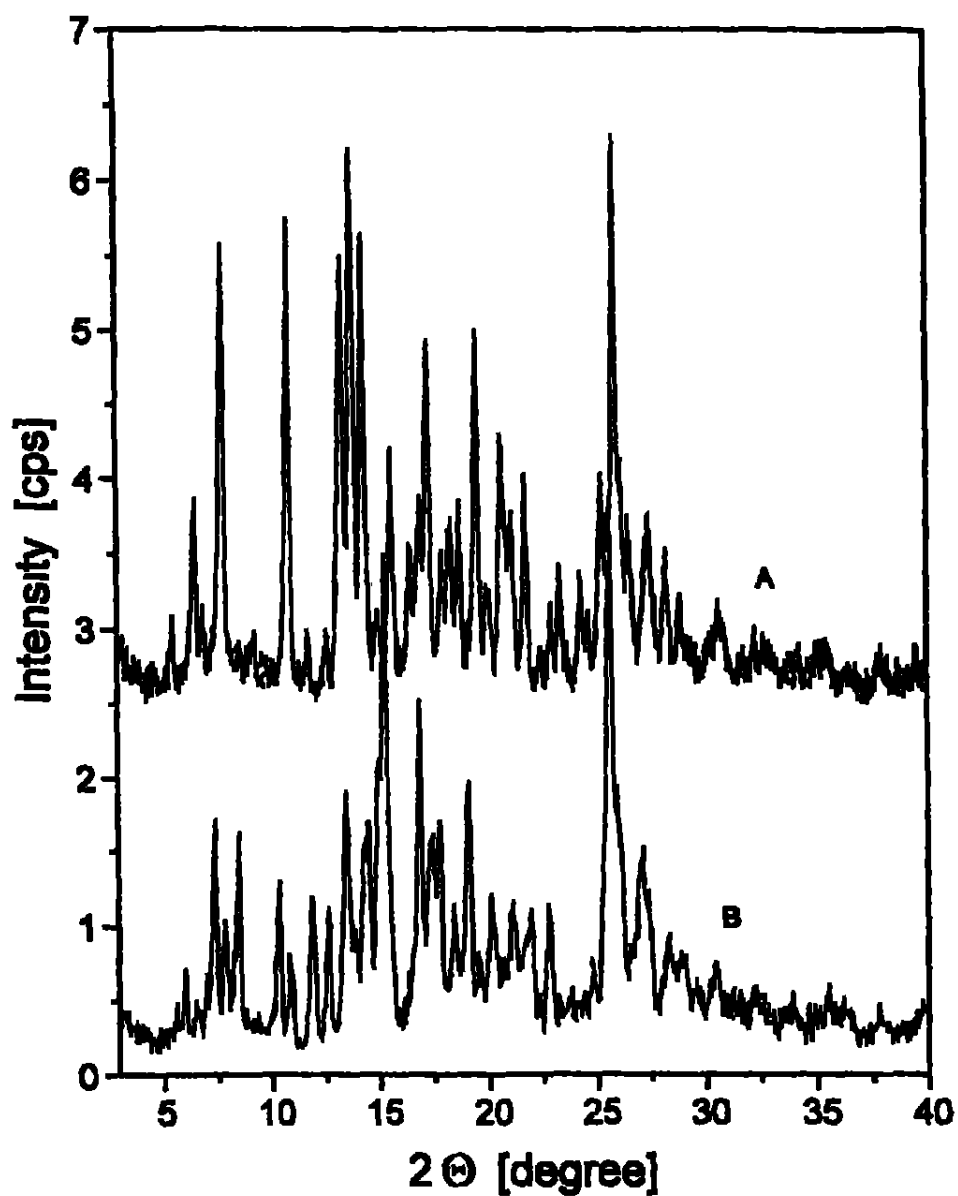


Figure 7 X-Ray Powder Diffraction diagrams during the conversion of meloxicam meglumin salt monohydrate into the anhydrous form

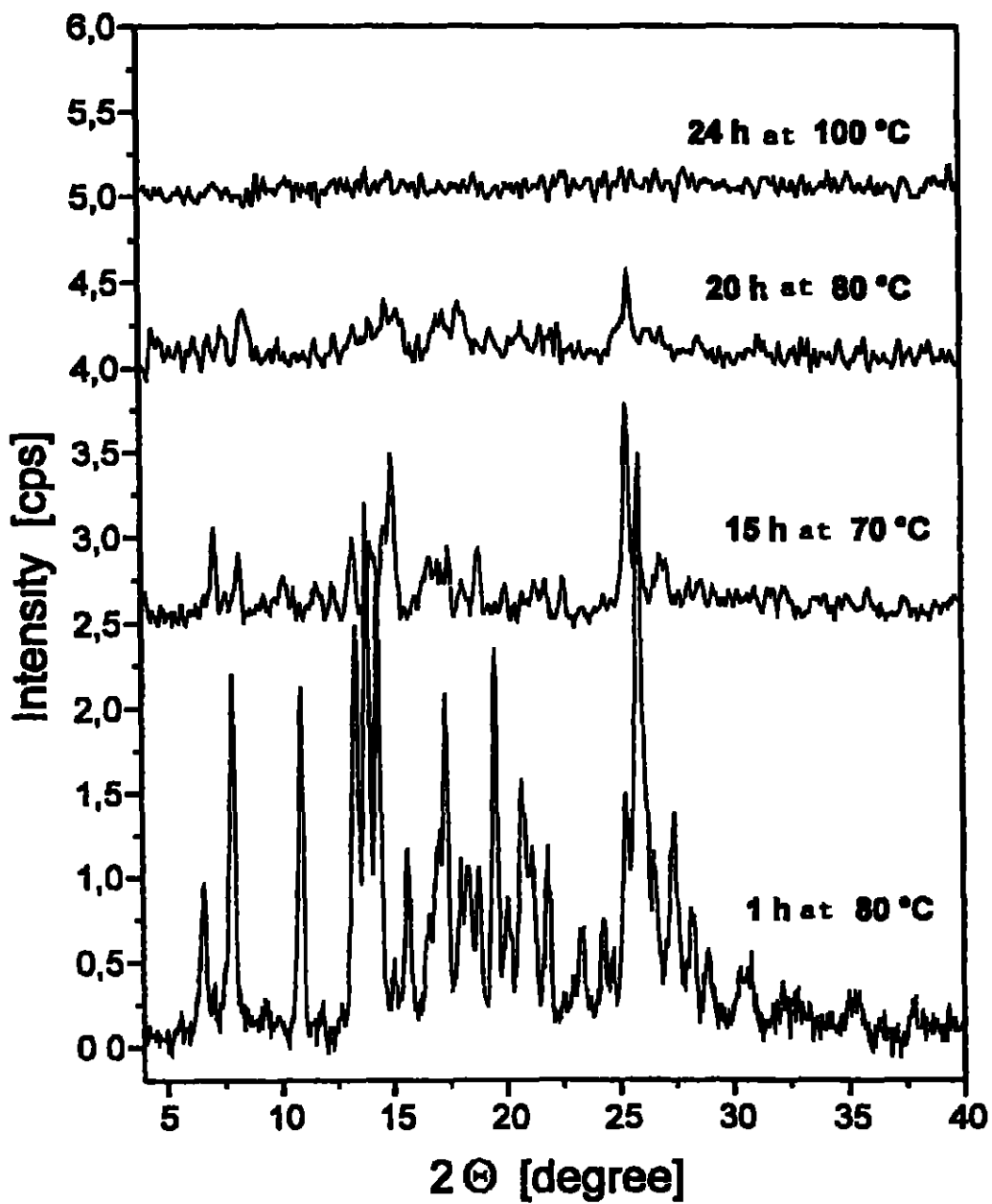
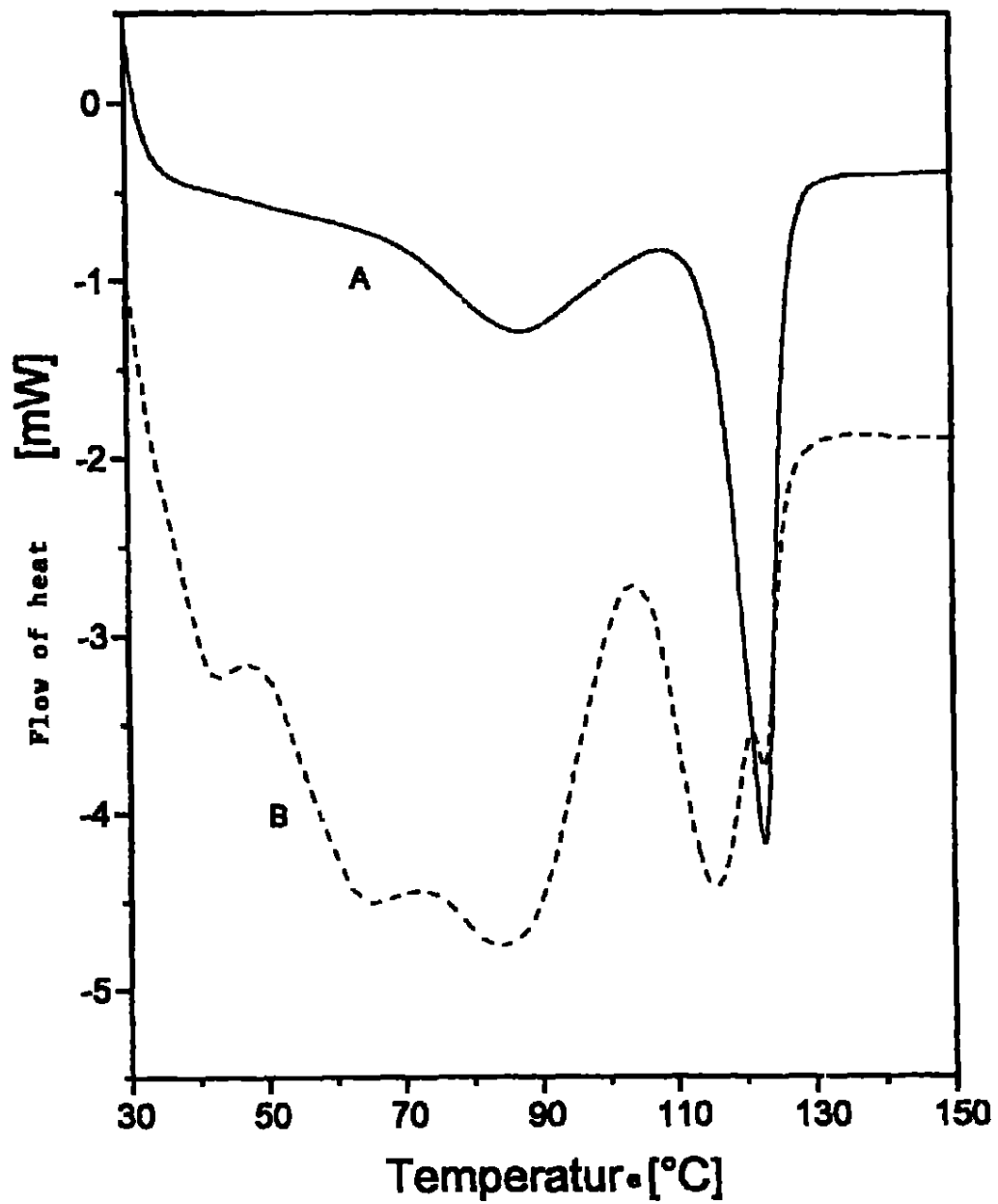


Figure 8 DSC diagrams of meloxicam meglumin salt monohydrate (A) and meloxicam meglumin salt dihydrate (B)





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(54) **HIGHLY CONCENTRATED STABLE
MELoxicam SOLUTIONS**

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(57) **ABSTRACT**

Aqueous cyclodextrin-free solution of meloxicam for administration by oral or parenteral route containing a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more suitable excipients, the content of dissolved meloxicam salt being more than 10 mg/mL. The formulation according to the invention has a shelf life of up to 24 months or more.

HIGHLY CONCENTRATED STABLE MELOXICAM SOLUTIONS

[0001] The present invention relates to highly concentrated stable meloxicam solutions for oral and parenteral administration, particularly for treating respiratory diseases in large farm animals.

BACKGROUND OF THE INVENTION

[0002] Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, 1,1-dioxide) is an active substance which belongs to the group of NSAIDs (non-steroidal antiinflammatory drugs). Meloxicam and the sodium and meglumine (N-methyl-D-glucamine) salt thereof are described in EP-A 0 002 482. EP-A 0 002 482 shows, inter alia, the example of a 0.2% injectable solution of meloxicam consisting of the meglumine salt of the active substance, sodium chloride, and water.

[0003] EP-A 0 945 134 discloses the pH dependent solubility characteristics of meloxicam and its salts, i.e. the sodium salt, the ammonium salt, and the meglumine salt in aqueous solution. According to EP-A 0 945 134, meloxicam is an active substance which does not dissolve readily in water and the meloxicam salts, particularly the meglumine salt, exhibit improved solubility as the pH increases between 4 and 10, as shown in Table 1 of EP-A 0 945 134. However, until now it has only been possible to produce stable, clear aqueous solutions with a low concentration of meloxicam. In addition to involving the in situ formation of a meloxicam salt, e.g. meglumine salt, and the addition of solubilizers, these prior art solutions were required to have a pH in the range of maximum possible solubility as well as being reasonably well tolerated and contain a high proportion of organic solvent. Formulation tests with the same or a similar recipe led to cloudiness of the solution if the meloxicam concentrations were higher, e.g. 2%.

[0004] WO9959634 A1 describes an eye drop solution containing 0.5% meloxicam but makes no reference to possible meloxicam concentrations over 1%. For example, a commercially available 0.5% meloxicam solution is used in small animals such as dogs, beifers, and calves to treat respiratory diseases.

[0005] Thus, it has not hitherto been possible to treat large farm animals with an injectable meloxicam solution as the low concentration of active substance in the injectable solution did not allow an acceptable, well tolerated injection volume due to the great weight of the animals. Furthermore, parenteral administration requires that the solution be free from particles, if there are particles in a parenteral drug, there is a risk of vascular damage or embolism. Moreover, organic solvents, solubilizers, and water-soluble substances can only be used in certain concentrations to achieve acceptable drug tolerance. These problems are solved by the present invention which provides particle free, highly concentrated meloxicam solutions which are stable over long periods and suitable for treating farm animals up to 750 kg in weight. The meloxicam solutions of the present invention should therefore be suitable for administration both orally or parenterally.

DESCRIPTION OF THE INVENTION

[0006] Surprisingly, it has been found that highly concentrated meloxicam solutions which contain, in addition to a

meloxicam salt and certain excipients, another excipient selected from among citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid, and EDTA or the salts thereof may be produced so as to be particle free and stable over long periods. The stability was achieved with an unexpectedly small amount of organic solubilizers. The formulation was found to be stable even when subjected to the process of final sterilization.

[0007] This results in the solution to the problem according to the invention as a formulation of a meloxicam solution which contains, in addition to a meloxicam salt, small concentrations of solubilizer, a preservative, a buffer substance for achieving the optimum pH range, and another excipient.

[0008] The invention relates to aqueous cyclodextrin free solutions of meloxicam for parenteral or oral administration which contain a pharmacologically acceptable meloxicam salt of an organic or inorganic base in a highly concentrated solution with 11.25 mg/mL of meloxicam together with suitable excipients.

[0009] The formulation according to the invention overcomes the problem arising from the prior art of providing an injectable solution of the active substance meloxicam which is also suitable for treating large farm animals, by permitting a high concentration of active substance in a particle free solution which is stable over the long term having the composition described hereinafter.

[0010] The formulation according to the invention may contain as the meloxicam salt the meglumine, sodium, potassium, or ammonium salt, preferably the meloxicam meglumine salt.

[0011] The solubilizers used may be, for example, polyethyleneglycols, polyoxyethylene polyoxypropylene copolymers (e.g. Poloxamer 188), glycofurool, arginine, lysine, castor oil, propyleneglycol, sulcatel, polysorbate, glycerol, sorbitol, mannitol, xylitol, polyvinylpyrrolidone, lecithin, cholesterol, 12-hydroxyoctadecanoic acid, PEG660-ester, propyleneglycol monostearate, polyoxy-40-hydrogenated castor oil, polyoxyl 10-oleyl ether, polyoxyl 20-cetostearyl ether, and polyoxyl-40-stearate or a mixture of sorbitol, mannitol, and xylitol, preferably polyethyleneglycols, polyoxyethylene polyoxypropylene copolymers, glycofurool, polyvinylpyrrolidone, lecithin, cholesterol, 12-hydroxyoctadecanoic acid, PEG660-esters, propyleneglycol monostearate, polyoxy-40-hydrogenated castor oil, polyoxyl 10-oleyl ether, polyoxyl 20-cetostearyl ether, and polyoxyl-40-stearate. Particularly preferred are polyethyleneglycols, glycofurool, and polyoxyethylene polyoxypropylene-copolymers, but especially polyethyleneglycols (e.g. Macrogol 300) and polyoxyethylene-polyoxypropylene copolymers (e.g. Poloxamer 188). The preservatives used may be, for example, ethanol, benzoic acid and the sodium or potassium salts thereof, sorbic acid and the sodium or potassium salts thereof, chlorobutanol, benzyl alcohol, phenylethanol, the methyl, ethyl, propyl, or butyl p-hydroxybenzoates, phenol, m-cresol, p-chloro-m-cresol, or benzalkonium chloride. Particularly preferred are ethanol, benzoic acid and the sodium or potassium salts thereof, sorbic acid and the sodium or potassium salts thereof, chlorobutanol, benzyl alcohol, phenylethanol, and the methyl, ethyl, propyl, or butyl p-hydroxybenzoates, but preferably ethanol, benzoic acid and the sodium or potassium salts thereof, but especially ethanol.

[0012] The buffer system used to achieve a pH of between 8 and 10 may be, for example, glycine, a mixture of glycine and HCl, a mixture of glycine and sodium hydroxide solution, and the sodium and potassium salts thereof, a mixture of potassium hydrogen phthalate and hydrochloric acid, a mixture of potassium hydrogen phthalate and sodium hydroxide solution, or a mixture of glutamic acid and glutamate. Glycine, a mixture of glycine and HCl, and a mixture of glycine/sodium hydroxide solution, especially glycine, are particularly preferred.

[0013] Other suitable excipients are citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid, and EDTA, or the alkali metal salts thereof, preferably tartaric acid and EDTA, or the alkali metal salts thereof, particularly disodium EDTA.

[0014] One embodiment of the invention contains, in addition to the meglumine or sodium salt of meloxicam, polyethyleneglycols, glycerol, and/or polyoxyethylene polyoxypropylene copolymers, but particularly polyethyl-oxglycols (e.g., Macrogol 300) and/or polyoxyethylene polyoxypropylene copolymers (e.g., Pluronic 188) as solubilizer, ethanol, benzoic acid, and the sodium or potassium salt thereof, or sorbic acid, and the sodium or potassium salts thereof, but particularly ethanol as preservative, and glycine, a mixture of glycine/HCl, or a mixture of glycine/sodium hydroxide solution, but preferably glycine as buffer, and disodium EDTA as an additional excipient.

[0015] The formulation according to the invention may contain meloxicam in a concentration of 11.25 mg/mL, preferably 13-24 mg/mL, preferably 16-23 mg/mL, particularly preferably 18-22 mg/mL, and especially 20 mg/mL.

[0016] The meglumine concentration may be between 12.5 and 16.5 mg/mL, preferably 13-16 mg/mL, preferably 13.5-15.5 mg/mL, more preferably 14-15 mg/mL, and especially about 14 mg/mL. The possible sodium, potassium, and ammonium concentrations are calculated accordingly.

[0017] The concentration of the solubilizers may be in the range from 20-200 mg/mL, preferably 30-150 mg/mL, preferably 40-130 mg/mL, more preferably 50-120 mg/mL, and especially 70-110 mg/mL.

[0018] The concentration of the preservative ethanol may be in the range from 100-200 mg/mL, preferably 120-180 mg/mL, and more preferably about 150 mg/mL.

[0019] The concentration of the preservatives benzoic acid and the sodium or potassium salts thereof, sorbic acid, and the sodium or potassium salts thereof, chlorobutanol, benzyl alcohol, phenylethanol, phenol, m-cresol, and p-chloro-m-cresol, may be in the range from 0.5-50 mg/mL, preferably 1-10 mg/mL, and more preferably 3-5 mg/mL.

[0020] The concentration of the preservatives benzalkonium chloride, phenylmercury nitrate, and methyl ethyl, propyl, or butyl-p-hydroxybenzoates, may be in the range from 0.01-4 mg/mL, preferably 0.02-3 mg/mL, and more preferably 0.1-0.5 mg/mL.

[0021] The concentration of the buffer substances may be between 4 and 50 mg/mL, preferably between 5 and 20 mg/mL, and more preferably between 8 and 10 mg/mL.

[0022] The concentration of the other excipients mentioned above, e.g., EDTA, citric acid, lecithin, gluconic acid,

tartaric acid, and phosphoric acid or the salts thereof, may be in the range from 0.2-3 mg/mL, preferably 0.3-2.5 mg/mL, preferably 0.5-2 mg/mL, most preferably 0.6-1.5 mg/mL, and in particular 0.7-1.0 mg/mL.

[0023] Meglumine and meloxicam may be used in a molar ratio of between 9:8 and 12:8, preferably in a molar ratio of 11:8, but especially in a molar ratio of 10:8.

[0024] In the formulation according to the invention, meloxicam and the other excipient, particularly disodium EDTA, may be present in a weight ratio of between 25:1 and 15:1, preferably between 24:1 and 16:1, preferably between 23:1 and 17:1, more preferably between 22:1 and 18:1, most preferably between 21:1 and 19:1, and in particular about 20:1.

[0025] The formulation according to the invention may have shelf life after opening of 28 days or more.

[0026] The shelf life of the solution in the sealed original packaging may be 1 month or more, in particular between 1 month and 24 months, but at least between 1 month and 18 months, preferably between 1 month and 12 months, more preferably between 1 month and 9 months, most preferably between 1 month and 6 months, particularly between 1 month and 3 months. Details of the stability tests by way of example can be found in Tables 1 and 2 which follow.

[0027] Test of Stability After Opening.

[0028] Packaging material: 50 mL colorless glass vials, glass type I, ethylene-propylene-norbornene terpolymer rubber stopper (Type WI 640 grey), aluminium flanged cap.

[0029] Recipe: analogous to Example 1 of the description.

[0030] 4 mL samples were taken from the storage samples three times a day for six days and on the seventh day 4 mL samples were taken four times. Storage was then continued until 28 days had elapsed and samples were taken again.

TABLE 1

Test No.	Storage conditions [°C / % relative humidity]	Storage time [days]	Meloxicam content [mg/mL]
1	-5 °C	0	19.7
	-5 °C / 60%	28	19
2	5 °C	0	20
	5 °C / 60%	28	19.2

[0031] In both samples, in addition to the meloxicam content, the parameters investigated, namely appearance (clear yellow solution), pH (8.0-9.7), ethanol content (13.5-15.75), disodium EDTA content (85.0-110.0 mg/100 mL), sterility (according to Ph. Eur. and USP), and the stability of the packaging material were found to be unchanged.

[0032] Long-term Stability Test in Sealed Original Packaging.

[0033] Packaging material: 50 mL colorless glass vials, glass type I, ethylene-propylene-norbornene terpolymer rubber stopper (Type WI 640 grey), aluminium flanged cap.

Example 3: 5% Meloxicam Solution

Component	Amount (g/L)
Meloxicam	25.0
Meglumine	17.5
PEG 400	150.0
Poloxamer	50.0
Ethanol	150.0
Glycine	5.0
EDTA-Na	1.0
1M HCl	q.s. ad pH 8.8
1M NaOH	q.s. ad pH 8.8
Water for injections	ad 1000 mL

[0049] Method

[0050] 25 g of meloxicam are dissolved in 500 ml of an aqueous meglumine solution (17.5 g/500 ml) at 90° C. The other excipients are added one after another to the solution according to the recipe given above. A pH of 8.8 is then achieved using 1M hydrochloric acid or 1M sodium hydroxide solution. Water is added to the solution until a volume of 1 liter is obtained.

Example 4: 1.5% Meloxicam Solution

Component	Amount (g/L)
Meloxicam	15.0
Meglumine	10.5
PEG 400	100.0
Poloxamer	50.0
Ethanol	150.0
Glycine	5.0
EDTA-Na	1.0
1M HCl	q.s. ad pH 8.8
1M NaOH	q.s. ad pH 8.8
Water for injections	ad 1000 mL

[0051] Method 15 g of meloxicam are dissolved in 500 mL of an aqueous meglumine solution (10.5 g/500 mL) at 90° C. The other excipients are added one after another to the solution according to the recipe given above. A pH of 8.8 is then achieved using 1M hydrochloric acid or 1M sodium hydroxide solution. Water is added to the solution until a volume of 1 liter is obtained.

Example 5: 2% Meloxicam Solution

Component	Amount (g/L)
Meloxicam	20.0
Meglum	14.0
PEG 400	150.0
Poloxamer	50.0
p-Chloro-m-cresol	2.0
Glycine	5.0
EDTA-Na	1.0
1M HCl	q.s. ad pH 8.8
1M NaOH	q.s. ad pH 8.8
Water for injections	ad 1000 mL

[0052] Method 20 g of meloxicam are dissolved in 500 mL of an aqueous meglumine solution (14 g/500 mL) at 90° C.

The other excipients are added one after another to the solution according to the recipe given above. A pH of 8.8 is then achieved using 1M hydrochloric acid or 1M sodium hydroxide solution. Water is added to the solution until a volume of 1 liter is obtained.

What is claimed is:

1. An aqueous cyclodextrin free solution of meloxicam for administration by oral or parenteral route, comprising a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more suitable excipients, wherein the concentration of dissolved meloxicam salt is more than 10 mg/mL.

2. The aqueous solution according to claim 1, wherein the meloxicam salt is the sodium or meglumine salt.

3. The aqueous solution according to claim 2, wherein the solution contains meglumine and meloxicam in a molar ratio of between 9:8 and 12:8.

4. The aqueous solution according to claim 3, wherein the solution contains meglumine and meloxicam in a molar ratio of 10:8.

5. The aqueous solution according to one of claims 1 to 4, wherein the one or more suitable excipients is selected from the group consisting of a buffer and a preservative.

6. The aqueous solution according to claim 5, wherein the preservative is selected from the group consisting of ethanol, benzoic acid and the sodium and potassium salts thereof, sorbic acid and the sodium and potassium salts thereof, chlorobutanol, benzyl alcohol, phenylethanol, the methyl, ethyl, propyl and butyl p-hydroxybenzoates, phenol, m-cresol, p-chloro-m-cresol, phenylmercury nitrate and benzalkonium chloride.

7. The aqueous solution according to claim 5, wherein the buffer is selected from the group consisting of glycine, a mixture of glycine and HCl, a mixture of glycine and sodium hydroxide solution, and the sodium and potassium salts thereof, a mixture of potassium hydrogen phthalate and hydrochloric acid, a mixture of potassium hydrogen phthalate and sodium hydroxide solution and a mixture of glutamic acid and glutamate.

8. The aqueous solution according to one of claims 1 to 4, wherein the one or more suitable excipients includes a solubilizer.

9. The aqueous solution according to claim 8, wherein the solubilizer is selected from the group consisting of polyethylene glycols, polyoxyethylene polyoxypropylene copolymers, glycofurol, arginine, lysine, castor oil, propylene glycol, solketal, polysorbate, glycerol, sorbitol, mannitol, xylitol, polyvinylpyrrolidone, lecithin, cholesterol, 12-hydroxystearic acid, PEG660-ester, propylene glycol monostearate, polyoxy-40-hydrogenated castor oil, polyoxy-10-oleyl ether, polyoxy-20-cetostearyl ether, polyoxy-40-stearate, and mixtures thereof.

10. The aqueous solution according to one of claims 1 to 4, wherein the one or more suitable excipients is selected from the group consisting of citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid, and EDTA and the alkali metal salts thereof.

11. The aqueous solution according to one of claims 1 to 4, wherein the shelf life of the solution after opening is 28 days or more at ambient temperature.

12. The aqueous solution according to claim 5, wherein the shelf life of the solution after opening is 28 days or more at ambient temperature.

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13 The aqueous solution according to claim 6 wherein the shelf life of the solution after opening is 28 days or more at ambient temperature

14 The aqueous solution according to claim 7 wherein the shelf life of the solution after opening is 28 days or more at ambient temperature

15 The aqueous solution according to claim 8, wherein the shelf life of the solution after opening is 28 days or more at ambient temperature

16 The aqueous solution according to claim 9 wherein the shelf life of the solution after opening is 28 days or more at ambient temperature

17 The aqueous solution according to claim 10 wherein the shelf life of the solution after opening is 28 days or more at ambient temperature

18 The aqueous solution according to one of claims 1 to 4 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

19 The aqueous solution according to claim 5 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

20 The aqueous solution according to claim 6 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

21 The aqueous solution according to claim 7 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

22 The aqueous solution according to claim 8 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

23 The aqueous solution according to claim 9 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

24 The aqueous solution according to claim 10 wherein the solution has a long term shelf life of 24 months or more at ambient temperature in its original packaging

25 The aqueous solution according to one of claims 1 to 4 wherein the solution has a pH of between 8.0 and 10

26 The aqueous solution according to claim 1 comprising meloxicam, meglumine, a polyethyleneglycol, a polyoxyethylene-polyoxypropylene copolymer, ethanol, glycine, disodium EDTA, and optionally sodium hydroxide or hydrochloric acid

27 The aqueous solution according to claim 1 consisting essentially of meloxicam, meglumine, a polyethyleneglycol, a polyoxyethylene-polyoxypropylene copolymer, ethanol, glycine, disodium EDTA, water suitable for injection, and optionally sodium hydroxide or hydrochloric acid

28 A method of treating pain, inflammation, fever, acute mastitis, diarrhea, lameness, problems with the locomotor apparatus, or respiratory complaints in a mammal, the method comprising administering to a mammal in need of such treatment the aqueous solution according to claim 1

29 The method according to claim 28 wherein the method is used in conjunction with antibiotic therapy

30 The method according to claim 28 wherein the solution according to claim 1 is administered in dosage range of from 0.2 to 1.0 mg of active substance/kg of bodyweight of the mammal

31 The method according to claim 30 wherein the solution according to claim 1 is administered in dosage range of from 0.4 to 0.8 mg of active substance/kg of bodyweight of the mammal

32 The method according to claim 30 wherein the solution according to claim 1 is administered in dosage range of from 0.5 to 0.7 mg of active substance/kg of bodyweight of the mammal

* * * * *

2020
Bogotá D C

Doctor
Emilio Ferrero
Apoderado

Oficio N° 1493

ASUNTO	Radicación PCT N°	05-50509
	Trámite	011
	Evento	379
	Actuación	440
	Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina se le comunica que la oposición presentada por el doctor Reinaldo Pinilla Moreno en su calidad de apoderado de Procaps S A reúne los requisitos formales exigidos por la ley al momento de su presentación

En cumplimiento de lo dispuesto en la citada norma se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio para que haga valer sus argumentaciones y presente pruebas

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


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha, 10 FEB. 2006

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