

24

- ☐ Marca Colectiva.
- ☐ Marca de Certificación.
- ☐ Lema Comercial.

Gaceta: 546

⑤ Comprobante de pago No. _____

Fecha _____

77

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.

20

⑦

NOMBRE: LUIS FERNANDO RINCÓN CUELLAR

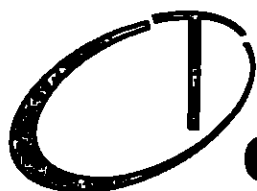
FIRMA:



C.C. 79.532.186

TP. 113438

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.



Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 03-078286
Asunto : Oposición a la solicitud de patente de Invención titulada
"METODO PARA PREPARAR
MICROPARTICULAS QUE CONTIENEN
METOPROLOL".
Solicitante :ASTRAZENECA AB.
Opositora :PROCAPS S.A.

**Publicada en la Gaceta de la Propiedad Industrial
N° 546 del 30 de Noviembre de 2004**

Yo, **Luis Fernando Rincón Cuellar**, abogado con tarjeta profesional N° 113438 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 "**METODO PARA PREPARAR MICROPARTICULAS QUE CONTIENEN METOPROLOL**", solicitada por **ASTRAZENECA AB.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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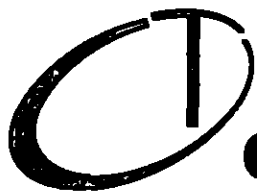
**1. INTERÉS PARA ACTUAR**

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 mi representada pretende con la presentación farmacéutica elaborada con base en el metoprolol. 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 oposición fue presentada en Colombia el 8 de Septiembre de 2003, reivindicando prioridad bajo SE01008242 del 9/03/2001, cuya fecha de inicio en la fase nacional fue el 9 de Octubre de 2003, con publicación internacional N° WO 02/072074 del 19 de septiembre de 2002 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 546, del 30 de Noviembre de 2004, bajo el numero de publicación NP. 579 (página 339).

2.2. La solicitud colombiana N° 03-078286 objeto de la presente oposición, comprende según sus cláusulas, un método para preparar micropartículas homogéneas de metoprolol y a la micropartícula como tal, donde el método comprende suministro de un medio líquido de granulación que comprende un contenido de sólidos de metopropol; aspersión del medio líquido de granulación dentro de un lecho fluidizado ; y selección de

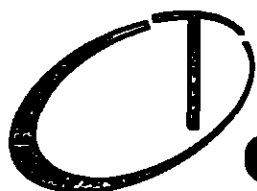


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micropartículas que tengan una distribución de tamaño de menos de 250µm, para obtener así micropartículas homogéneas secas que tienen por lo menos 80% en peso de metropolol; donde el medio líquido de granulación comprende adicionalmente un polímero y/o agente dispersante; donde el medio líquido de granulación comprende adicionalmente un polímero seleccionado del grupo conformado por un polímero soluble en agua ó uno insoluble en agua, en donde el polímero se encuentra por lo menos al 5% en peso con base en el contenido de sólidos; y, un líquido en el cual el polímero es soluble; donde el líquido en el cual el polímero es soluble se selecciona del grupo conformado por agua, alcohol butílico terciario, ciclohexano, cloruro de metileno, metanol, etanol y mezclas de éstos; y, donde el porcentaje en peso de metropolol se sitúa el rango entre 90-100%. Igualmente, esta solicitud se refiere a un método de prevención para prevenir desordenes cardiovasculares y al uso de dichas micropartículas.

2.3. En primera instancia, las reivindicaciones referidas al método terapéutico no son objeto de patentabilidad a la luz de la norma vigente en Colombia. La Decisión 486 de la CAN, en el artículo 20: *"No serán patentables: ...d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales"*. De aquí se deduce claramente que el objeto referido al método de prevención definido en la presente solicitud no puede ser objeto de patente en Colombia.

2.4. Igual y conjuntamente, el artículo 14 de la Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en*



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todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado interior lo que se está reclamando es un método de prevención. Adicionalmente, los usos no están contemplados como objeto de protección, sólo los productos o procedimientos. Adicionalmente, ni el uso ni el método terapéutico definido en la presente solicitud tienen aplicación industrial, porque primero no se obtiene un producto o proceso a partir de los mismos; y, segundo no es reproducible o repetible a escala industrial.

2.5. Ese mismo artículo 14 de la Decisión 486 de la CAN, se refiere a que 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 el siguiente documento que afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: EP0220143. 29 de Abril de 1987.
- D2: US 5883047. 16 de Marzo de 1999.
- D3: US4946654. 7 de Agosto de 1990.

2.6. Como lo indica en el documento D1, en sus reivindicaciones y ejemplos, se revela una preparación de liberación controlada que contiene sales de metoprolol caracterizado en que dicha preparación contiene un número de partículas comprendiendo una sal de metoprolol como el principal componente soluble, preferiblemente al menos de 95%, y donde dichas partículas están cubiertas con una membrana polimérica. En este documento D1, las partículas están en el rango de 0,25 a 2mm.

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Igualmente, esta solicitud se refiere a un método de prevención para prevenir desordenes cardiovasculares y al uso de dichas partículas. Así las cosas, la presentación farmacéutica pretendida en la presente solicitud define las mismas características del arte revelado en el documento D1 advirtiéndose que lo que se pretende es conocido en la técnica desde 1987, donde se ha descrito el hecho de preparar una composición de micropartículas que tengan una distribución de tamaño de por lo menos de 0,25mm, para obtener así micropartículas que tienen por lo menos 95% de metoprolol y donde dichas partículas están cubiertas con una membrana polimérica. Lo allí pretendido, no es más que una presentación farmacéutica conocida de una molécula conocida. A todas luces, este documento anterior D1 revela materia reivindicada en la solicitud objeto de oposición. Por lo tanto, la presente solicitud a la luz del documento D1, carece del requisito de NOVEDAD en sus cláusulas referidas a la presentación farmacéutica, dado que lo que pretende ya se encontraba publicado mucho antes de la radicación de la prioridad de la solicitud Colombiana.

- 2.7. Ahora bien, el método de preparación se puede derivar del estado del arte. Por ejemplo, el método para producir particularmente gránulos de metoprolol según las reivindicaciones de la presente solicitud objeto de oposición, se puede derivar de manera evidente a partir de la anterioridad D1 en el ejemplo 1, donde las partículas son producidas bajo lecho fluidizado, combinado con lo expuesto en los documentos D2 y D3, donde se revelan métodos de producción en lecho fluidizado con selección de partículas, similar a lo aquí expuesto. Particularmente en el documento D2, se relacionan gránulos solubles en agua recubiertos que tienen un tamaño de grano en el rango de 200 a 2000 µm. El documento D3, describe un método para la preparación

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de gránulos que tiene un tamaño de partícula de entre 0,1 mm y 3 mm, preferiblemente entre 0,2 y 2 mm, en donde la distribución de tamaño de grano es muy estrecho. Según los ejemplos 1, 2 y 3 de dicho documento D3, se revelan la producción de gránulos por lecho fluidizado con una selección de partículas expuesta según las curvas 1, 2 y 3 respectivamente, de la figura 7. Obviamente, una persona versada en la materia a partir de lo que dictan en combinación dichos documentos D1, D2, y D3 puede deducir el método reivindicado. Así las cosas, estos documentos combinados, afectarían de manera directa el requisito de ALTURA INVENTIVA respecto al método de preparación de una composición de micropartículas que tienen por lo menos 95% de metoprolol y que están cubiertas con una membrana polimérica.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 03-078286 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. Qué 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, 9 de marzo de 2001, ya era conocido, pues como se demostró, era parte del arte anterior la composición de micropartículas que tienen por lo menos 95% de metoprolol y que están cubiertas con una membrana

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polimérica sobre la cual busca protección en el capítulo reivindicatorio con base en D1.

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, 9 de marzo de 2001, a partir de los documentos D1, D2 y D3 en combinación, es posible derivar de manera evidente un método para la preparación de una composición de micropartículas que tienen por lo menos 95% de metoprolol y que están cubiertas con una membrana polimérica.

2.9.3. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 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. La presente solicitud carece de aplicación Industrial ya que como se demostró lo que se está reclamando es un método de prevención para prevenir desordenes cardiovasculares y al uso de dichas micropartículas. Éstos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

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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 tres requisitos de patentabilidad.

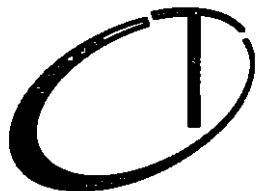
2.11. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

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 **"METODO PARA PREPARAR MICROPARTICULAS QUE CONTIENEN METOPROLOL"**, solicitada por **ASTRAZENECA AB**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 546 del 30 de Noviembre de 2004, en la página 339, bajo el NP 579.

3. PRUEBAS

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

- D1: EP0220143. 29 de Abril de 1987.
- D2: US 5883047. 16 de Marzo de 1999.
- D3: US4946654. 7 de Agosto de 1990.



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4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.2. En las demás normas concordantes.

5. ANEXOS

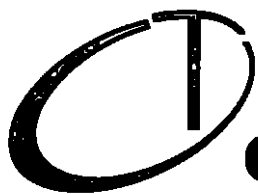
Para los efectos correspondientes anexo al presente, aquellas referenciadas en el capítulo de pruebas así como los siguientes documentos:

5.1. Recibo de pago expedido por el Fondo Especial de esa Superintendencia, en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitación de esta oposición.

5.2. Copia de la oposición para el traslado al solicitante.

5.3. Poder para actuar a nombre de mi representada.

5.4. Documento que acredita la existencia y representación legal de la empresa.



Optimum

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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

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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 de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señora Jefe,



LUIS FERNANDO RINCÓN CUELLAR

C.C. 79'532.186 de Bogotá

T.P.A. 113.438 del C.S. de la J.

97 88

SUPERINDUSTRIA Y COMERCIO
Radiacion : 03070206 00000003 Folios: 70
Fecha (AMD): 2005-02-07 17:18:03
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 8,944
FECHA : FEBRERO 7 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	37689246	27/01/2005	470,000.
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	37689247	27/01/2005	235,000.00
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	37689248	27/01/2005	716,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30003-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	235,000.00
		TOTAL :	\$ 235,000.00

SOM: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



PODER ESPECIAL

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 **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 03-078.286, de título: "**MÉTODO PARA PREPARAR MICROPARTÍCULAS QUE CONTIENEN METOPROLOL**", publicada en la gaceta No. 546 del 30 Noviembre de 2004, número de publicación 578.

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 24 días del mes de enero de 2005.


PROCAPS S.A.

WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal


Acepto.

LUIS FERNANDO RINCÓN CUÉLLAR
C.C. No. 79.532.186
T.P. 113438

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 960 DE 1970 - ART. 64

MARIA DEL S. ROMAN DE ARTETA - NOTARIA SEGUNDA DE BARRANQUILLA

CERTIFICA

En Barranquilla a los 07 días del mes de ENERO de 2005 Firmaron esta diligencia en su presencia: WOLFF FANOKO TOLEDO

Portaciones de las cédulas

16251.923

Expedidas en

PAQUIE

y dieron que es cierto el contenido del documento que antecede y es autorizado con sus firmas

Comparecientes

[Firmas]

I.A. NOTARIA

REPÚBLICA DE COLOMBIA
NOTARIA SEGUNDA DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL

Ante el Notario Once del Circulo de Santafé de Bogotá

Quien exhibió la C.C. No. 1131

expedida en PAQUIE
y declaró que la firma y huella que aparecen en el presente memorial son suyas y que el contenido del mismo es cierto.
Memorial dirigido a

Santafé de Bogotá, D.C.

07 FEB 2005

Autorizó la anterior diligencia
NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ

REPÚBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTAFÉ DE BOGOTÁ, D.C.

EULMA NAVARRO DE BAUTISTA
NOTARIA ONCE

90
43



***** Pag.01
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
08*****
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 Publica Nro. 1190 del 22 de Julio de 1,976,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 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 Publica Nro. 1307 del 28 de Junio de 1,979,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 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 Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 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 Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 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 Publica Nro. 3615 del 6 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo

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

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.**

PROCAPS S.A. -----

el No. 67,218 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 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	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004

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

94
91

***** Pag.02

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricaci n de capsulas y otros productos similares a partir de materiales 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,alimentos y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos,quirurgicos,odontologicos,y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones 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 asesoria y consultoria en las areas administrativas, de mercade , 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 industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, de-

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

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A.

sarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, 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, comprar, 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 celebre con terceros relativas a su objeto; celebrar y ejecutar todo 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 Acci n
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde 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 voto 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 c n

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

CAMARA DE COMERCIO
DE BARRANQUILLA

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

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 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 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 fij 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 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

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

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.**

PROCAPS S.A. -----

ello acreditar la ausencia del principal. La sociedad tendra un gerente general con su respectivo suplente, quienes tambien ejerceran la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el presidente y el vicepresidente. 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 superior al equivalente en pesos colombianos 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 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. Las demas funciones que les correspondan como representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El gerente lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades.-----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales	Suplentes
1. Minski Gontovnik Ruben	Minski Zilberblum Elliot
2. Minski Gontovnik Meyer	Minski Deitel Daniel
3. Minski Gontovnik Jose	Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
-------	--------	----------------

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



***** Pag.04
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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

Presidente.	Minski Gontovnik Ruben	C.*****7,463,982=
Suplente del Presidente	Minski Minski Abraham	C.*****802,575=
Vicepresidente	Minski Gontovnik Meyer	C.*****7,461,324=
Suplente del vicepresidente	Minski Gontovnik Jose	C.*****8,671,834=

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

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 segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificaci n
Suplente del Gerente.	Tanaka Walter ✓	C.***16,251,923=

C E R T I F I C 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\$800.000.00 (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 DIAZ GRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de un (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, com-

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

CAMARA DE COMERCIO
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

parecer 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 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

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

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.**

PROCAPS S.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, ampli 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 senor 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 en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.-----

C E R T I F I C A

Que su ultima Renovacion fue el: 31 de Marzo de 2,004. -----

La informacion sobre embargos de establecimientos se suministra en Certificados de Matricula, la de contratos sujetos a registro, en Certificados Especiales.

NO CAUSA IMPUESTO DE TIMBRE

EL SECRETARIO
MARIBEL REYES OVIEDO

48 95

ANEXO 1

(12)

EUROPEAN PATENT APPLICATION

(71) Application number: 86860330.1

(91) Int. Cl.⁴: **A 61 K 9/22**
A 61 K 31/135

(22) Date of filing: 02.10.86

(30) Priority: 11.10.85 SE 8504721

(41) Date of publication of application:
29.04.87 Bulletin 87/18

(54) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: Aktiebolaget Hässle
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(72) Inventor: Sandberg, John Anders
Hågerödsgatan 57
S-431 28 Mölndal(SE)

(72) Inventor: Sjögren, John Albert
Kullbäckstorpavägen 40
S-436 00 Mölndals(SE)

(74) Representative: Hjertman, Ivan T. et al,
AB ASTRA Patent and Trade Mark Department
S-151 86 Södertälje(SE)

(84) New pharmaceutical preparation with controlled release of metoprolol, a method for the manufacture thereof and the use of the new preparation.

(87) Controlled release preparation containing a number of beads comprising a salt of metoprolol as the main soluble component, a method for the production thereof and the use in the treatment of cardiovascular disorders.

100 97

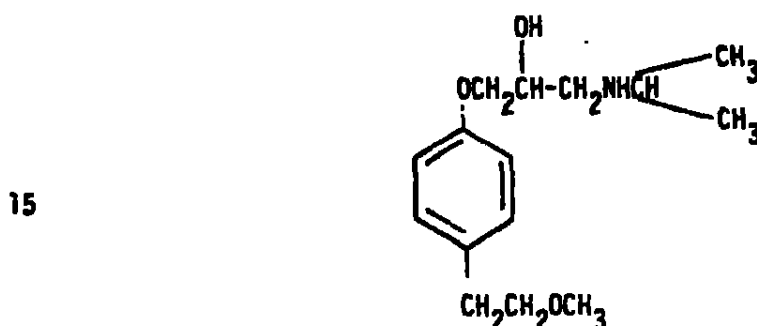
New pharmaceutical preparation with controlled release of metoprolol,
a method for the manufacture thereof and the use of the new preparation

Field of the Invention

The present invention is related to a new pharmaceutical preparation
with controlled release of metoprolol, to a method for the manufacture
5 of such a preparation and to a method for treatment of cardiovascular
disorders using the new pharmaceutical preparation.

Background of the Invention

10 Metoprolol, which has the structural formula



20 is known from e.g. DE-2 106 209. The drug, which is a β -adrenoceptor
antagonist has preferably been used as a salt, e.g. the tartrate.

Metoprolol blocks the adrenergic stimulation of the heart and thus re-
duces the oxygen demand of the cardiac tissue. Apparently, this explains
its beneficial effects in angina pectoris and cardioprotective action
25 in myocardial infarction. In addition metoprolol normalizes blood
pressure in a large proportion of patients with arterial hypertension
which probably is due to an additional action on the control of peri-
pheral resistance to blood-flow.

30 For patients suffering from cardiovascular disorders it is advantageous
to have a constant concentration of the administered drug in the blood.
Thus, a controlled release of the drug over a long period of time is
desirable. According to the most common treatment, the patients are
ordered one fast dissolving tablet twice a day. This gives a varying
35 concentration with high peak and trough values of the drug during the

22

For dosage once a day metoprolol has been incorporated in controlled release tablets of the insoluble matrix type, e.g. Durules[®]. However the drug release from the matrix tablets is not satisfying as about 50 per cent of the dose is released within a few hours after administration. It has thus been a demand to find a way to obtain a drug preparation having a more constant controlled release of the active component for approximately 20-24 hours, whereby smoother blood concentration and effect profiles will be obtained over the entire dosage interval.

10 A drug delivery system named Oros[®] may be used to obtain a controlled release of e.g. metoprolol for once daily dosage. The system is described in U.S. Patent 4 036 227 and in a supplement to British Journal of Clinical Pharmacology (1985), 19, 695-765 by Theeuwes F et al. Oros[®] is a single-unit system consisting of an osmotically active
15 core composed mainly of the drug substance surrounded by a semipermeable membrane through which a single small opening is drilled. The release of the drug from the system remains constant as long as a steady osmotic pressure is maintained across the membrane. 50-60% of the total content of the drug is released at a constant rate.

20

In SE-A-8400085 it has been proposed to prepare an enteric coated product, containing e.g. metoprolol, and with slow release of the active compound close to the colon. Such a preparation does not give the constant and slow pH-independent release of metoprolol, which the preparation according to this invention gives.

25

Depot preparations comprising a large number of smaller units are also known e.g. from EP 13263. This patent describes pharmaceutically indifferent cores covered by the active compound. The cores are made of
30 soluble material e.g. lactose.

30

There are advantages of a depot preparation comprising a large number of small units, each of which releases the drug at a controlled rate over a depot preparation consisting of one single unit, e.g. a matrix tablet or a tablet surrounded by a coating, which controls the release. It is for example possible to obtain a reproducible emptying of units

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- from the stomach when the particles used are smaller than 1-2 mm. Cf. Bogentoft C et al. : Influence of food on the absorption of acetylsalicylic acid from enteric-coated dosage forms. Europ J Clin Pharmacol 1978, 14, 351-355. Dispersion over a great area in the gastrointestinal canal gives a more reproducible total time of the passage which is of advantage for the absorption. Cf. Edgar B, Bogentoft C and Lagerström P O : Comparison of two enteric-coated acetylsalicylic acid preparations by monitoring steady-state levels of salicylic acid and its metabolites in plasma and urine. Biopharmaceutics & Drug Disposition 1984, 5, 251-260. In addition a multiple unit preparation is preferable to one single drug unit as the dose is spread out in the intestine. The risk of local irritation and accumulation of several doses due to constriction in the alimentary canal is also considerably lower.
- 15 A further advantage with a multiple unit preparation is that it may be divided into smaller portions all having the same absorption properties. This makes it possible to obtain greater flexibility in selecting the size of the dose.

20 Outline of the invention

- The present invention is related to a preparation containing metoprolol as active ingredient and having a controlled rate of drug release during at least 15 hours. By making a preparation containing a large number of small compact particles all comprising a salt of metoprolol as the main soluble component and coated with a polymeric membrane containing derivatives of cellulose without protolysable groups it has been possible to prepare a suitable dosage form having a controlled rate of release of metoprolol, virtually independent of pH, during 16-24 hours.

The small particles, beads, containing metoprolol have a size of 0.25-2 mm, preferably 0.35-1.0 mm.

35

24

The beads may contain metoprolol alone or may consist of insoluble cores coated with metoprolol. The beads have a very high content of metoprolol, preferably 95-100 w/w% of the soluble part of the beads. The insoluble cores have a size of 0.1-1.0 mm, preferably 0.15-0.3 mm.

5 Examples of insoluble cores according to the invention are silicon dioxide and small particles of glass.

The beads according to the invention are compact, which means that their porosity is less than 15 per cent.

10

As can be seen from figure 1 the new preparation is characterized in that at least 75% of the metoprolol is released within 20 hours and at least 50% of the dose of metoprolol is released at the rate 3-7 w/w %/hour.

15

Metoprolol used in the preparation may be in the form of the racemate, or one of the enantiomers, preferably the S-isomer.

20

Suitable soluble salts of metoprolol have a solubility less than 600 mg/ml in water at 25°C, preferably 30-600 mg/ml in water at 25°C. Examples of suitable salts are salts formed of organic carboxylic acids, preferably of low molecular weight. Especially preferred are the succinate, fumarate or benzoate of racemic metoprolol and the benzoate or sorbate of the S-enantiomer of metoprolol.

25

Very soluble salts, e.g. tartrate, hydrochloride are less suitable according to the present invention.

30

Examples of suitable polymeric materials are ethyl cellulose or a mixture of ethyl cellulose with hydroxypropylmethyl cellulose, hydroxypropyl cellulose, Eudragit RL or Eudragit RS.

35

Ethyl cellulose is available in variants having different grades of viscosity. According to the invention it is suitable to use ethyl cellulose having a viscosity between 10-50 cps, but also other types of ethyl cellulose may be used.

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5 Eudragit® is the trade name for a number of filmcoating substances on an acrylic resin basis produced by Röhm Pharma. Eudragit RL and RS are copolymers synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:20 for Eudragit RL and 1:40 for Eudragit RS, resulting in different permeability characteristics.

10 Plasticizers and/or pigments may be added to the polymeric layer in order to improve the technical properties of the layer or change the permeability of the coating. Examples of suitable plasticizers are citrate esters, acetylated monoglycerides and glycerinetriacetate, especially preferred is acetyltributylcitrate.

15 The polymeric membrane is made of one or more polymers and gives a membrane with virtually pH-independent permeability characteristics within the pH range 1.0-8.0.

20 Each coated bead of metoprolol according to this invention forms an individual controlled release unit, releasing the drug at a pre-determined rate. Therefore, the coated beads according to this invention make it possible to formulate and administer the preparation in different dosage forms. They can be filled into e.g. hard gelatin capsules or sachets or compressed to tablets and still give the desired plasma
25 concentration profile and duration of the effect.

When the small coated particles of metoprolol are tabletted they are mixed with additives e.g. microcrystalline cellulose such as Avicel®, which improves the tableting properties and facilitates the disintegration of the tablet, whereby the individual beads are liberated.
30

The invention makes it possible to formulate pharmaceutical dosage forms which can be given once daily and still produce almost constant concentrations of the drug in the blood during the entire dosage interval
35 until the next dose is administered.

26

Preparation

A process for the manufacture of the controlled release preparation represents a further aspect of the invention. After the initial forming
5 of the beads containing metoprolol, the beads obtained are coated with the polymeric layer described in the examples. The polymeric mixture is dissolved in an organic solvent such as ethanol, isopropyl alcohol and/or methylene chloride. The spraying can be carried out in a coating pan, but is preferably carried out in a fluidized bed. Ethyl cellulose
10 can also be applied from an aqueous dispersion (latex).

The preparation according to the invention is particularly advantageous in the treatment of cardiovascular disorders, and a method for the treatment of such conditions represents a further aspect of the invention.
15

The invention is described in detail in the following examples:

EXAMPLES20 Example 1

Metoprolol fumarate	1440 g
Methylene chloride	9618 g
Ethanol 95%	3888 g
25 SiO ₂ (0.15-0.25 mm)	375 g

Polymeric layer

30 Ethyl cellulose 10 cps	265.6 g
Hydroxypropylmethyl cellulose	58.4 g
Acetyltributylcitrate	36.0 g
Methylene chloride	6141 g
Isopropyl alcohol	1544 g

35

In a fluidized bed granulator metoprolol fumarate was sprayed onto the cores of silicon dioxide from a solution of ethanol 95%. 400 g of the beads (granules) so formed (fraction 0.4-0.63 mm) were covered with the polymeric layer containing ethyl cellulose 10 cps, hydroxypropylmethyl cellulose and acetyltributylcitrate by spraying a solution of the mentioned substances in methylene chloride and isopropyl alcohol. The coated beads were then filled into hard gelatine capsules.

Example 2

10	Metoprolol succinate	1440 g
	Methylene chloride	9618 g
	Ethanol 95%	3888 g
	SiO ₂ (0.15-0.25 mm)	375 g

15

Polymeric layer

	Ethylcellulose 50 cps	168.1 g
	Hydroxypropylmethyl cellulose	36.9 g
20	Acetyltributylcitrate	22.8 g
	Methylene chloride	4167 g
	Isopropyl alcohol	815 g

Tablet additives

25	Microcrystalline cellulose	470.3 g
	Maize starch	117.6 g
	Potato starch	10.6 g
	Water purified	342.2 g
30	Magnesium stearate	1.2 g

Metoprolol succinate was sprayed onto the cores of silicon dioxide according to the process described in Example 1. 400 g of the granules so formed were coated with a polymeric film containing ethyl cellulose 50 cps, hydroxypropylmethyl cellulose and acetyltributylcitrate. An additional tablet mass was made by wet granulation of the dry mixture

of microcrystalline cellulose and maize starch with the potato starch-water solution in a planetary mixer. Equal amounts (600 g) of the active and additional granules were finally mixed with Mg-stearate 0.1% and compressed to tablets.

5

Example 3

Metoprolol succinate 100% in the form of compact spherical granules and having an average particle size of 0.42 mm

10

400 g of the metoprolol succinate granules above with particles less than 0.63 mm were coated with

15	Ethylcellulose 10 cps	177.1 g
	Hydroxypropylmethyl cellulose	38.9 g
	Acetyltributylcitrate	24.0 g
	Methylene chloride	4094 g
	Isopropyl alcohol	1029 g

20

The beads obtained were formed into pharmaceutical preparations as described above.

Example 4

25	Metoprolol succinate	1440 g
	Methylene chloride	9618 g
	Ethanol 95%	3888 g
	SiO ₂ (0.15-0.25 mm)	375 g

30

Polymeric layer

	Ethylcellulose N-10	166.2 g
	Hydroxypropylmethyl cellulose	39.0 g
	Acetyltributylcitrate	22.8 g
35	Methylene chloride	3889 g
	Isopropyl alcohol	978 g

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Tablet additives

	Microcrystalline cellulose	429.3 g
	Maize starch	67.1 g
5	Lactose powder	40.3 g
	Polyvidone	55.5 g
	Water purified	314.7 g
	Magnesium stearate	1.2 g

10 Tablet coating (12.500 tablets)

	Hydroxypropylmethyl cellulose	159.6 g
	Polyethylene glycol 6000	39.9 g
	Colour Titanium Dioxide	39.9 g
15	Water purified	1356 g
	Paraffin special	1.6 g

20 Metoprolol succinate was sprayed onto the cores of silicon dioxide according to the process described in Examples 1 and 2 above. 400 g of the so obtained beads (fraction 0.4-0.63 mm) were coated with the polymeric mixture also described above. The coated beads of metoprolol succinate obtained were mixed with the additives in equal portions and after addition of Mg-stearate 0.1%, the dry mixture was compressed to tablets. Finally, the tablets were coated in a coating pan with the

25 tablet coating described above.

Example 5

30 S-enantiomeric metoprolol sorbate in the form of compact spherical granules in the fraction 0.4-0.63 mm

40 g of the metoprolol sorbate granules above with particles less than 0.63 mm together with 360 g of non-pareil granules with particles between 0.75-1.0 mm were coated with

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	Ethylcellulose 10 cps	51.7 g
	Hydroxypropylmethyl cellulose	11.3 g
	Acetyltributylcitrate	7.0 g
	Methylene chloride	1194 g
5	Isopropyl alcohol	300 g

The beads obtained were formed into pharmaceutical preparations as described above.

10 Biopharmaceutical studies

The plasma concentrations of metoprolol after a single dose of a controlled release preparation containing metoprolol succinate 190 mg according to example 4 of the description and the plasma concentrations
15 after a single dose of Durules[®] containing 200 mg of metoprolol tartrate are shown in the attached Figure 2. 190 mg of the succinate salt is equivalent to 200 mg of metoprolol tartrate. The comparison has been carried out in 10 subjects. Each point represents the mean data from the 10 subjects. As can be seen the preparation according to the
20 invention gives an almost constant concentration of metoprolol during more than 20 hours, whereas the insoluble matrix preparation gives unwanted high plasma concentration during the first hours after administration.

25 Reduction of exercise heart rate

12 subjects were given an ordinary tablet containing 100 mg of metoprolol tartrate once a day and the reduction of the exercise heart rate on day 5 of the treatment was measured and compared with the
30 reduction of the exercise heart rate on day 5 in subjects given a controlled release preparation according to Example 4 of the invention containing 95 mg metoprolol succinate (equivalent to 100 mg metoprolol tartrate). The reduction of the heart rate is illustrated in Fig. 3. As can be seen the preparation according to the invention gives an even
35 pharmacodynamic effect for 24 hours.

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The best mode of carrying out the invention is at present considered to be Example 4.

5 Table 1 illustrates the in vitro release of metoprolol from the compositions according to Examples 1-4. As can be seen from the table at least 50% of the dose of metoprolol is released at a rate varying between 3-7 w/w %/hour.

Table 1. Cumulative in vitro dissolution of metoprolol in a phosphate buffer pH 6.8.
Method: USP apparatus No. II, rotating paddle at 100 rpm.

Example No.	Preparation	Per cent released over time (h)											
		1	2	3	4	6	8	10	12	14	16	18	20
1	capsule	1	2	5	11	25	39	52	62	69	74	78	81
2	tablet	7	11	16	19	29	40	50	59	68	76	82	86
3	capsule	3	7	12	17	27	37	44	52	60	67	74	80
4	tablet	7	13	18	23	33	43	52	61	69	76	82	86
5	capsule	4	9	15	21	34	47	58	67	74	80	84	88

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CLAIMS

1. Controlled release preparation containing a salt of metoprolol
c h a r a c t e r i z e d in that the preparation contains a number
5 of beads comprising a salt of metoprolol as the main soluble component
and that said beads are coated with a polymeric membrane containing
derivatives of cellulose without protolysable groups and whereby at
least 75% of the dose of metoprolol is released within 20 hours
virtually independent of the pH in the interval 1-8.
10
2. Preparation according to claim 1 c h a r a c t e r i z e d in
that the size of the beads is in the range of 0.25-2 mm.
3. Preparation according to claim 2 c h a r a c t e r i z e d in
15 that the size of the beads is in the range of 0.35-1.0 mm.
4. Preparation according to claim 1 c h a r a c t e r i z e d in
that at least 50% of the dose of metoprolol is released at the rate
3-7 w/w %/hour.
20
5. Preparation according to claim 1 c h a r a c t e r i z e d in
that the salt of metoprolol has a solubility less than 600 mg/ml in
water at 25°C, preferably 30-600 mg/ml.
- 25 6. Preparation according to claim 5 c h a r a c t e r i z e d in
that the salt is formed of an organic carboxylic acid.
7. Preparation according to claim 6 c h a r a c t e r i z e d in
30 that the salt of metoprolol is the succinate or fumarate of racemic
metoprolol.
8. Preparation according to claim 6 c h a r a c t e r i z e d in
that the salt of metoprolol is the benzoate or sorbate of the
S-enantiomer of metoprolol.
35
9. Preparation according to claim 1 c h a r a c t e r i z e d in
that the uncoated beads comprise at least 95 w/w % of metoprolol.

10. Preparation according to claim 1 characterized in that the uncoated beads comprise a salt of metoprolol applied on an insoluble core.
- 5 11. Preparation according to claim 10 characterized in that the insoluble cores have a size of 0.1-1.0 mm, preferably 0.15-0.3 mm.
- 10 12. Preparation according to claim 10 characterized in that the insoluble cores have a size of 0.15-0.3 mm and are covered by a salt of metoprolol to give beads having a size of 0.35-1.0 mm which are coated with the polymeric membrane.
- 15 13. Preparation according to claim 9 characterized in that the uncoated beads having a size of 0.35-1.0 mm comprise a salt of metoprolol as such and are coated with the polymeric membrane.
- 20 14. Preparation according to claim 1 characterized in that the polymeric membrane contains ethyl cellulose.
- 15 15. Preparation according to claim 1 characterized in that the polymeric membrane contains ethyl cellulose together with hydroxypropylmethyl cellulose.
- 25 16. A pharmaceutical preparation containing the controlled release preparation according to claim 1 characterized in that the coated beads are filled into hard gelatine capsules.
- 30 17. A pharmaceutical preparation containing the controlled release preparation according to claim 1 characterized in that the coated beads together with pharmaceutical additives are compressed to tablets which disintegrate into the primary formed coated beads when the tablets are brought into contact with gastro-intestinal fluids.
- 35 18. Method of producing a preparation according to claim 1 characterized in that beads comprising a salt of metoprolol as the main soluble component are spray coated with a membrane-forming solution containing derivatives of cellulose. 35

19. Use of a preparation according to claim 1 in the manufacture of a pharmaceutical preparation for treatment of cardiovascular disorders.

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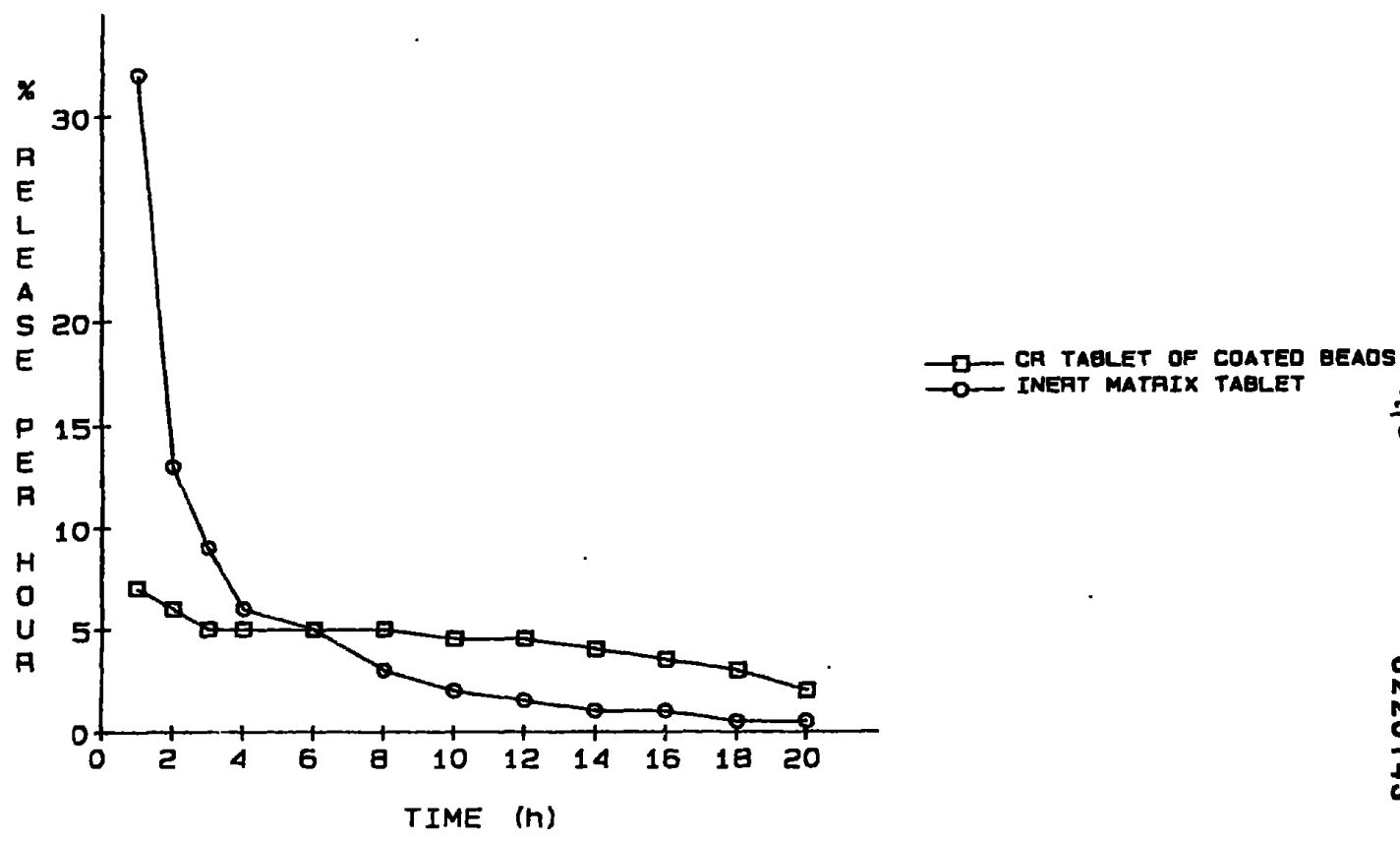
Claims for Austria, Greece and Spain

1. Process for the preparation of a controlled release preparation containing a salt of metoprolol characterized in that
5 a number of beads comprising a salt of metoprolol as the main soluble component are spray-coated with a membrane-forming solution giving a polymeric membrane containing derivatives of cellulose without proto-
lyzable groups whereby a preparation is obtained which releases at least
75% of the dose of metoprolol within 20 hours virtually independent
10 of the pH in the interval 1-8.
2. Process according to claim 1 characterized in that
the size of the beads is in the range of 0.25-2 mm.
- 15 3. Process according to claim 2 characterized in that
the size of the beads is in the range of 0.35-1.0 mm.
4. Process according to claim 1 characterized in that
at least 50% of the dose of metoprolol is released at the rate
20 3-7 w/w %/hour.
5. Process according to claim 1 characterized in that
the salt of metoprolol has a solubility less than 600 mg/ml in water
at 25°C, preferably 30-600 mg/ml.
25
6. Process according to claim 5 characterized in that
the salt is formed of an organic carboxylic acid.
7. Process according to claim 6 characterized in that
30 the salt of metoprolol is the succinate or fumarate of racemic
metoprolol.
8. Process according to claim 6 characterized in that
the salt of metoprolol is the benzoate or sorbate of the S-enantiomer
35 of metoprolol.
9. Process according to claim 1 characterized in that
the coated beads comprise at least 95 w/w % of metoprolol.

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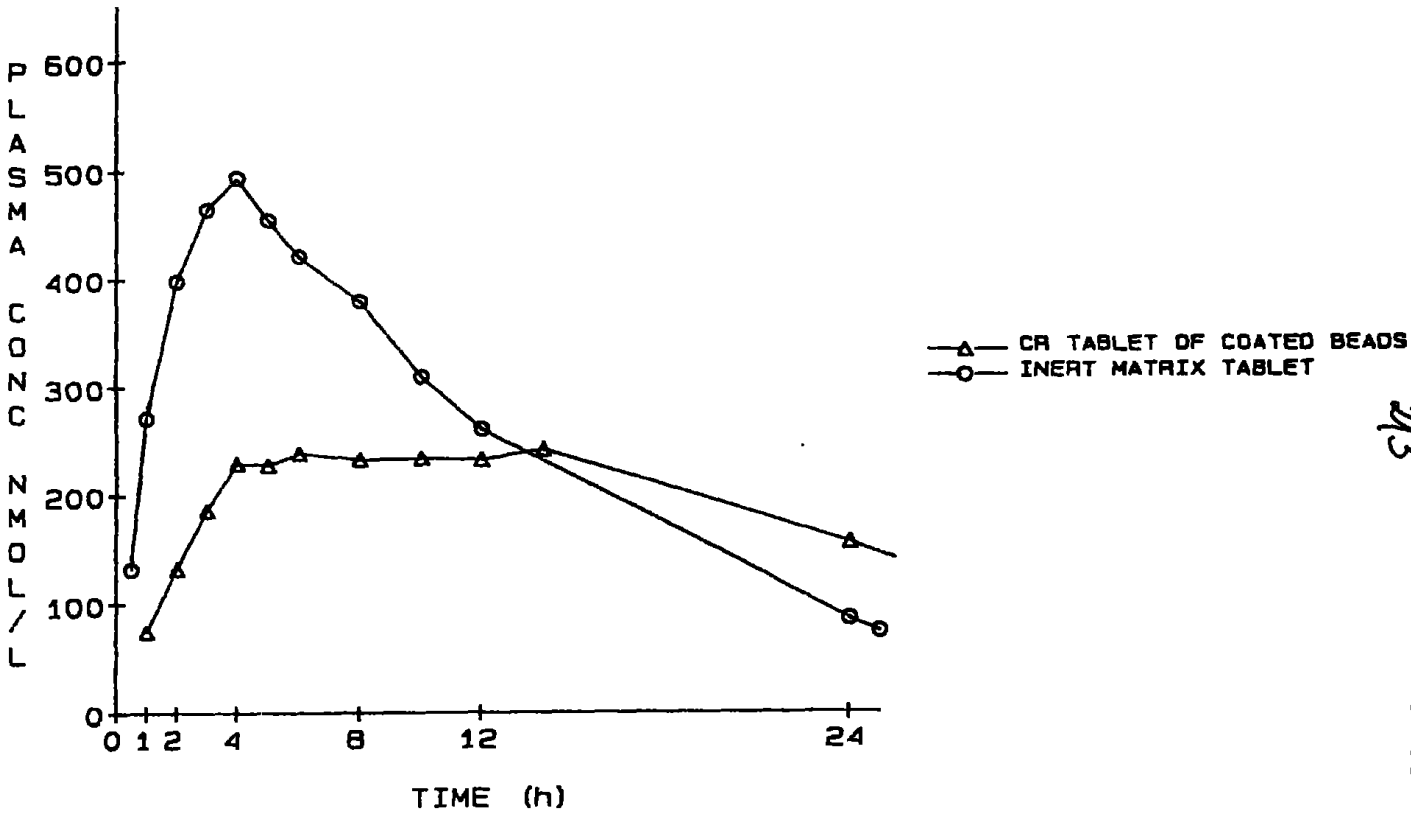
10. Process according to claim 1 characterized in that the uncoated beads comprise a salt of metoprolol applied on an insoluble core.
- 5 11. Process according to claim 10 characterized in that the insoluble cores have a size of 0.1-1.0 mm, preferably 0.15-0.3 mm.
12. Process according to claim 10 characterized in that the insoluble cores have a size of 0.15-0.3 mm and are covered by a
10 salt of metoprolol to give beads having a size of 0.35-1.0 mm which are coated with the polymeric membrane.
13. Process according to claim 9 characterized in that the uncoated beads having a size of 0.35-1.0 mm comprise a salt of
15 metoprolol as such and are coated with the polymeric membrane.
14. Process according to claim 1 characterized in that the polymeric membrane contains ethyl cellulose.
- 20 15. Process according to claim 1 characterized in that the polymeric membrane contains ethyl cellulose together with hydroxypropylmethyl cellulose.
16. A process for the manufacture of a pharmaceutical preparation
25 containing the controlled release preparation according to claim 1 characterized in that the coated beads are filled into hard gelatine capsules.
17. A process for the manufacture of a pharmaceutical preparation
30 containing the controlled release preparation according to claim 1 characterized in that the coated beads together with pharmaceutical additives are compressed to tablets which disintegrate into the primary formed coated beads when the tablets are brought into contact with gastro-intestinal fluids.
- 35 18. Use of a preparation produced according to claim 1 in the manufacture of a preparation for treatment of cardiovascular disorders.

FIGURE 1 . IN VITRO RELEASE OF METOPROLOL
RATE PLOT (%/h) VERSUS TIME



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FIGURE 2 . MEAN (n=10) PLASMA CONCENTRATIONS OF METOPROLOL AFTER SINGLE-DOSE ADMINISTRATION. DOSE: METOPROLOL CORRESP. 200 MG TARTRATE SALT

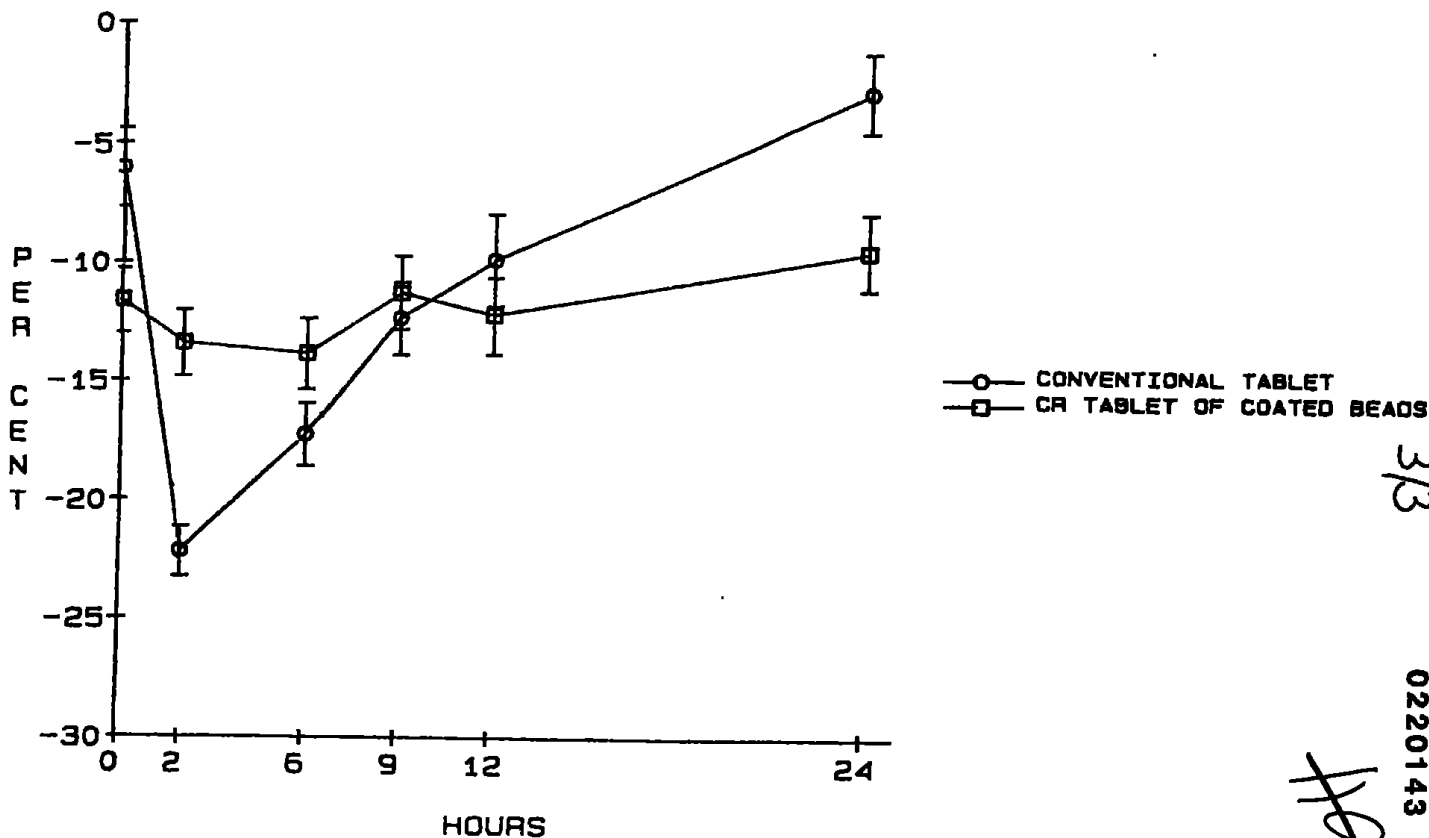


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FIGURE 3 . MEAN $\pm$ SEM (n=12) REDUCTION OF EXERCISE HEART RATE ON DAY 5 AFTER ONCE DAILY ADMINISTRATION
DOSE: METOPROLOL CORRESP. 100 MG TARTRATE SALT



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ANEXO 2



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United States Patent [19]
Jäger et al.

[11] **Patent Number:** **5,883,047**
[45] **Date of Patent:** **Mar. 16, 1999**

- [54] **GRANULES OF HYGROSCOPIC, WATER-SOLUBLE PRODUCTS**
- [75] **Inventors:** **Karl-Friedrich Jäger; Hans-Michael Fricke**, both of Limburgerhof, Germany
- [73] **Assignee:** **BASF Aktiengesellschaft**, Ludwigshafen, Germany
- [21] **Appl. No.:** **820,077**
- [22] **Filed:** **Mar. 19, 1997**
- [30] **Foreign Application Priority Data**

Apr. 3, 1996 [DE] Germany 196 13 395.5

- [51] **Int. Cl.⁶** **A01N 25/12; C05G 5/00**
- [52] **U.S. Cl.** **504/116; 71/64.03; 424/405; 514/951**
- [58] **Field of Search** **504/116; 424/405; 514/951; 71/64.03**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,015,970 4/1977 Hennart 71/11

4,936,901 6/1990 Surgant, Sr. et al. 71/92

5,516,521 5/1996 Fensch et al. 424/409

FOREIGN PATENT DOCUMENTS

32 48 514 7/1983 European Pat. Off. .

0 388 867 9/1990 European Pat. Off. .

26 27 085 1/1977 Germany .

OTHER PUBLICATIONS

K.C. Lin et al, "Development of Solid Pesticide Formulations by Fluidized-Bed Technology". *ACS Symposium Series Pesticide Formulations*, Jan. 11, 1988, pp. 251-259, Series 371.

Michael Rosch et al, "Granulation in der Wirbelachicht". *Verfahrenstechnik*, 9, 1975, Nr. 2, pp. 59-64.

Primary Examiner—S. Mark Clardy

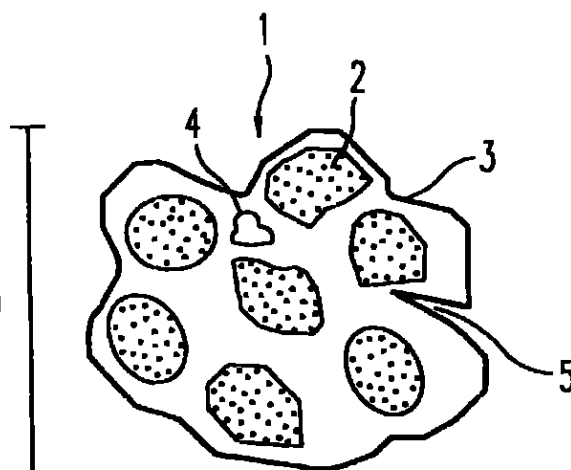
Attorney, Agent, or Firm—Ohlson, Spivak, McClelland, Maier & Neustadt, P.C.

[57] **ABSTRACT**

The present invention relates to granules of water-soluble, hygroscopic products having a mean grain size in the range from 200 to 2000 μm , the granule grains consisting of an agglomerate of fine product particles having a mean particle size in the range from 5 to 200 μm , which are covered with a product layer.

21 Claims, 3 Drawing Sheets

ABOUT 2000 μm



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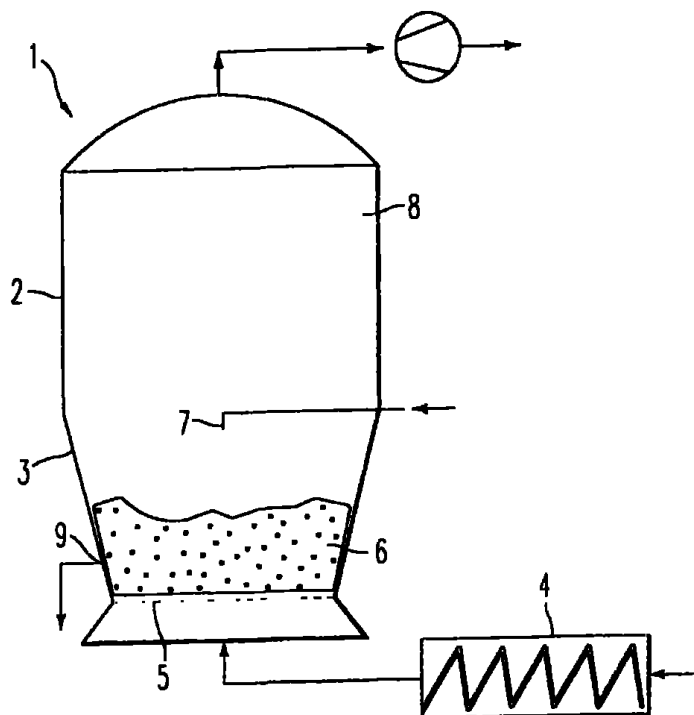


FIG. 4

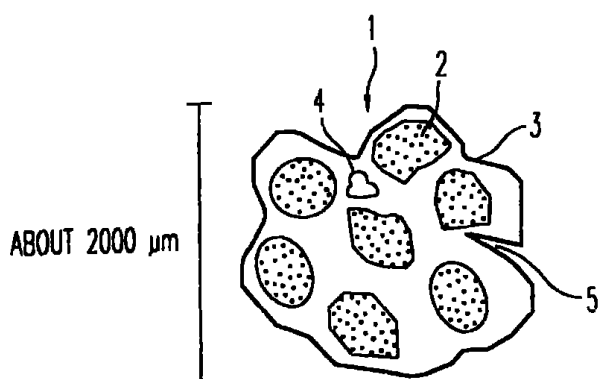


FIG. 1



FIG. 2

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FIG. 3

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GRANULES OF HYGROSCOPIC, WATER-SOLUBLE PRODUCTS

The invention relates to granules of hygroscopic, water-soluble products, in particular products having biological action, such as drugs, crop treatment compositions, feeds and foodstuffs, and to a process for preparing the granules.

In the formulation of products having biological action, attention is also to be paid to product safety with regard to the user and the environment. Furthermore, no problems must occur during storage and transport, and the disposal of the product residues and the packaging must at least meet the current requirements.

In many areas, granules have proven to be the optimum form of formulation which fulfils the above requirements. Granules are usually low in dust and stable on storage and therefore offer high user safety. Additionally, they frequently have a relatively high bulk weight such that, in comparison to solutions, suspensions or powder formulations, less packaging material has to be used.

Granules can be prepared in a known manner, most expediently in a mixer, extruder, spray tower or in a fluidized bed. If the product to be granulated, however, is hygroscopic and tacky, problems occur. In a mixer or spray tower, highly concentrated granule formulations of the required quality and grain size cannot be prepared. On the contrary, finely divided powders are obtained which have a high dust content. Thus in these processes, only removal of the solvent occurs without granulation taking place. Because of the high tackiness of the moist powder compositions, it is not possible to carry out extruder processes.

U.S. Pat. No. 5,266,553 describes a process of this type, namely a process for preparing a water-soluble herbicide salt in dry, solid form, the water being removed from an aqueous solution of a salt of a herbicide at less than about 80° C. The removal of the water is carried out with the aid of customary apparatuses, namely a horizontally arranged, cylindrical dryer which works in a batchwise mode and is equipped with a plowshare attached to an axially rotating shaft and a radially arranged chopping tool. In this manner the herbicide salt, eg. the sodium salt of bentazone, is obtained in the form of a free-flowing, crystalline powder which dissolves completely and rapidly in cold water with formation of a clear solution. However, it has been shown that the product contains a high proportion of fine particles and therefore clumps severely.

Fluidized-bed granulation is a frequently used and well investigated method for preparing granules. For example, units and operating procedures for fluidized-bed granulation are described in *Verfahrenstechnik* [Process Technology] 9 (1975), 59-64. In a company publication of Glatt GmbH of 1986, *Introduction to Fluid Bed Granulating*, the product and process variables which have an influence on the granules to be obtained are investigated. None of these publications goes into the granulation of a hygroscopic, tacky product.

Despite all the investigations and knowledge about fluidized bed granulation, it was also not possible by this method until now to prepare granules of hygroscopic, tacky products. In conventional fluidized-bed granulation, a differentiation is made between, namely, a moist granulation phase and a drying phase. During the moist granulation phase, the water content in the fluidized bed increases and the granular particles are built up by the formation of liquid bridges with simultaneous drying. In the drying phase, the liquid bridges are completely dried and the granule structure is fixed. In the fluidized-bed granulation of hygroscopic,

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tacky products, this results in the formation of product particles whose surface is covered with a film of a saturated solution of the product to be granulated. This film determines the product behavior. Under normal operating conditions, on account of the tendency to agglomerate, large agglomerates are observed, such that the fluidized bed collapses or adequate drying of the product does not take place.

It is an object of the present invention to make available granules of hygroscopic, water-soluble products and a process for preparing these granules.

Surprisingly, we have found that this object is achieved if a fluidized-bed granulation is carried out under control of the product moistness of the granules.

The present invention therefore relates to granules of hygroscopic, water-soluble products having a mean grain size in the range from 200 to 2000 μm , the granule grains consisting of an agglomerate of fine product particles having a mean particle size in the range from 5 to 200 μm , which are covered with a layer of the product.

BRIEF DESCRIPTION OF THE DRAWINGS

The structure of the granule grains according to the invention is shown in FIGS. 1 to 3, where

FIG. 1 is a schematic drawing of a granule grain according to the invention (sodium bentazone),

FIG. 2 is the photograph of a granule grain according to the invention (sodium bentazone) using a scanning electron microscope at 1300-times magnification,

FIG. 3 is the photograph of a granule grain according to the invention (sodium bentazone) using a scanning electron microscope at 800-times magnification.

FIG. 4 is a graph of a fluidized-bed granulator useful for preparing the granules of the invention.

It can be inferred from FIG. 1 that a granule grain 1 comprises several particles 2 having a mean particle size in the range from 5 to 200 μm . These particles are connected to one another by means of solid bridges of solidified hygroscopic product, which cover a large part of the particle surface and if necessary can even form a matrix. The particles thus form an agglomerate which is covered with a layer 3 of the hygroscopic product (coating). The granule grains have an essentially round, compact form and exhibit capillary-active cavities 4 and pores 5. FIG. 2 shows this particularly clearly.

On account of the coating layer, the fine particles are well bound into the granules. Additionally, the coating layer rounds out the granule grain and provides for a compact, smooth outer surface, see FIG. 3. The granules are therefore particularly stable to abrasion. The binding of the fine fractions mentioned and the stability to abrasion have the result that the granules have only a very low dust content. The proportion of dust of ≤ 0.1 mm, determined according to C'ipac MT170, "Trockensiebung von Granulaten" [Dry Screening of Granules] is $\leq 1\%$, in particular $\leq 0.5\%$.

The mean grain size of the granules is in the range from 200 to 2000 μm , preferably 500 to 1500 μm , at least 95% by weight of the granules having a grain size in the range from 0.1 mm to 3.0 mm.

On account of the grain size and the narrow grain size distribution, the granules are free-flowing. Additionally, the contact surfaces of the granules with one another are minimized. As a result, the tackiness and danger of caking of the granules

on handling in moist air is minimized. Despite the hygroscopic constituents, the granules are thus easy and safe to meter in practice even in moist air.

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The granules preferably have a bulk weight in the range from 300 to 800 g/l, in particular 400 to 800 g/l and preferably 600 to 800 g/l.

On account of the cavities and pores present in the granule grain, despite the compact coating layer a porosity adequate for rapid dissolution of the granules is retained. If the granules are introduced in a concentration of 0.5% by weight into water at 20° C. in a slowly rotating standing cylindrical vessel, they dissolve completely in less than 2 minutes and in particular less than 1 minute. A rapid, practically appropriate preparation of an aqueous solution or dispersion of the product is thus guaranteed.

The preparation of the granules according to the invention is explained below. For this purpose, customary apparatuses can be used for fluidized-bed granulation. A suitable apparatus is shown in FIG. 4, which is explained in greater detail in Example 1. The starting material used is an aqueous solution or dispersion of the hygroscopic, water-soluble (tacky) product, which in general contains from 20 to 70% by weight and in particular at least 40% by weight of the product. Beside water, the aqueous solution or dispersion can also contain organic solvents, for example alcohols, such as methanol, ethanol or glycol, ketones, such as acetone or methyl ethyl ketone, dimethylformamide or dimethyl sulfoxide. Preferably, however, the preparation is carried out in a purely aqueous solution or dispersion.

The aqueous solution or dispersion is subjected to fluidized-bed granulation, the aqueous solution or dispersion being sprayed onto the fluidized bed against the direction of flow of the heated fluidized gas, and the temperature and amount of the fluidized gas, the spray rate of the product and the concentration of the product in the aqueous solution or dispersion being selected such that the product moisture during the granulation is not more than approximately 50%, preferably not more than approximately 20%, higher than the residual moisture of the finished granules. Product moisture is in the present case understood as meaning the total product moisture, i.e. the mean value of the moisture of the granules present at any time in the entire fluidized bed.

If the process is carried out under the conditions given above, it is no longer possible, as in conventional fluidized-bed granulation, to differentiate between the moist granulation phase and the drying phase. On the contrary, the process is operated near the final residual moisture of the product in the fluidized bed.

Preferably, the process is carried out at a product moisture of $\leq 6\%$ and in particular $\leq 2\%$.

The product moisture can be controlled by the interaction of temperature and amount of the fluidized gas, the spray rate of the product and the concentration of the product in the aqueous solution or dispersion. The process is in this case preferably carried out under the following conditions:

Inlet temperature of the fluidized gas: from 50° to 220° C., in particular from 70° to 200° C.

Amount of fluidized gas: from 10 to 500 and in particular from 50 to 300 m³/min per m² of incident flow area of the fluidized bed.

The spray rate and the concentration of the product in the aqueous solution or dispersion must in this case always be adapted to the particular conditions. The suitable values can be determined by means of a few routine tests.

It has further proven advantageous to work with a fluidized bed packing of from 50 to 2000 kg/m² of area of the incident flow base, preferably from 100 to 1000 kg/m². In the continuous procedure the "hold up" and in the batch

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process the batch size, i.e. the amount of packing at the end of granulation, is meant by fluidized bed packing.

For spraying with nozzle of the aqueous solution or dispersion, one or more two-substance nozzles or three-substance nozzles are preferably used, which are operated using an inert gas, in general compressed air, at from 1.2 to 5.0 bar. The temperature of the compressed air is in general in the range from 15° to 100° C.

It has proven particularly advantageous to apply the nozzle at a distance from the incident flow base which corresponds to 1.5- to 10-times, in particular 2- to 8-times, the height of the layer of the resting fluidized bed packing. If the nozzle is too close above the fluidized bed or dips into the fluidized bed, severe agglomeration occurs and the fluidized bed collapses. If the distance of the nozzle from the fluidized bed is too large, the finely sprayed particles have time to begin drying, so that in general a powder and not granules, but at least a product having a high dust content, is obtained.

The process according to the invention can be carried out continuously or batchwise.

The residual moisture of the granules obtained is preferably $\leq 4\%$ by weight, in particular $\leq 2\%$ by weight and particularly preferably $\leq 1\%$ by weight.

Beside the hygroscopic product, the aqueous solution or dispersion to be sprayed into the fluidized bed can, if desired, also contain inert filling materials, wetting agents and dispersants, binders and/or additives, such as preservatives and colorants.

Suitable inert filling materials are customarily used fillers and carriers, for example inorganic salts, such as alkali metal, magnesium and ammonium chlorides and sulfates, in particular magnesium sulfate, potassium sulfate, sodium sulfate, potassium chloride, ammonium sulfate, lithium sulfate and ammonium chloride, as well as oxides, for example magnesium oxide, nitrates, carbonates, hydrogen carbonates, silicates, talc, chalk, quartz powder, kaolin, and also urea and urea derivatives, such as hexamethylenetetramine, carbohydrates, such as starch, sugar, alginates and their derivatives, cereal flours such as wheat flour and rice flour and finally water-soluble polymers, such as polyvinyl alcohol and polyvinylpyrrolidone.

Suitable wetting agents and dispersants are anionic or cationic, amphoteric or nonionic surface-active substances, in particular anionic wetting agents, such as condensation products of aromatic sulfonic acids and formaldehyde, lignosulfonic acid salts, such as sodium, potassium and ammonium salts of lignosulfonic acid, alkylsulfonates as well as polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, etc.

Suitable binders (adhesives) are, in particular, polyvinylpyrrolidone, polyvinyl alcohol and polyvinyl acetate.

Examples of suitable preservatives are 2-hydroxybiphenyl, sorbic acid, p-hydroxybenzaldehyde, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate and benzoic acid.

Examples of suitable colorants are inorganic pigments such as iron oxide, titanium dioxide and Prussian Blue and organic dyes, such as alizarin, azo and metal phthalocyanine dyes.

Granulation can be carried out in air or inert gases, such as nitrogen. Granulation can be started in the empty fluidized bed apparatus, finely divided material first being produced

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as granulation cores. Granulation cores of this type, however, can also be added to the fluidized bed apparatus, for example a powder of the product to be granulated or the abovementioned inert materials. It is also possible to start the granulation in a fluidized bed apparatus in which starter granules are already contained.

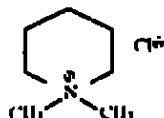
The fine material fractions escaping with the off-gas from the fluidized bed are deposited in the customary manner; they can be fed back into the fluidized bed as seeds for granule formation. In this case, both internal and external recycling of fine material is possible. For the deposition of the fine material fractions and their recycling, all apparatuses customarily employed for purposes of this type can be used.

The finished granules are discharged by means of one or more suitable apparatuses. Those suitable for this purpose are all customary apparatuses, for example countercurrent gravity sifters, zigzag sifters or discharge via a valve.

According to the invention, granules of all hygroscopic, water-soluble and tacky products can be prepared. The granules according to the invention are in particular of importance in products having biological action, such as drugs, including veterinary drugs, fertilizers, feeds, food-stuffs and preferably crop treatment compositions such as crop protection compositions.

The hygroscopic product is particularly preferably a crop protection composition, and in particular bentazone salts, such as sodium- or potassium-bentazone, salts of 2-methyl-4-chloro-phenoxyacetic acid (MCPA), salts of 2-(2-methyl-4-chlorophenoxy)-propionic acid (MCP), 2-methyl-4-chlorophenoxybutyric acid (MCPB), 2,4-dichlorophenoxyacetic acid (2,4-D), 2-(2,4-dichlorophenoxy)propionic acid (2,4-DP) and 2,4-dichlorophenoxybutyric acid (2,4-PB). These salts are in particular the alkali metal salts, such as the sodium or potassium salts, or the ammonium salts including the substituted ammonium salts, such as hydroxy-alkylammonium salt, dihydroxyalkylammonium salt, alkylammonium salt, dialkylammonium salt or trialkylammonium salt.

Further preferred hygroscopic products are mepiquat chloride of the formula



and chloromequat chloride of the formula



Granules of hygroscopic cyclohexenone herbicides can furthermore be prepared. Examples of herbicides of this type are sethoxydim, cycloxydim, 2-(1-(3-chloroallyloxy) iminopropyl)-5-(tetrahydropyran-4-yl)-3-hydroxycyclohex-2-enone or mixtures thereof.

Granules of the sodium or potassium salts of acifluorfen can also be prepared.

The granules according to the invention in general contain the hygroscopic product in an amount from 40 to 100% by weight and in particular from 60 to 100% by weight.

The present invention also relates to compositions which comprise the granules according to the invention. These compositions can also contain customary formulation substances and additives as well as other active ingredients. For example, beside a crop protection agent, the compositions

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according to the invention can also contain fertilizers, such as ammonium sulfate or ureas, growth regulators, other crop protection agents, pesticides, etc.

Suitable formulation agents and additives are customary products which are necessary for the applicational properties and the optimum biological action of the active ingredients. Examples of formulation auxiliaries and additives of this type are antilaking agents, flow auxiliaries, etc.

Preferably, however, the granules according to the invention are used without auxiliaries and additives.

The following examples explain the invention without restricting it.

The granules described in the examples were prepared in a fluidized bed apparatus of the type shown in FIG. 4. This is a customary fluidized-bed granulator 1, which comprises a cylindrical section 2 and a conical section 3. The fluidized gas used was air, which was heated in the heat exchanger 4 and passed, through the incident flow base 5 into the fluidized bed 6. The product to be granulated was sprayed onto the fluidized bed 6 in the form of an aqueous solution by means of a two-substance nozzle 7. The fine material fraction was separated off by the tube filters 8 attached above the two-substance nozzle 7 and washed back from time to time with compressed air. The waste air leaving the fluidized-bed granulator was recirculated via the heat exchanger 4. The granules obtained were discharged via a discharge valve 9.

EXAMPLE 1

Preparation of Sodium Bentazone Granules

190 g of powdered ammonium sulfate were initially introduced into a laboratory fluidized-bed granulator of the type shown in FIG. 4 and fluidized at a feed air temperature of 120° C. with a feed air quantity of 32 m³/h. 16 cm above the fluidized-bed base was a two-substance nozzle. The fluidized-bed base had an incident flow area of 153 cm².

414 g of powdered sodium bentazone were dissolved in 300 g of water. This solution was sprayed into the fluidized bed for 100 minutes and dried. The two-substance nozzle was operated at a compressed air pressure of 2 bar. After completion of the spraying-in, the heating was turned off and fluidization was carried out for 1 minute further. The unit was then switched off and the product was removed. At the end of the experiment, the product in the fluidized bed had a bed height of 6 cm above the fluidizing base in the resting state.

The product contained 68.9% of sodium bentazone and had a residual moisture of 0.9%. The granules had round, compact agglomerate structures of the type shown in FIGS. 1 to 3. The mean grain size was 0.36 mm. The product was almost dust-free. The fine fraction in the product was 0.1% less than 0.1 mm. The bulk weight had a value of 741 g/l. The granules dissolved completely within 1 minute at a concentration of 0.5% in water at 20° C. in a standing cylindrical vessel which was slowly rotated. The product was free-flowing.

EXAMPLE 2

Continuous Granulation of Sodium Bentazone

79 kg of sodium bentazone granules containing 99% sodium bentazone and 1% residual moisture were packed into an Institute of Technology fluidized-bed granulating unit of the type shown in FIG. 4. The fluidizing base of the unit had an incident flow area of 0.26 m². Above the

fluidizing base was situated a two-substances nozzle at a distance of 140 cm. A feed air quantity of 3000 kg of air/h was sucked through the unit with an inlet temperature of 140° C. The aqueous sodium bentazone solution was sprayed into the fluidized granule layer via the two-substance nozzle in a concentration of 55% at a spray rate of 100 kg/h. This corresponds to a sprayed-in water quantity of 45 kg/h. Atomization through the two-substance nozzle was carried out using 100 kg/h of nozzle gas. The product was continuously discharged through a valve in the vicinity of the sieve base at a rate of 55 kg/h. In the resting state, the bed height of the product was 31.5 cm relative to the fluidizing base. The granules discharged contained 99% of sodium bentazone and had a residual moisture of 1%. The mean granule grain size was 0.5 mm; fine fractions <0.1 mm were not present. The bulk weight had a value of 700 g/l. The granules were dust-free and stable to abrasion. In an abrasion test, the product was stressed in a glass bottle at a speed of rotation of 76 rpm for 3 hours in a tumble mixer. In this process, 0.7% abraded material having a grain size of less than 0.05 mm resulted. The granule structure was a round, compact agglomerate. The granules dissolved completely at a concentration of 0.5% in water at 10° C. within 1 minute in a standing cylindrical vessel which was slowly rotated. The product was free-flowing.

EXAMPLE 3

Preparation of Mepiquat Chloride Granules

221 g of sodium lignosulfonate were mixed in 3.5 kg of an aqueous solution of mepiquat chloride (concentration 57% mepiquat chloride).

The solution was then sprayed through a nozzle into a laboratory fluidized-bed granulator of the type shown in FIG. 4 at an air inlet temperature of 130° C. by means of a two-substance nozzle for 115 minutes. The area of the incident flow base was 221 cm². The nozzle was 34 cm above the incident flow base. The nozzle was operated using compressed air at 2 bar. The feed air quantity was 120 m³/h. With simultaneous drying, the product granulated during the spraying-in operation. After completion of spraying-in, the heating was turned off and the product was fluidized further for 1 minute to cool it. After turning off the unit, the product in the fluidizing container in the resting state had a bed height of 17 cm above the fluidizing base.

The product contained 90% mepiquat chloride and had a residual moisture of 0.2%. The granules had compact agglomerate structures of the type shown in FIGS. 1 to 3. The mean grain size was 0.65 mm. The product was dust-free; no fine fraction of less than 0.1 mm was present. The bulk weight had a value of 400 g/l. The granules dissolved completely within 30 seconds in water at 10° C. in a concentration of 0.5% in a standing cylindrical vessel (250 ml) which was slowly rotated. The product was free-flowing.

EXAMPLE 4

Preparation of Chlormequat Chloride Granules

A solution of 300 g of sodium naphthalene-2-sulfo acid-formaldehyde condensate in 430 g of water was mixed in 4.188 kg of an aqueous solution of chlormequat chloride (concentration 69% chlormequat chloride). This solution was then sprayed through a nozzle for 170 minutes into a laboratory fluidized-bed granulator of the type shown in FIG. 4 by means of a two-substance nozzle. The area of the

incident flow base was 221 cm². The nozzle was 34 cm above the incident flow base and was operated using compressed air at 2 bar. The feed air quantity was 120 m³/h; the feed air temperature was 130° C. With simultaneous drying, the product granulated during the spraying-in operation. After completion of spraying-in, the heating was turned off and the product was further fluidized for 1 minute to cool it. After turning off the unit, the product in the fluidizing container in the resting state had a bed height of 22 cm above the incident flow base.

The product contained 90% chlormequat chloride and had a residual moisture of 0.7%. The granules had compact agglomerate structures of the type shown in FIGS. 1 to 3. The mean grain size was 0.5 mm. The product was almost dust-free; 0.03% fine fractions of less than 0.10 mm were present. The bulk weight had a value of 468 g/l. The granules dissolved completely in water at 10° C. in a concentration of 0.5% within 30 seconds in a slowly rotated standing cylindrical vessel (250 ml). The product was free-flowing.

EXAMPLE 5

Preparation of Potassium Mecoprop (MCP) Granules

4 kg of potassium mecoprop solution (58.4% potassium mecoprop) were sprayed through a nozzle for 117 minutes into a laboratory fluidized-bed granulator of the type shown in FIG. 4 by means of a two-substance nozzle. The area of the incident flow base was 221 cm². The nozzle was 34 cm above the fluidizing base and was operated using compressed air at 2 bar. The feed air quantity was 120 m³/h; the feed air temperature was 130° C. On simultaneous drying, the product granulated during the spraying-in operation. After completion of spraying-in, the heating was turned off and the product was further fluidized for 1 minute to cool it. After turning off the unit, the product in the fluidizing container in the resting state had a bed height of 16 cm above the incident flow base.

The product contained 99.9% potassium mecoprop and had a residual moisture of 0.1%. The granules consisted of compact agglomerate structures of the type shown in FIGS. 1 to 3. The mean grain size was 0.5 mm. The granules were dust-free. No fractions of less than 0.16 mm were present in the product. The bulk weight had a value of 460 g/l. The granules dissolved completely in water at 10° C. in a concentration of 0.5% within 1 minute in a slowly rotated standing cylindrical vessel (250 ml). The product was free-flowing.

Comparison Example 1

Spray drying of sodium bentazone using a two-substance nozzle

A 55% aqueous solution of sodium bentazone was sprayed into an Institute of Technology spray tower by means of a two-substance nozzle and dried. The tower inlet temperature of the drying air was 170° C., the tower outlet temperature 90° C. The two-substance nozzle was operated at a spray pressure of 2 bar. The air throughput through the spray tower was 360 m³/h, the spray rate of liquid 16 l/h.

A fine sodium bentazone powder containing 2.0% residual moisture was obtained in the downstream cyclone. The powder had a bulk weight of 673 g/l. The grain size of the product was 100% less than 0.1 mm. The product dusted severely.

This experiment shows that a severely dusting product is obtained. No granules were formed.

Comparison Example 2

Drying of sodium bentazone in a vacuum mixer

70 kg of aqueous sodium bentazone solution (56% w/w) were dispensed into a batch vacuum mixer (Littleford) of 130 l volume. The mixer had a heatable, cylindrical container. In the inside of the mixer was axially arranged a rotating mixer with plowshares. A chopping tool which could be rotated at high speeds of rotation was attached to the container wall. The mixer was operated under vacuum at 60° C. until 30.7 kg of water were evaporated. A product having a residual water content of 0.4% and a bulk weight of 0.7 kg/l was obtained. The product contained a large powder fraction (30% less than 0.15 mm) and exhibited severe dusting.

This experiment was carried out essentially similarly to Example 8 of U.S. Pat. No. 5,266,553. It is evident that no granules, but a severely dusting product, was obtained.

Comparison Example 3

Granulation experiment in a vortex mixer

4125 g of sodium bentazone powder from Comparison Example 1 were mixed in a laboratory vortex mixer (PK-Niro) having a chopper shaft and integrated liquid metering device. The mixer ran at a speed of rotation of 60 rpm. The chopper shaft was operated at a speed of rotation of 1100 rpm. 768 g of aqueous sodium bentazone solution (56% w/w) were slowly introduced via the chopper shaft. Moist granules could not be detected during this introduction process. Energy is introduced by means of the chopper shaft. At a temperature of 43° C., a sharp transition from moist, nongranulated powder to a viscous material resulted at the end of the introduction of liquid. Granules could not be prepared.

We claim:

1. A granule of water-soluble, hygroscopic product, consisting of:
 - fine hygroscopic product particles having a mean particle size in the range from 5-200 μm covered with a layer of hygroscopic product resulting in granules of hygroscopic product ranging in size from 200-2,000 μm .
 2. A granule as claimed in claim 1, wherein the mean grain size is in the range from 500 to 1500 μm .
 3. A granule as claimed in claim 1 or 2, which has a bulk weight in the range from 300 to 800 g/l.
 4. A granule as claimed in claim 1, which dissolves in water at 20° C. in less than 2 minutes at a concentration of 0.5% by weight.
 5. A granule as claimed in claim 1, wherein the residual moisture is $\leq 4\%$ by weight.
 6. A granule as claimed in claim 5, wherein said residual moisture content is $\leq 2\%$ by weight.
 7. A granule as claimed in claim 1, the hygroscopic product being a crop protection active compound which is selected from the group consisting of bentazone salts, salts of 2,4-dichlorophenoxyacetic acid, 2-(2,4-dichlorophenoxy)-propionic acid, 2,4-dichlorophenoxybutyric acid, 2-methyl-4-chlorophenoxyacetic acid, 2-(2-methyl-4-chlorophenoxy)propionic acid, and 2-methyl-4-chlorophenoxybutyric acid, mequiquat salts, chlormequat salts, methoxydim, cycloxydim, tepraloxym and salts of acifluorfen.
 8. A granule as claimed in claim 7, wherein said mequiquat salt is mequiquat chloride and said chlormequat salt is chlormequat chloride.

9. A granule as claimed in claim 7, wherein the crop protection active compound is sodium or potassium bentazone.

10. A granule as claimed in claim 9, wherein the bulk weight is at least 600 g/l.

11. A granule as claimed in claim 1, wherein the agglomerate comprises particles of an inert material or of another product having biological action.

12. A granule as claimed in claim 1, wherein the proportion of the hygroscopic product in the granule is in the range from 20 to 100% by weight.

13. A composition comprising granules of the water-soluble hygroscopic granule product of claim 1, and at least one member selected from the group consisting of formulating substances, additives and active ingredients.

14. The composition as claimed in claim 13, wherein said active ingredient is fertilizers, plant growth regulators, other crop protection agents and pesticides.

15. A granule of water-soluble, hygroscopic product, consisting of:

fine hygroscopic product combined with at least one material selected from the group consisting of wetting agents, dispersants and binders as particles having a mean particle size in the range from 5-200 μm joined together and covered with a layer of hygroscopic product combined with at least one material selected from the group consisting of wetting agents, dispersants and binders resulting in granule product ranging in size from 200-2,000 μm .

16. A process for preparing the granule as claimed in claim 1, which comprises:

subjecting an aqueous solution or dispersion of the hygroscopic product, optionally containing a wetting agent, dispersant, binder or combination thereof, to fluidized-bed granulation by spraying the aqueous solution or dispersion through a nozzle onto the fluidized bed against the direction of flow of a heated fluidized gas passed through the fluidized bed, the temperature and the amount of fluidized gas, the spray rate of the hygroscopic product and the concentration of the hygroscopic product in the aqueous solution or dispersion being selected such that the product moisture during granulation is not more than approximately 50% higher than the residual moisture of the finished granules.

17. A process as claimed in claim 16, wherein the product moisture is $\leq 6\%$ by weight.

18. A process as claimed in claim 17, wherein the product moisture is $\leq 2\%$ by weight.

19. A process as claimed in claim 16 or 17, wherein the temperature of the fluidized gas is in the range from 50 to 220° C.

20. A process as claimed in claim 16, wherein the fluidized gas amount is from 10 to 500 m^3/min per m^2 of incident flow area of the fluidizing base.

21. A process as claimed in claim 16, wherein the distance of the nozzle from which the aqueous solution or dispersion of the hygroscopic product is sprayed onto the fluidized bed is 1.5- to 10-times the height of the layer of the resting fluidized bed packing.

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ANEXO 3

United States Patent [19]

Uhlemann et al.

[11] Patent Number:

4,946,654

[45] Date of Patent:

Aug. 7, 1990

[54] PROCESS FOR PREPARING GRANULATES

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[73] Assignee: Bayer Aktiengesellschaft, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: 224,524

[22] Filed: Jul. 26, 1988

Related U.S. Application Data

[63] Continuation of Ser. No. 718,129, Apr. 1, 1984, abandoned.

[30] Foreign Application Priority Data

Apr. 7, 1984 [DE] Fed. Rep. of Germany 3413200

Mar. 2, 1985 [DE] Fed. Rep. of Germany 3507376

[51] Int. Cl.³ B01J 2/02; B01J 8/22

[52] U.S. Cl. 422/140; 118/DIG. 5; 118/62; 118/303; 422/143; 422/145; 422/147; 427/213

[58] Field of Search 422/140, 143, 145, 147; 118/DIG. 5, 62, 303; 427/213

[56] References Cited

U.S. PATENT DOCUMENTS

3,880,968 4/1975 Kasper et al. .
4,217,127 8/1980 Kono et al. .
4,337,722 7/1982 Debayoux et al. 118/DIG. 5
4,353,709 10/1982 Nish et al. .
4,387,120 7/1983 Barnett 118/DIG. 5

FOREIGN PATENT DOCUMENTS

0037066 10/1981 European Pat. Off. .
139326 1/1980 Fed. Rep. of Germany .
140005 2/1980 Fed. Rep. of Germany .
3248504 7/1983 Fed. Rep. of Germany .
1142046 2/1969 United Kingdom .

OTHER PUBLICATIONS

Granulation in der Wirbelschicht, Michael Rosch und Richard Probst, pp. 1-6, 9 Jahrgang, Nr. 2, Feb. 1975, Sonderdruck aus verfahrenstechnik.
Berechnung der Verteilungskurven von Feststoffgranulatteilchen in Wirbelschichtapparaten mit Klassieren-

dem Abzug, pp. 242-245, Chem. Techn., 30. Jg., Heft 5. Mai 1978.

Zum Kugelwachstum bei Wirbelschichttrocknung von Suspensionen oder Lösungen, pp. 540-542 Chem. Techn. 29, Jg., Heft 10. Oktober 1977.

Abstract, Japan Koho 83/44014, "Granulating Apparatus", 9/83.

Abstract, Eur. Pat. Appl. 26,918, "Granulation Process", 4/81.

Abstract, Eur. Pat. Appl. 30,192, "Device for introducing a gaseous current . . .", 6/81.

Abstract, Jpn. Tokkyo Koho 80/45253, "Particle flow rate . . .", 11/80.

Abstract, Eur. Pat. Appl. 31,264, "Apparatus for granulating and/or coating in a spouting bed", 7/81.

Abstract, Belg. BE 886,412, "Device for the spraying of feed material . . .", 3/81.

Abstract, "Analysis of continuous spouted-bed granulation", Ind. Eng. Chem. Process Des. Dev. 1978.

Abstract, "Analysis of spouted-bed coating and granulation", Ind. Eng. Chem. Process Des. Dev. 1983.

Abstract, USSR, Teplomassobmen, 5th "Hydrodynamics and heat transfer during granulation . . .", 1976.

Article "Granulation of Ammonium Sulfate Fertilizer in a Spouted Bed", Uemaki et al, Ind. Eng. Chem., Process Des. Dev., vol. 15, No. 4, 1976, pp. 504-508.

Primary Examiner—Robert J. Warden

Assistant Examiner—Timothy M. McMahon

Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57]

ABSTRACT

A new process for continuously preparing granules having narrow grain size distribution, comprising
a. spraying the product to be granulated in liquid form into a fluidized bed,

b. separating the proportions of fine material escaping from the fluidized bed from the off-gas and returning said fine material to the fluidized bed as nuclei for granule formation,

c. setting the fluidizing gas flow such that granules are formed which are of a predetermined size, and

d. removing the completed granules solely by way of at least one countercurrent gravity classifier inserted into the outflow bottom of the fluidized-bed vessel.

A new apparatus for carrying out the process according to the invention and new granules.

5 Claims, 7 Drawing Sheets

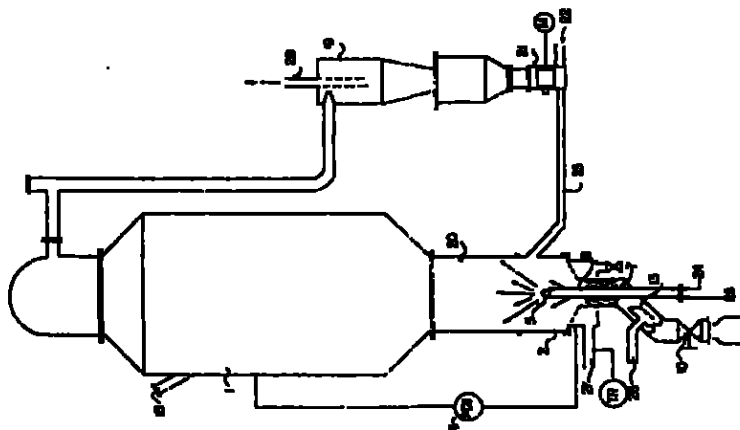
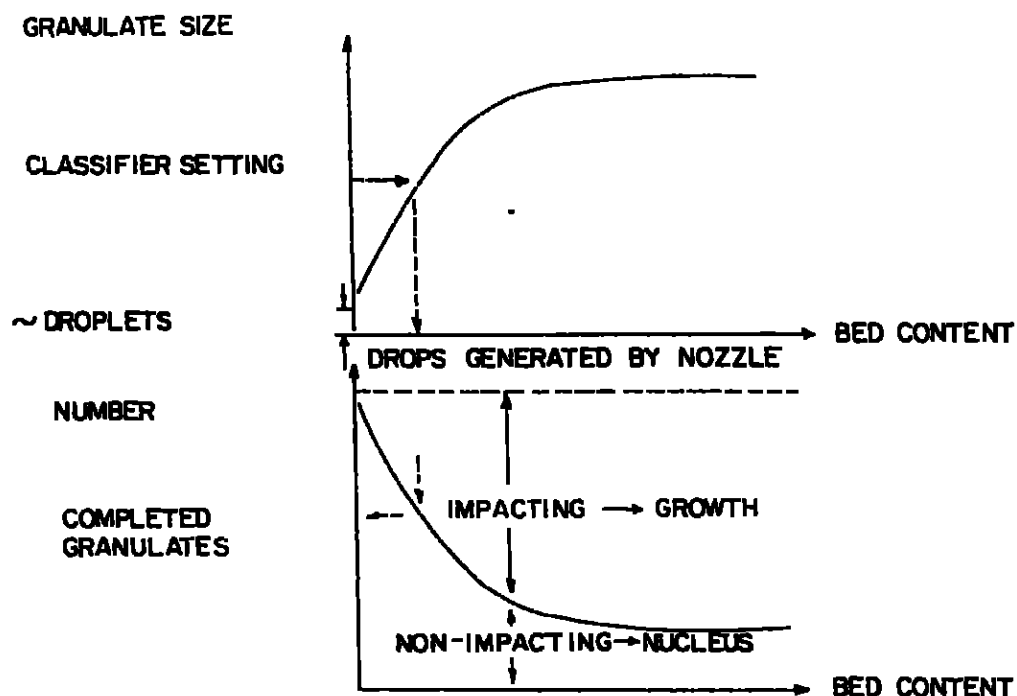


FIG. 1



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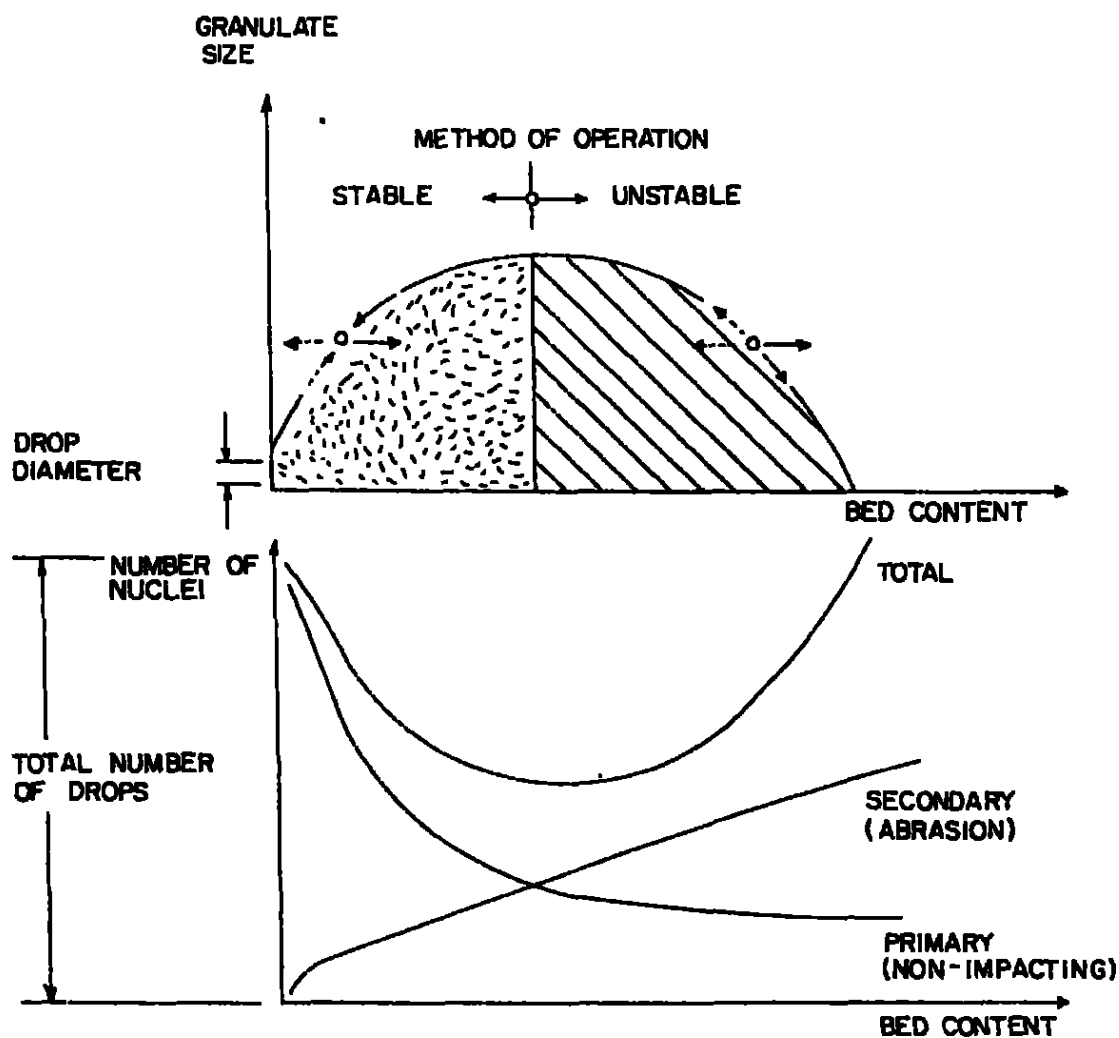


FIG. 2

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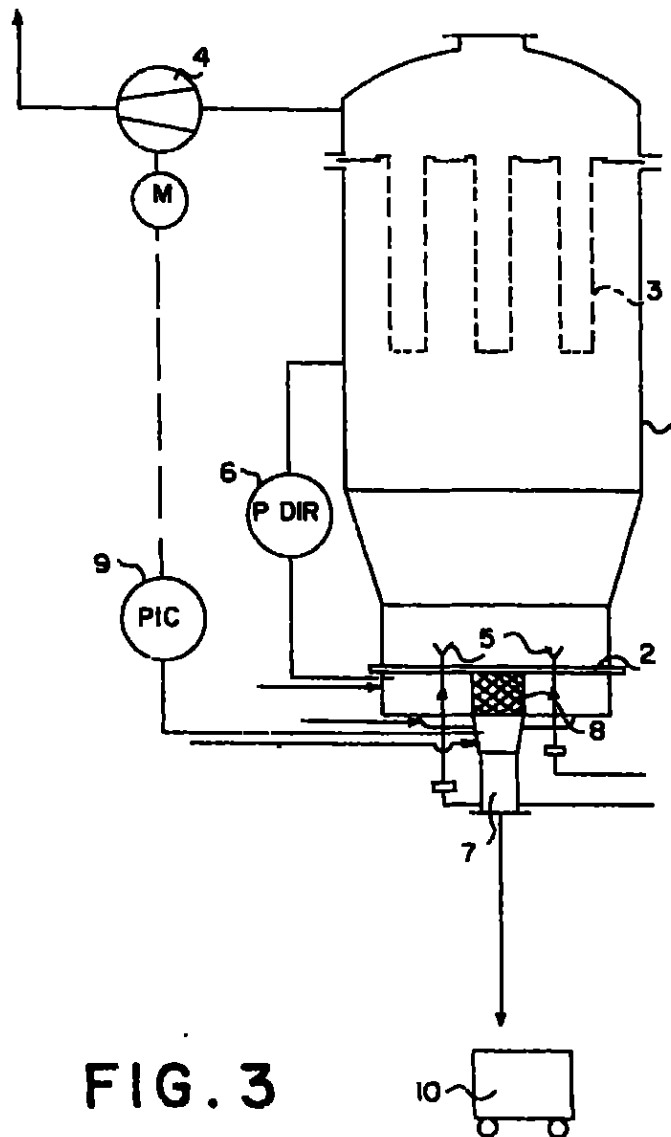


FIG. 3

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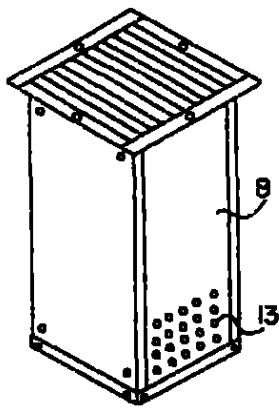


FIG. 4

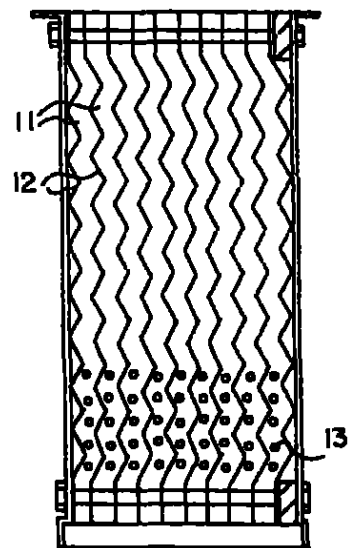


FIG. 5

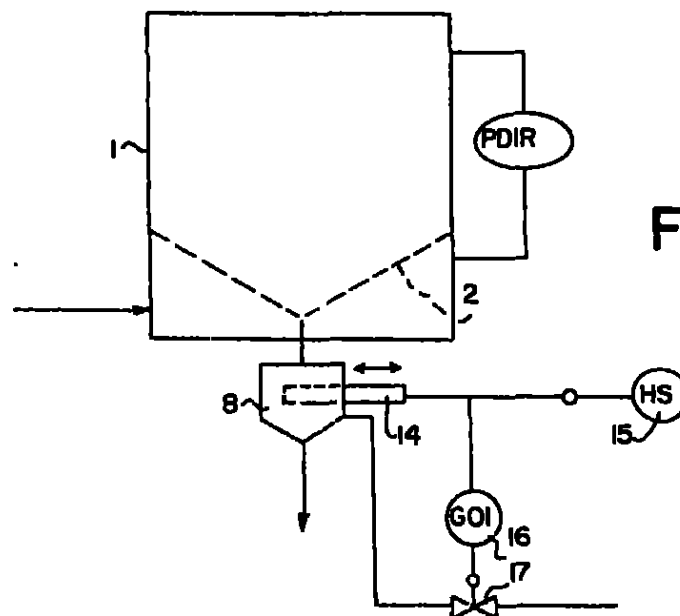


FIG. 6

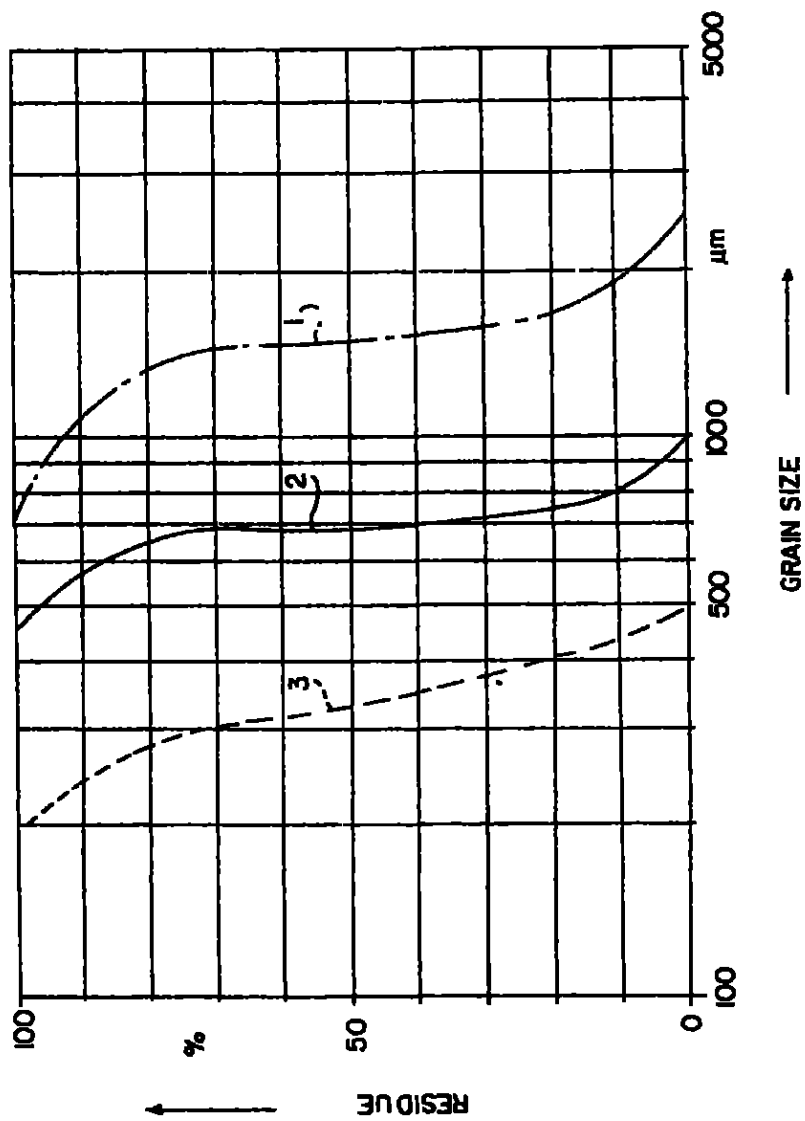


FIG. 7

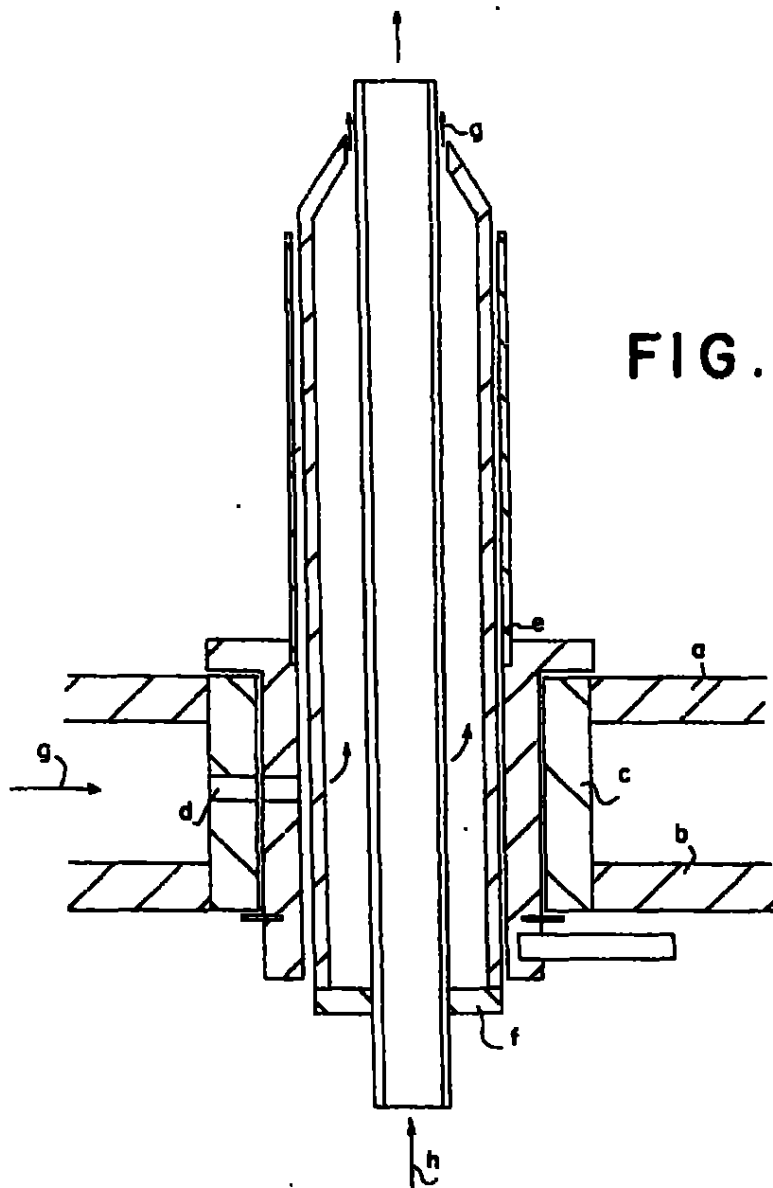


FIG. 8

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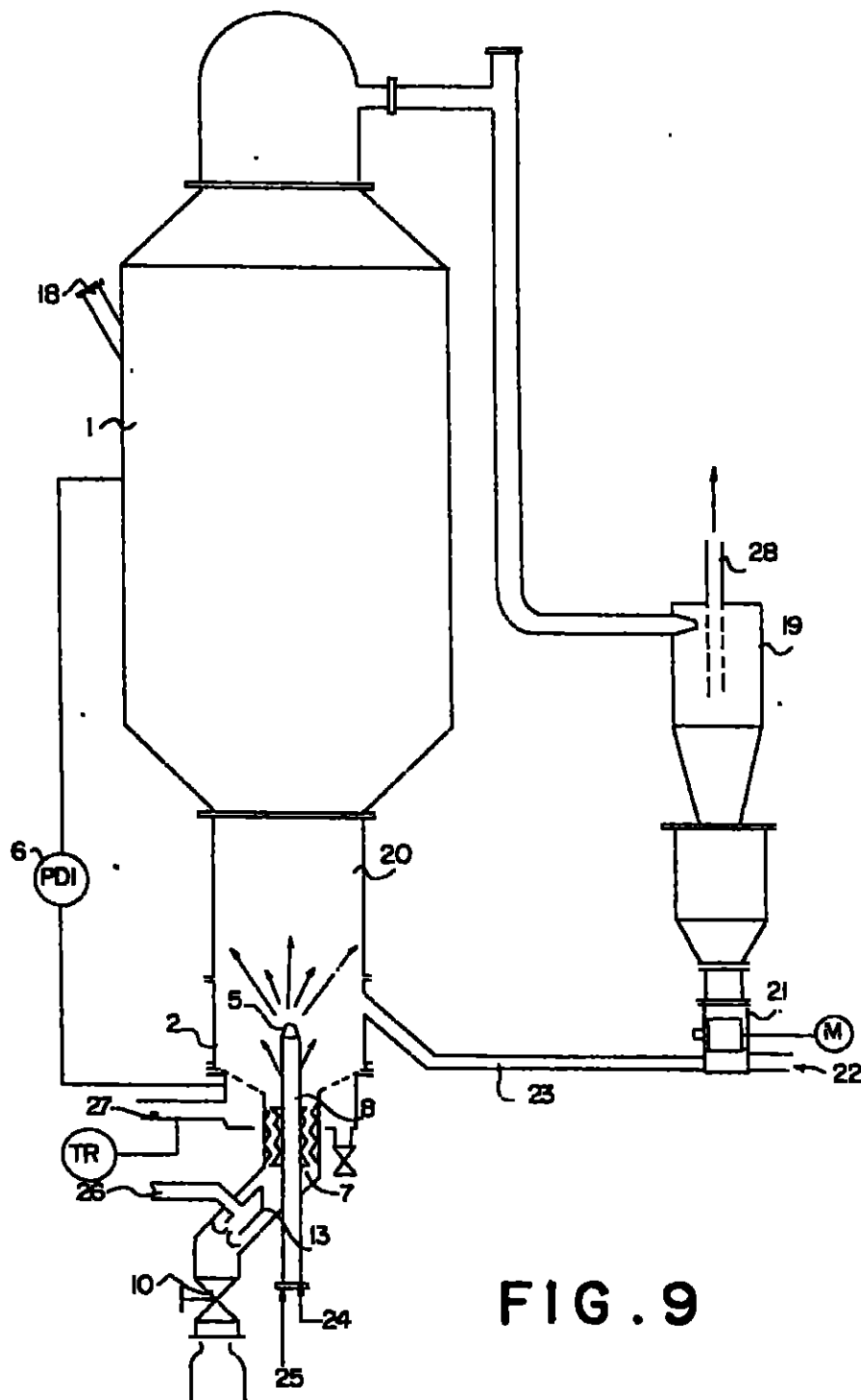


FIG. 9

PROCESS FOR PREPARING GRANULATES

This is a continuation, of application Ser. No. 06/718,129, filed Apr. 1, 1988, now abandoned.

The present invention relates to a new process and a new apparatus for preparing granulates. The invention also relates to granulates which are obtained by means of the new process.

There already are numerous known processes for preparing granular material by fluidised-bed granulation (compare Chem. Ing. Techn. 45, 736-739 (1973), DE-OS (German Published Specification) 2,231,445, DE-OS (German Published Specification) 2,553,917 and EP-OS (European Published Specification) 0,087,039). In these disclosed processes, which are carried out continuously, the ready-to-use granulate is obtained in one step without separate post-drying. In essence, it is possible to distinguish three different methods in this context which, however, are all based on the same granulate formation process. Thus, in each case the product to be granulated is of sprayable consistency, that is to say in the form of a melt, suspension or solution, when sprayed into a fluidised bed. The sprayed-in liquid product first wets the surface of the solid particles in the fluidised bed and then solidifies by drying on or cooling down. In this way the particles grow in shell-like fashion, and their size increases the longer they dwell in the fluidised bed. For that reason the granulate size depends critically upon the bed content.

The growth of the particles starts in the fluidised bed from nuclei which either are formed in the fluidised bed itself by non-impacting solidifying drops of spray or are produced by abrasion of solid particles already present, or which are fed into the fluidised bed from the outside. Nucleation which takes place in the fluidised bed (internal nucleation) is affected by the content of the fluidised bed in such a way that as the bed content grows there is on the one hand a decrease in the number of non impacting droplets of spray and on the other an increase in the number of nuclei produced by abrasion.

The process which is required for producing granulates in a predetermined grain size is, in fluidised-bed granulation, the interaction of nucleus availability and granulate growth. Therefore, the process of granulation can be affected in many and varied ways. Thus, for example, the availability of nuclei can be increased by adding nuclei from the outside.

Steady-state granulation conditions have been reached when the bed content remains constant. In the steady state the mass of solid material fed into the fluidised bed must correspond to the mass of completed granulates removed from the bed. In addition to this mass balance, however, the particles need also to be in balance. That is to say, all the granulates removed from the fluidised bed must be replaced in number by new nuclei. In the known methods, a constant granulate formation process is forced on the system. The methods differ in the manner in which this constancy is obtained.

In the case of the processes disclosed in DE-OS (German Published Specification) 2,231,445 and EP-OS (European Published Specification) 0,087,039, only internally formed nuclei are used. The control of the associated low fluidised-bed content actuates a discharge element according to the principle of fill level control and hence ensures that the granulate removal matches product intake. The granulate emerging from the granulator is classified, and the resulting fines are

returned into the granulator. Since, however, in the case of different throughputs through the serially connected apparatus elements of classifying line and discharge element the fill level control gets out of step, the only classifying line which can be used in this case is a classifying line where the amount of granular material which is let through matches the required throughput through the discharge element irrespective of separating efficiency. Accordingly, the classifying line employed in the methods described in DE-OS (German Published Specification) 2,231,445 and EP-OS (European Published Specification) 0,087,039 is in each case a second fluidised bed. This second fluidised bed provides only very inefficient classification of the granulates. For that reason, this process is unsuitable for producing granulates having a narrow grain size distribution.

The granulating process communicated in DE-OS (German Published Specification) 2,263,968 is in principle identical to the method described above. However, the classifying line employed in this instance is not a second fluidised bed but an efficiently separating sieve. The necessary synchronisation of the throughputs through the classifying line and the discharge element is achieved by not removing a portion of the granular material but instead grinding it and then returning it to the fluidised bed. This additional availability of nuclei needs to be compensated by reducing nucleation in the fluidised bed. The reduction of nucleation in the fluidised bed is achieved by operating the granulator at a high bed content. However, the prerequisite for this mode of operation is an abrasion-resistant granulate. This method thus provides granulates of narrow grain size distribution. However, it is a disadvantage that a comparatively high amount of apparatus needs to be used. In addition, this method cannot be used for granulating solvent-moist or dust explosion hazard products, since the apparatus required in addition to the fluidised-bed granulator cannot be inerted nor be installed to withstand explosive pressures.

In the third alternative disclosed in DE-OS (German Published Specification) 2,553,917 for producing granulates by the fluidised-bed/spray method, the discharge element used is a countercurrent gravity classifier. This classifier combines the functions of classifying line and discharge element.

Using this apparatus, only granulates which have reached the desired grain size are removed from the fluidised bed. Any variation in the number of discharged granulates has an immediate effect on the bed content. If, for example, the bed content rises, the granulates produced are too small. Consequently, the growth of granulates needs to be promoted and the feed of nuclei, which is in this case from the outside, needs to be cut back. To be able to apply effective control measures to the number of nuclei available for the granulation process it is necessary for internal nucleation to be minimised, which, in the case of abrasion-resistant granulates, can be obtained by granulation with high bed content. In the final analysis this known method produces granulates within a narrow grain size distribution. However, it is a disadvantage that the method requires controlled outside supply of nuclei which is complicated. Furthermore, conversion of the process from a certain mean grain size to another mean grain size is associated with extensive preliminary experimental work to determine the exact settings. That is also true of the other processes described above.

A new process has now been found for the continuous preparation of granulates having narrow grain size distribution, characterized in that

- a. the product to be granulated is sprayed in liquid form into a fluidised bed,
- b. the proportions of fine material escaping from the fluidised bed in the off-gas are separated off and returned into the fluidised bed as nuclei for granulate formation,
- c. the granulation process in the fluidised bed is influenced solely by setting the classifying gas stream in such a way that granulates are formed which are of the size predetermined by the classifying gas stream, and
- d. the completed granulate is removed solely by way of one or several countercurrent gravity classifiers which are inserted into the outflow bottom of the fluidised-bed apparatus, and
- e. if desired the granulates thus obtained are subjected to a thermal aftertreatment.

A new apparatus for the continuous preparation of granulates having a narrow grain size distribution has also been found. The apparatus essentially comprises a fluidised-bed reactor

- which contains devices for dispersing the product supplied in sprayable form,
- which further contains a system suitable for returning proportions of fine material escaping from the fluidised bed and
- to the outflow bottom of which there are directly attached one or several countercurrent gravity classifiers.

Finally, new granulates found and prepared by the process according to the invention

- contain 1 to 100 per cent by weight of at least one active component, 0 to 99 per cent by weight of inert filler material and 0 to 40 per cent by weight of dispersing and/or binding agent and optionally additives,
- have a mean grain size of 0.1 to 3 mm,
- have a narrow grain size distribution wherein the largest and the smallest particle diameters differ from the mean by at most half an average grain size,
- are uniformly shaped and homogeneously constituted and have a compact microporous structure and
- are spontaneously dispersible or soluble in water or other solvents.

The process according to the invention differs from all the corresponding predisclosed processes in that the granulate formation process, through the interaction between granulate growth and nucleation, automatically adjusts to the size of the discharged granulates which is predetermined by the classifying gas supply.

The process according to the invention is distinguished from the analogous predisclosed methods by a number of advantages. For instance, granulates of whichever particle size is desired can be prepared and the particle diameter (grain spectrum) is within very narrow limits. Furthermore, the size of the particles can be varied from case to case in a simple manner by means of the classifying gas supply; no changes to the apparatus are necessary. On the contrary, the particle size can even be changed without interruption of production.

It is of particular advantage that only granular material, i.e. granulates, of the desired size is produced. No material is lost, since undersize grain—that is to say particles which are too small—remain in the fluidised

bed until they have reached the desired size. Oversize grain—that is to say excessively large particles—is likewise not formed since the particles are removed from the fluidised bed by constant classifying. Grinding processes and sieving processes are therefore dispensed with completely. Nor is it necessary to add outside nuclei to affect the process. It is also favourable that the liquid products to be sprayed into the fluidised bed in the course of the process according to the invention can have a very high solids content. The resulting granulates are uniformly shaped and homogeneously constituted and, despite high strength, are spontaneously dispersible or dissolvable in water or other solvents. Since the process makes low demands on the abrasion resistance of the granulates, it is also possible to prepare granulates of low binder content, thereby favouring their dispersing properties. Finally, the process according to the invention can also be used for processing solvent-moist and dust explosion hazard products since the required apparatus can be inertised and be constructed to withstand explosive pressures.

In the process according to the invention, the product to be granulated is sprayed in liquid form into a fluidised bed. This liquid form can be a melt, solution or suspension (slurry).

The liquid to be sprayed in can contain one or more active components. Suitable active components are not only substances which are solid at room temperature but also those which are liquid at room temperature. The only precondition for the use of liquid active components is that they are applied to solid carrier substances before granulation. The active components can be soluble or insoluble in water. They need to be stable to hydrolysis to the extent that, in the course of the process according to the invention and in the course of application of the resulting granulates, they do not undergo noticeable decomposition in the presence of water.

Possible active components are agrochemical active substances, active substances for combating pests in the domestic and hygiene areas, pharmacologically active substances, nutrients, sweeteners, dyestuffs and organic or inorganic chemicals.

Agrochemical substances are to be understood as meaning in the present case active substances which are customarily usable in crop protection. They preferably include insecticides, acaricides, nematocides, fungicides, herbicides, growth regulators and fertilisers. Specific examples of such active substances are: 0,0-diethyl 0-(4-nitrophenyl) thionophosphate, 0,0-dimethyl 0-(4-nitrophenyl) thionophosphate, 0-ethyl 0-(4-methylthiophenyl) S-propyldithiophosphate, (0,0-diethylthionophosphoryl)- α -oxominophenylacetoneitrile, 2-isopropoxyphenyl N-methylcarbamate, 3,4-dichloropropionanilide, 3-(3,4-dichlorophenyl)-1,1-dimethylurea, 3-(4-chlorophenyl) 1,1-dimethylurea, N-(2-benzothiazolyl)-N,N'-dimethylurea, 3-(3-chloro-4-methylphenyl)-1,1-dimethylurea, 3-(4-isopropylphenyl)-1,1-dimethylurea, 4-amino-6-(1,1-dimethylethyl)-3-methylthio-1,2,4-triazin-5(4H)-one, 4-amino-6-(6,1-dimethylethyl)-3-ethylthio-1,2,4-triazin-5(4H)-one, 1-amino-6-ethylthio-3-(2,2-dimethylpropyl)-1,3,5-triazine-2,4-(1H,3H)-dione, 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4H)-one, 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine, the R-enantiomer of the trimethylsilylmethyl ester of 2-[4-(3,5-dichloropyridyl)-2-oxy]-phenoxy]-propanoic acid, the R-enantiomer of the 2-benzoyloxyethyl ester of 2-[4-(3,5-dichloropyridyl-

2-oxy)-phenoxy]-propionic acid, 2,4-dichlorophenoxyacetic acid, 2-(2,4-dichlorophenoxy)propionic acid, 4-chloro-2-methylphenoxyacetic acid, 2-(2-methyl-3-chlorophenoxy)-propionic acid, 3,5-dihydro-4-hydroxybenzonitrile, 3,5-dibromo-4-hydroxybenzonitrile and diphenyl ethers and phenylpyridazines, such as, for example, pyridates, furthermore 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate, 3,5-dimethyl-4-methylthiophenyl N-methylcarbamate, 0,0-diethyl 0-(3-chloro-4-methyl-7-coumarinyl) thiophosphate, N,N-dimethyl-N'-(fluorodichloromethylmercapto)-N'-(4-methylphenyl) sulfamide, 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-butan-2-one, 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-butan-2-ol, 1-cyclohexyl-4,4-dimethyl-3-hydroxy-2-(1,2,4-triazol-1-yl)pent-1-ene, 2-(2-furyl)-benzimidazole, 5-amino-1-bis(dimethylamido)-phosphoryl-3-phenyl-1,2,4-triazole, 4-hydroxy-3-(1,2,4-tetrahydro-1-naphthyl)-coumarin, 0,0-dimethyl S-[1,2-bis-(ethoxycarbonyl)-ethyl]-dithiophosphate, 0,0-dimethyl 0-(4-methylmercapto-3-methylphenyl)-thionophosphate, 0-ethyl 0-(2-isopropoxyloxycarbonylphenyl) N-isopropylamidothiophosphate and (S)- α -cyano-3-phenoxybenzyl (1R)-cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate.

Active substances for combating pest in the domestic and hygiene areas are to be understood as meaning in the present case substances which can customarily be used for such purposes. Examples which may be mentioned are: 2-isopropoxyphenyl-N methylcarbamate, 0,0-diethyl 0-(4-nitrophenyl) thionophosphate, 0,0-dimethyl 0-(4-nitrophenyl) thionophosphate, 0,0-dimethyl S-[1,2-bis-(ethoxycarbonyl)-ethyl]-dithiophosphate, 0,0-dimethyl 0-(3-methyl-4-nitrophenyl) thionophosphate, 0,0-dimethyl 0-(4-methylmercapto-3-methylphenyl) thionophosphate, cyclohex-1-ene-1,2-dicarboximidomethyl 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylate.

Pharmacologically active substances is to be understood as meaning in the present case not only substances which can be used in veterinary medicine but also substances which can be used in human medicine. An example which may be mentioned of a substance which can be used in veterinary medicine is α -cyano-3-phenoxy-4-fluorobenzyl 2,2-dimethyl-3-[β -(p-chlorophenyl)- β -chlorovinyl]-cyclopropanecarboxylate. An example which may be mentioned of a substance which can be used in human medicine is acetylsalicylic acid.

Nutrients is to be understood as meaning not only substances for human consumption but also substances for animal consumption. Examples which may be mentioned are: citric acid, vitamins, coffee powder, tea powder and cocoa powder.

Examples, which may be mentioned of sweeteners are sodium cyclamate and saccharin.

Dyestuffs is to be understood as meaning in the present case substances suitable for preparing dyestuff dispersion or dyestuff solutions which are used as colorants and/or paints. For instance, water-soluble dyestuffs, such as anionic, cationic and reactive dyestuffs, or water-insoluble dyestuffs, such as vat dyestuffs, polyester dyestuffs and pigment dyestuffs, can be used. Examples which may be mentioned are: indanthrene dyestuffs, cerofix dyestuffs, estrazone dyestuffs, triarylamines dyestuffs, triarylmethane dyestuffs, methine dyestuffs, anthraquinone dyestuffs, indigo dyestuffs, salphar dyestuffs, azo dyestuffs and pigment dyestuffs.

Suitable organic and inorganic chemicals are those substances which are preferably used in the form of aqueous dispersions for synthetic purposes. It is also possible to use aqueous zeolite suspensions. Zeolites is to be understood as meaning substances of this type as described in Ullmann, 4th edition, volume 17, pages 9 et seq. under the entry "Molekularsiebe" [Molecular sieves]. It is also possible to use suspensions of organic oxides which are suitable for preparing catalysts or catalyst supports. Examples which may be mentioned thereof are aluminium oxide and silicon dioxide.

The liquid product to be sprayed into the fluidised bed in the course of the process according to the invention, in addition to the active components and to any liquid diluent present, can also contain inert fillers, dispersants, binders and/or additives, such as, for example, preservatives and dyestuffs.

The fillers can be any filler and carrier substance customarily used in water-dispersible or water-soluble granulates or in oil- and oil-soluble granulates. Substances of that type which are preferably used are inorganic salts, such as alkali metal, magnesium and ammonium chlorides and sulphates, for example magnesium sulphate, potassium sulphate, sodium sulphate, potassium chloride, ammonium sulphate, lithium sulphate and ammonium chloride, furthermore oxides, such as magnesium oxide, nitrates, carbonates, hydrogen carbonates, silicates, talc, chalk, quartz powder, kaolin, montmorillonite, bentonite, attapulgite and sepiolite, and also graphite, furthermore urea and urea derivatives, such as hexamethylenetetramine and casein, and also carbohydrates, such as starch, sugar, alginates and derivatives thereof, cereal flours, such as wheat flour and rice flour, and also kelcane, methylcellulose and hydroxypropylmethylcellulose, and finally water-soluble polymers, such as polyvinyl alcohol and polyvinylpyrrolidone.

The dispersants used are preferably: condensation products of aromatic sulphonic acids and formaldehyde, such as condensation products of sulphonated ditolyl ether and formaldehyde, and also ligninsulphonic acid salts, such as lithium, sodium, potassium, magnesium, calcium and ammonium salts of ligninsulphonic acid, and also methylcellulose, polyoxyethylene/fatty acid ester, polyoxyethylene/fatty alcohol ether, for example alkylaryl polyglycol ether, alkyl sulphates and protein hydrolysates.

Even dispersants themselves can be processed from their solutions into readily redissolvable granulates.

It is also possible to process slurries of anionic detergents, if desired in the presence of additives of nonionic surfactants, builders, optical brighteners, of softeners and/or of scents.

The binders can be any binder (adhesive) customarily present in water-dispersible and water-soluble granulates or in oil-dispersible and oil-soluble granulates. Preference is given to the use of solutions, emulsions or latexes of natural or synthetic substances, such as methylcellulose, dextrose, sugar, starch, alginates, glycols, polyvinylpyrrolidone, ligninsulphonate, gum arabic and polyvinyl alcohol and polyvinyl acetate in water or low-boiling organic solvents, such as methanol, ethanol, butanol and methylene chloride. In some cases it is even possible to use waterglass and silica sol.

Examples of preservatives which can be present in the liquid products to be sprayed in the course of the process according to the invention are 2-hydroxybiphenyl, sorbic acid, p-hydroxybenzaldehyde, methyl p-

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hydroxybenzoate, benzaldehyde, benzoic acid and propyl p-hydrobenzoate. Examples which may be mentioned of dyestuffs which can also be used as additive are inorganic pigments, such as iron oxide, titanate and blue ferrocyanide, and organic dyestuffs, such as alizarin, azo and metal-phthalocyanine dyestuffs.

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If, in the course of the process according to the invention, use is made of active components and binders which are present in the form of solids at room temperature, it is necessary to introduce these active components or binders into the fluidised bed in the form of a melt, of a solution or a suspension. To prepare solutions or suspensions of such active components or binders any customary inert organic solvent and water can be used. Organic solvents which can be preferably used for this purpose are alcohols, such as ethanol and glycol, and also aliphatic and aromatic, optionally halogenated hydrocarbons, such as ligroin, hexane, petrol, benzene, toluene, xylene, methylene chloride, carbon tetrachloride and chlorobenzene, and also ethers, such as dioxane, tetrahydrofuran and anisole, and also ketones, such as acetone, methyl ethyl ketone and cyclohexanone, and furthermore highly polar solvents, such as hexamethylphosphoramide, acetonitrile, dimethylformamide and dimethyl sulphoxide. Particular preference is given to the use of water.

The solids content of the liquid products sprayed into the fluidised bed in the course of the process according to the invention can be varied within a relatively wide range. In general the solids content on the use of suspensions (slurries) is between 5 and 75% by weight, preferably between 10 and 65% by weight.

The liquid products to be sprayed are prepared in conventional manner by mixing the constituents in the desired mixing ratios and, if appropriate, subsequently heating the resulting mixtures.

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The granulation can be carried out in air or in inert gases, such as, for example, nitrogen. In the process according to the invention, the granulation can be started up in a fluidised-bed apparatus which already contains starting granulate. However, it is also possible to start the granulation in an empty apparatus. In this case the fluidised-bed granulation according to the invention starts off as a spray-drying. Through gradual build-up of the fluidised bed it then leads to a packed bed wherein the granulates reach the desired size and are discharged. If the products used tend to form deposits on the walls of the apparatus, it is advantageous to start up the process by presenting starting granulate. The effect of this measure is substantially to avoid possible spraying against the walls.

The liquid product to be granulated is introduced into the fluidised bed in the course of the process according to the invention by means of spray nozzles. It is particularly advantageous to use two-material nozzles.

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The atomisation gas used can be any gas which is inert under the operating conditions. Preference is given to the use of air or inert gases, such as, for example, nitrogen. The amount of atomisation gas can be varied within a relatively wide range, and it generally depends on the dimensions of the apparatus and on the nature and the amount of the product to be sprayed in. In general, the amounts of atomisation gas used are, relative to the product used, 0.1 kg of gas/kg of feed to 10 kg of gas/kg of feed, preferably 0.5 kg of gas/kg of feed to 5 kg of gas/kg of feed. The temperature of the atomisation gas stream can likewise be varied within a relatively wide range. The atomisation gas tempera-

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tures used are generally between 0° C. and 250° C., preferably between 20° C. and 200° C.

The proportions of fine material which escape from the fluidised bed in the off-gas are separated off and are returned into the fluidised bed as nuclei for the granulate formation process. The way the fine material is returned can be internal or external. In the internal return of fine material, the dust is separated off at a filter placed directly on the fluidised bed and is transported back into the fluidised bed by means of cleaning-off pulses. In the external return of fine material, the dust is separated from the off-gas outside the granulator. To separate the escaping proportions of fine material, any apparatus customarily used for such purposes can be used. In a particularly preferred embodiment, the fine material is separated off by means of a cyclone or a dust filter. The separated-off fine material is transported back into the spray zone of the fluidised bed. This return transport is preferably effected pneumatically. The drive gas used can be any customary gas which is inert under the operating conditions. Preference is given to the use of air and inert gases, such as, for example, nitrogen. The amount of drive gas can be varied within a relatively wide range; it depends in general on the dimensions of the apparatus and on the escaping amount of fine material. The amounts of drive gas used are in general 0.01 kg of gas per kg of fine material to 2 kg of gas per kg of fine material, preferably 0.1 to 1 kg of gas per kg of fine material. The temperature of the drive gas stream can likewise be varied within a relatively wide range. The temperatures used are generally between 20° C. and 350° C., preferably between 30° C. and 300° C.

The granulation process in the fluidised bed in the process according to the invention is maintained solely by the sprayed-in rate of the liquid product to be granulated and the intensity of the classifying gas stream. No additional nuclei are supplied from the outside. The classifying gas used can be any customary gas which is inert under the operating conditions. Preference is given to the use of air and inert gases, such as, for example, nitrogen. The amount of classifying gas can be varied within a relatively wide range; it depends on the dimensions of the apparatus and the grain size and the mass flow of the granulates to be discharged. The classifying gas amounts used are in general between 0.2 kg of gas per kg of granulate and 5 kg of gas per kg of granulate, preferably between 0.4 and 2 kg of gas per kg of granulate. The temperature of the classifying gas stream can likewise be varied within a relatively wide range. The classifying gas temperatures used are in general between 20° C. and 350° C., preferably between 30° C. and 300° C.

The classifying gas speed depends on the grain size and the density of the granulate to be discharged. The classifying gas speeds used are in general between 0.5 and 15 m/sec, preferably between 1 and 5 m/sec.

The completed granulates is discharged in the course of the process according to the invention by way of one or several countercurrent gravity classifiers. This type of discharging elements can be any customary classifier which works by the principle of countercurrent gravity classification. If a particularly narrow grain distribution is desired, a zig-zag classifier is used as a specific embodiment. In order to keep the amount of classifying gas as low as possible, for reasons of energy, in carrying out the process according to the invention preference is given to the use of a classifier having a zig-zag cross-section (=zig-zig classifier) where the gap length and

hence the classifier cross-section can be set by means of bars which are connected to one another in the manner of a comb, which are adapted to the zig-zag cross-section and which are slideable at rightangles to the axis of the classifier. In a preferred embodiment, the classifier contains and adjusting means for the bars which is connected to a regulating device which regulates the classifying gas stream in such a way that the flow velocity in the classifier remains constant despite the variable cross-section.

The process according to the invention is generally carried out under atmospheric pressure. However, it is also possible to work under superatmospheric pressure or reduced pressure. The output point of the counter-current gravity classifier is generally kept under atmospheric pressure. Said atmospheric pressure is obtained by connecting to the classifier, in between the off-air fan and the output point, a pressure regulator which adjusts the off-air fan or a butterfly valve or an analogous device and which constantly adapts the pressure at the output point of the classifier to the ambient pressure. If no atmospheric pressure prevails at the output point of the classifier, it is necessary to install locks for maintaining the desired pressure.

The course of the process according to the invention and the apparatus required therefor are illustrated in the accompanying drawings, in which

FIG. 1 shows a diagram for elucidating the interaction between granulate growth and nucleation without consideration of abrasion,

FIG. 2 shows a diagram for elucidating the interaction between granulate growth and nucleation with consideration of abrasion,

FIG. 3 shows a schematic representation of the entire apparatus according to the invention in the embodiment featuring internal return of fine material,

FIG. 4 shows a perspectival representation of the zig-zag classifier present at the discharge point of the fluidised-bed apparatus,

FIG. 5 shows a cross-section through the zig-zag classifier,

FIG. 6 shows the adjusting means on the zig-zag classifier for adjusting the discharge cross-section,

FIG. 7 shows the grain size distribution obtained at the output of the classifier, which was determined on those granulates whose preparation is described in Examples 1 to 3 and

FIG. 8 shows a cross-section through a two-material nozzle which is replaceable during operation.

The dependence depicted in FIG. 1 between the size and the number of the granulate particles upon the content of the fluidised bed corresponds to the conditions which are likely in the production of a completely abrasion-resistant product.

Some of the droplets generated by the nozzle impact on the particles circulating in the fluidised bed and hence cause these particles to grow. The non-impacting droplets solidify. They become rigid in the case of a melt; they dry in the case of a suspension; and they crystallise in small particles in the case of a solution being sprayed. They are separated out of the off-gas and are returned into the spray zone of the fluidised bed. They consequently become new nuclei on which further particles can accumulate. With increasing bed content (the start corresponds to spray-drying) the growth of the particles is favoured at the expense of nucleation. The size of the discharged granulates in the steady state depends directly on the number of nuclei formed, since

the number of completed granulates which need to be discharged is the same as the number of nuclei formed. The dry weight which is fed in needs to become distributed over the number of completed granulates. Consequently, the size of the granulates is predetermined, for simplicity the size of the granulates being understood here as meaning of weight of a granulate grain.

A large number of nuclei and a correspondingly low bed content can therefore be used to produce many small granulates—as is depicted in the upper graph of FIG. 1—, while a high bed content under otherwise identical conditions leads to the production of few big granulates. If the target size of the completed granulates is fixed by setting the classifying discharge then, under steady-state conditions this necessitates, given the relationship mentioned and as drawn in FIG. 1, a bed content which provides exactly the corresponding number of nuclei. This bed content becomes established automatically without outside interference.

In this consideration, further effect which contributes to nucleation has been deliberately disregarded, namely the effect of abrasion. Abrasion, which is highly product-dependent, makes the situation somewhat more complex.

In contrast to the primary nuclei considered so far, the number of secondary nuclei formed by abrasion increases with growing bed content, as can be seen in the bottom half of FIG. 2. Primary and secondary nuclei taken together constitute the total number of available nuclei. The total number of nuclei passes through a minimum. The consequence in turn is that a maximum granulate size cannot be exceeded. Moreover, a granulate size is associated with two different bed contents. This suggests that the two operating points be examined for stability.

As is known, a state is only stable when the reactions to perturbations are such that the perturbations are reversed again. For example, let the perturbation be an increase in the bed content in the left operating point. The reaction to this perturbation consists in an enlargement of the granulates and, in the classifying discharge, in an increased discharge of granulate. The bed content thus becomes smaller again. The same reversing reaction occurs when the perturbations is in the other direction. The operating point is thus stable.

The test has a different result in the right operating point. In this case, a larger bed content results in a smaller granulate. The classifying discharge allows less granulates through. The bed content grows and consequently the overall state of the system moves away from the operating point. The same result is obtained on assuming that the perturbation acts in the other direction. The operating point is thus not stable.

The maximum point of the curve consequently defines the operating range of the self-regulating process. The granulation process is only stable on the left-hand side and therefore should only be used there.

Whether and where a maximum forms depends on the nucleation mechanism, which is primarily dependent upon the product. The essential product properties in relation to primary nucleation are the viscosity and surface tension of the feed. The number of primary nuclei can be affected by the fineness of the spray. Another factor is the rate of solidification, which is affected by the fluidising gas temperature.

The secondary nuclei are primarily affected by the blinding action of the adhering solid. Other important

factors are particle size, inflow, velocity and residence time in the bed.

The process according to the invention can be carried out in a fluidised-bed apparatus of the type schematically depicted in FIG. 3 in the version featuring internal return of fine material. It consists of a vertically upright vessel 1 having a perforated outflow bottom 2 at the lower end and an attached off-gas filter 3 at the upper end. The resulting off-gas is extracted by the fan 4. Gas is blown through the perforated outflow bottom 2, so that a fluidised bed forms above the bottom in the granulation vessel 1.

The process according to the invention is preferably carried out in a fluidised-bed granulator which constitutes a two-part, preferably cylindrical, vessel. The granulation process takes place in the lower part of said vessel. The upper part, which preferably has twice the diameter of the lower part, serves for the preliminary separation of middle grain from the off-gas and for solidifying those droplets in the spray which have not impacted on particles in the fluidised bed.

The separation of fine material or dust from the off-gas can take place either inside or outside the fluidised-bed granulator. Internal separation preferably takes place on filter tubes 3 arranged in the upper part of the vessel 1. The precondition for the use of this type of filter tube is that the product agglomerates on the surface of the tube. The fine material thus agglomerated, on being cleaned off the filter tubes, falls back into the fluidised bed with sufficient speed of drop. External separation from the off-gas of fine material carried along therein is preferably affected by means of a cyclone or a filter. In this case, the separated-off fine material falls into a star wheel lock which is required for maintaining the pressure difference between fluidised bed and dust collector. From the star wheel lock the fine material is returned into the fluidised bed, preferably into the spray zone of the nozzles, preferably pneumatically by means of a drive gas stream by way of a separate line, so that a uniform growing of all particles of the grain size spectrum is ensured. It is also possible to use other customary methods of returning the fine material, as long as they ensure uniform distribution in the fluidised bed.

In the lower part of the fluidised-bed granulator, the gas serving as fluidising gas and for solidifying the sprayed-in product is passed in in the case of the process according to the invention by way of a perforated outflow bottom. the fluidising gas used can be any customary gas which is inert under the operating conditions. Preference is given to the use of air and inert gases, such as, for example, nitrogen.

The temperature of the fluidising gas can be varied within relatively wide range. The temperatures used are generally between -20° and $+700^{\circ}$ C., preferably between 0° and 650° C.

The speed of the fluidising gas can be varied within a relatively wide range. The gas speeds (=empty tube speeds) used are in general 0.4 to 4 m/sec., preferably 0.5 to 2 m/sec.

The amount of the fluidising gas is calculated on basis of the speed of the fluidising gas, the density and the cross-section area of the granulation part of the apparatus.

The speed of the fluidising gas is chosen to be such that a highly agitated fluidised bed is maintained so that, on the one hand, there is no occurrence of undesirable caking together of the particles and, on the other,

the abrasion in the fluidised bed and the off-gas removal of solids from the fluidised bed do not reach excessive levels.

The outflow bottom in the apparatus for carrying out the process according to the invention is either plane or funnel-shaped. The outflow bottom is preferably constructed in the shape of a funnel, the aperture angle of which can be varied within a certain range. The funnel preferably has an aperture angle between 140° and 160° . By using outflow bottoms which have such aperture angles and which are made of perforated metal trays ensure a radially inwardly directed outflow, in particular the larger particles in the fluidised bed are guided towards the classifying discharge, the entry port of which is in the centre of the outflow bottom.

However, other kinds of the outflow bottom classifier arrangement are also possible. For instance, the granulator can also be constructed in a rectangular form with a plane or inclined bottom. The use of several classifiers distributed over the overflow area is also possible. The bottom segments can be plane or inclined towards the classifier. In a particularly preferred embodiment, the cross-sectional area of the bottom segment has the shape of a hexagon. Similar to the arrangement depicted in FIG. 9, a nozzle surrounded by a circular classifier is mounted in the centre of each of the bottom segments. In this manner, the granulator is built up above a plurality of bottom segments of the same kind. It is achieved with this arrangement that the frequency of the classification remains constant independently of the dimensions of the apparatus.

As is also revealed in FIG. 3, attached at the level of the fluidised bed are spray nozzles 5 with which the liquid product is fed into the fluidised bed in finely divided form. The attainment and maintenance of the steady state in the fluidised bed are controlled by way of the self-adjusting bed pressure loss. The bed pressure loss is indicated and recorded by the pressure-measuring instrument 6. Deviations from the standard value indicate the presence of perturbations in the granulation process. Mounted in the centre of the outflow bottom 2 is a discharge tube 7, into the upper part of which, the part adjoining the outflow bottom 2, a zig-zag classifier 8 is installed to be flush with the outflow bottom 2. A further pressure regulator 9 is contained between the output point of the zig-zag classifier 8 and the off-gas fan 4. This regulator 9 regulates the off-gas fan 4 in such a way that there is constantly a pressure which is only slightly below atmospheric pressure at the output point of the zig-zag classifier. In this way it is possible to dispense with any further element sealing off the zig-zag classifier, such as, for example, a lock. The completed granulate falls unhindered from the discharge 7 and is collected in a reservoir vessel 10.

In the process according to the invention, the liquid product which is injected into the fluidised bed is preferably sprayed upward into the fluidised bed.

To spray the liquid product into the fluidised bed, the process according to the invention preferably uses two-material nozzles which give fine atomisation of the liquid product and also contribute to a thorough mixing of the fluidised bed.

If the neutral point of the pressure profile is located in the classifying discharge, a diminished pressure exists in the granulator. The nozzles can be replaced in the course of current operation but that air escapes into the environment. The air streaming into the granulator from outside through the installation gaps of the nozzles

further prevents the escape of product. An embodiment is preferred in which atomisation gas is streaming against the penetrating air in order to avoid a penetration of air into inertised plants during the replacement, mixing of the fluidised bed. In a particularly preferred embodiment, these nozzles are installed in such a way that they can be replaced during the granulation process.

A schematic representation of such an arrangement is reproduced in FIG. 8. In this figure,

- a denotes the bottom of the outflow vault
- b denotes a further bottom
- c denotes a bushing
- d denotes a lateral bore
- e denotes a nozzle guide tube
- f denotes a two-material nozzle
- g denotes an atomisation gas supply line
- h denotes a product supply line

The gas (g) serving for atomising the liquid product is in this case passed through a space which is formed below the outflow bottom (a) by an additional bottom (b). The bottoms bounding the space have therein for each nozzle (f) a bushing (c) which has a bore (d) on the side and is intended for receiving the nozzle guide tube (e). The nozzle guide tube is of a length such that it reaches from the under edge of the bushing to just above the outflow bottom. It is likewise provided with a lateral bore, so that by turning the nozzle guide tube the supply of atomisation gas to the nozzle can be completely or partially interrupted. When the nozzle has been pulled out of the nozzle guide tube, it is necessary that sufficient atomisation gas streams into the installation gap that no particles can fall out of the fluidised bed through this opening and besides no environmental air penetrates into the granulator. The two-material nozzle likewise contains a lateral bore through which the atomisation gas, when the nozzle has been installed, can flow from the nozzle guide tube into the gas guide passageway of the nozzle.

The feed of the liquid product in carrying out the process according to the invention is regulated in the manner customary in the case of granulators and spray dryers, namely via the temperature of the off-air.

As can be seen in FIGS. 4 and 5, the zig-zag classifier 8 in the depicted apparatus according to the invention consists of a plurality of straight rectangular channels 11 which meet at an angle of about 120°. The channels 11 are bounded by riffling metals 12 bent into a zig-zag shape. At the lower end of the zig-zag classifier 8 is a gas divider 13 by means of which the same amount of gas is introduced into all the classifying gas channels. A vortex roll forms in every classifier element, classifier element to be understood as meaning in this case the stretch between two adjacent classifying places. The material to be classified slides down along the lower surface in each case, passes through the classifying gas stream, then moves upwardly along the upper surface in each case, and then passes again through the classifying gas stream. On each pass through the classifying gas stream, classification is effected, so that despite the low separating efficiency in the individual classifier elements the repetition ensures that overall the separating efficiency is high.

In working with zig-zag classifiers, it is particularly advantageous to use a classifier of adjustable cross-section (compare FIG. 5).

The required minimum passage cross-section of the classification line in the zig-zag classifier needs to be

decided experimentally, since said cross-section depends on the grain distribution of the bed and the granulate stream to be discharged. If the passage cross-section is too small, then steady-state operation in accordance with FIG. 1 is not possible, since an insufficient amount of granulate is discharged and in this case bed content and grain size grow uncontrolled. If, on the other hand, the passage cross-section is too large, then it is true that granulate formation is not perturbed, but this mode of operation can be unfavourable from energy aspects. Therefore, to change the passage cross-section, the classifier (compare FIG. 6) contains an adjusting means 14 with which the gap length in the zig-zag classifier and hence the classifier cross-section can be changed. The adjusting means is comprised of bars which are connected to one another like a comb, which are adapted to the zig-zag cross-section and which are slideable transversely, that is to say perpendicularly to the axis of the classifier, by means of a pushing device 15. The adjusting means 14 is connected to a regulating device 16 which regulates the classifying gas stream by way of valve 17 in such a way that the flow velocity in the zig-zag classifier 8 remains constant despite the variable cross-section. The optimal setting of the adjusting means is determined empirically by first seeking the classifying gas throughput required for the desired granulate size in the fully opened state. The bed content adjusts automatically. Then the free classifier cross-section is reduced by means of the adjusting means until the bed content (measured via the bed pressure loss) increases. That represents the minimum classifier cross-section required for the granulation process. For steady-state operation, the classifier cross-section is chosen to be somewhat larger than absolutely necessary, in order to ensure stable operating conditions.

A particularly advantageous apparatus for carrying out the process according to the invention is schematically depicted in FIG. 9. In this drawing, the indicated numbers have the following meanings:

- 1=granulator vessel
- 2=outflow bottom
- 3=spray nozzle
- 6=pressure-measuring instrument
- 7=discharge tube
- 8=zig-zag classifier in circular gap form
- 10=product discharge
- 13=classifying gas distributor
- 18=intake port for the starting granulate
- 19=fine material separator (cyclone)
- 20=cylindrical shot
- 21=star wheel lock
- 22=drive gas supply line
- 23=fine material return
- 24=atomisation gas supply line
- 25=supply line for the product to be sprayed
- 26=classifying gas supply line
- 27=supply line for the fluidising gas
- 28=off-gas exit to the fan

In the granulates according to the invention, the percentages of the components contained therein can be varied within a relatively wide range. The proportion of active component or of active components is generally between 1 and 100% by weight. If the individual active substances are sprayed in as melts or solutions, the resulting granulate is composed up to 100% by weight of the respective substances, and if desired up to 5% by weight of solvents or diluents are present. If the matter sprayed is liquids which, in addition to the active

components, contain further constituents, such as inert filler materials, dispersants, binders and/or other additives, the proportion of active components is generally between 5 and 95% by weight, preferably between 10 and 80% by weight. The proportion of inert filler materials is generally 0 to 99% by weight, preferably 0 to 95% by weight. Dispersants and/or binders and if desired further additives are generally present in proportions of 0 to 40% by weight, preferably 0 to 30% by weight.

The granulate particles according to the invention generally have a particle size of 0.1 to 3 mm, preferably 0.2 to 2 mm. The grain size of the granulate particles according to the invention depends on the specific intended use of the granulates. The grain size distribution is very narrow, compared to conventionally produced granulates. In general, the particle diameter only differs by at most half a mean grain size from the mean particle diameter (d_{50}).

The granulate particles according to the invention are uniformly shaped and are of high strength. They have a compact microporous structure and are nevertheless spontaneously dispersible or soluble in water or other solvents. Spontaneous dispersibility or solubility is to be understood as meaning in the present case that the particles completely disperse or dissolve in general in 0.5 to 3 minutes, preferably in 1 to 2 minutes.

The granulates according to the invention, depending on the active components that they contain, can be used for all manner of purposes. Those granulates which contain agrochemical active substances as active components can be used by conventional methods in crop protection. For example, granulates of this type are dispersed or dissolved in water. The resulting dispersions and solutions, if desired after previous dilution, can be applied to the crops and/or their habitat by conventional methods, that is to say for example by spraying, stoming or pouring. The application level depends on the concentration of the dispersion or solution and on the specific indication and on the active components contained therein.

If the granulates according to the invention contain not agrochemical active substances but other active components, the application is effected by the methods which are customary in the respective technical field. In this case too the application level is dependent on the specific active components and on the specific indication.

In some case the granulates prepared using the process according to the invention can also be subjected to a thermal aftertreatment. For instance, zeolite granules can be hardened or activated by heating to temperatures between 300° and 700° C., preferably between 350° and 650° C. Granulates which contain inorganic oxides and come into consideration for use as catalysts or catalyst supports can be hardened by heating to temperatures between 500° and 1,000° C.

The process according to the invention is illustrated by the following examples.

PREPARATION EXAMPLES

EXAMPLE 1

A granulating apparatus according to the invention of the type depicted in FIG. 9 having the following dimensions

Diameter of outflow bottom	225 mm
Diameter of settling space	430 mm
Total height of granulator about	3 m
Spray nozzles	1 two-material nozzle
Classifier cross-section	880 mm ²
Zip-ang classifier	10 elements

is used to carry out a granulation of an aqueous sodium chloride solution containing 23% by weight of sodium chloride. This solution is sprayed at a temperature of 20° C. into the fluidised-bed granulator. To fluidise the bed content, air is blown in at a rate of 127.5 kg per hour. The entry temperature of the fluidising gas is 180° C.; the exit temperature is 80° C. The classifying gas blown in is air at a rate of 18 kg/hour. The temperature of classifying gas is 20° C. The content of the fluidised bed is 3 kg; the granulation output is 1.5 kg per hour. The result is a free-flowing granulate having a bulk density of 1,075 kg/m³ and a mean particle size d_{50} = 1.5 mm. The particle size distribution determined by sieve analysis is plotted as curve 1 in FIG. 7.

EXAMPLE 2

The apparatus described in Example 1 is used to carry out the granulation of an aqueous suspension.

First, a pulverulent premix which consists of 50% by weight of 2-isopropoxyphenyl N-methylcarbamate, 2% by weight of magnesium oxide, 4% by weight of highly disperse silica, 10% by weight of alkylarylsulphonate and 34% by weight of ground rock is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 60% by weight. This suspension is sprayed at a temperature of 20° C. into the fluidised-bed granulator. The granulation takes place under the conditions indicated hereinafter.

Fluidising gas:	Air Gas throughput 127.5 kg/h Entry temperature 95° C. Exit temperature 35° C.
Classifying gas:	Air Gas throughput 12 kg/h Gas temperature 20° C.
Bed content:	1.2 kg
Granulation output	4 kg/h

The result is a free-flowing granulate having a bulk density of 785 kg/m³ and a mean particle size d_{50} = 0.7 mm. The particle size distribution determined by sieve analysis is plotted as curve 2 in FIG. 7.

EXAMPLE 3

The apparatus described in Example 1 is used to granulate a melt.

An alkyl polyglycol ether which melts at 60° C. is sprayed at a temperature of 70° C. into the fluidised-bed granulator. The granulation takes place under the conditions indicated hereinafter.

Fluidising gas:	Air Gas throughput 127.5 kg/h Entry temperature 18° C. Exit temperature 25° C.
Classifying gas:	Air Gas throughput 8 kg/h Gas temperature 20° C.
Bed content:	1.8 kg

-continued

Granulation output: 3 kg/h

The result is a free-flowing granulate having a bulk density of 535 kg/m³ and a mean particle size d_{50} = 0.36 mm. The particle size distribution determined by sieve analysis is plotted as curve 3 in FIG. 7.

EXAMPLE 4

An apparatus according to the invention as described in Example 1 is used to granulate an aqueous suspension (slurry). The spray nozzle in said apparatus is a two-material nozzle. The classifier used is a zig-zag classifier. The fine material is separated externally by means of a cyclone.

First a premix which consists of 70% by weight of 6-phenyl-4-amino-3-methyl-1,2,4-triazin-5(4H)-one, 5% by weight of alkylarylsulphonate, 5% by weight of ground alumina and 20% by weight of a dispersant based on ligninsulphonate is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 65% by weight. This slurry is sprayed at a temperature of 20° C. by means of air into the fluidised-bed granulator. The continuous granulation is carried out under the conditions indicated hereinafter.

Fluidizing gas:	Air Gas throughput 130 kg/h Entry temperature 96° C. Exit temperature 60° C.
Classifying gas:	Air Gas throughput 8 kg/h Gas temperature 20° C.
Drive gas:	Air Gas throughput 9 kg/h
Granulation output:	24 kg/h

The result is a dust-free free-flowing granulate having a bulk density of

The granulate particles are virtually round. Mean grain size d_{50} =

The granulate is dispersible in water within seconds.

EXAMPLE 5

The apparatus mentioned in Example 1 is used to granulate an aqueous suspension (slurry).

First a pulverulent premix which contains N-(5-ethylsulphonyl-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 60% by weight. This suspension is sprayed into the fluidised-bed granulator by means of atomisation gas. The granulation takes place under the conditions indicated hereinafter.

Fluidizing gas:	Nitrogen Gas throughput 127 kg/h Entry temperature 80° C. Exit temperature 40° C.
Classifying gas:	Nitrogen Gas throughput 9 kg/h Gas temperature 40° C.
Atomisation gas:	Nitrogen Gas throughput 6 kg/h Gas temperature 20° C.
Drive gas return:	Nitrogen Gas throughput 15 kg/h Gas temperature 40° C.

-continued

Granulation output: 3 kg/h

The result is a dust-free free-flowing granulate having a bulk density of 690 kg/m³. Mean particle size d_{50} = 500 μ m.

EXAMPLE 6

The apparatus mentioned in Example 1 is used to granulate an aqueous suspension (slurry).

A pulverulent premix which contains N,N-dimethyl-N'-(fluorodichloro-methylmercapto)-N'-(4-methylphenyl)-sulphamide, is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 60% by weight. This suspension is sprayed into the fluidised-bed granulator by means of atomisation gas. The granulation takes place under the conditions indicated hereinafter.

Fluidizing gas:	Nitrogen Gas throughput 127 kg/h Entry temperature 95° C. Exit temperature 35° C.
Classifying gas:	Nitrogen Gas throughput 11.5 kg/h Gas temperature 40° C.
Atomisation gas:	Nitrogen Gas throughput 6 kg/h Gas temperature 20° C.
Drive gas (return):	Nitrogen Gas throughput 20.8 kg/h Gas temperature 40° C.
Granulation output:	3.8 kg/h

The result is a dust-free free-flowing granulate having a bulk density of 683 kg/m³. Mean particle size d_{50} = 400 μ m.

EXAMPLE 7

The apparatus mentioned in Example 1 is used to granulate an aqueous suspension (slurry).

First a pulverulent premix which contains 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-butan-2-ol is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 50% by weight. This suspension is sprayed into the fluidised-bed granulator by means of atomisation gas. The granulation takes place under the conditions indicated hereinafter.

Fluidizing gas:	Nitrogen Gas throughput 127 kg/h Entry temperature 85° C. Exit temperature 35° C.
Classifying gas:	Nitrogen Gas throughput 11.5 kg/h Gas temperature 35° C.
Atomisation gas:	Nitrogen Gas throughput 6.5 kg/h Gas temperature 20° C.
Drive gas (return):	Nitrogen Gas throughput 19 kg/h Gas temperature 35° C.
Granulation output:	2.5 kg/h

The result is a dust-free free-flowing granulate having a bulk density of 942 kg/m³. Mean particle size d_{50} = 400 μ m.

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EXAMPLE 8

The apparatus mentioned in Example 1 is used to granulate an aqueous suspension (slurry).

First a pulverulent premix which contains 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-butan-2-one is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 60% by weight. This suspension is sprayed into the fluidized-bed granulator by means of atomization gas. The granulation takes place under the conditions indicated hereinafter.

Fluidizing gas:	Nitrogen Gas throughput 127 kg/h Entry temperature 30° C. Exit temperature 29° C.
Classifying gas:	Nitrogen Gas throughput 25 kg/h Gas temperature 40° C.
Atomization gas:	Nitrogen Gas throughput 6 kg/h Gas temperature 20° C.
Drive gas (return):	Nitrogen Gas throughput 10 kg/h Gas temperature 40° C.
Granulation output:	1.5 kg/h

The result is a dust-free free-flowing granulate having a bulk density of 667 kg/m³. Mean particle size d₅₀=500 μm.

EXAMPLE 9

The apparatus mentioned in Example 1 is used to granulate an aqueous suspension (slurry).

First a pulverulent premix which contains N-(2-benzothiazolyl)-N,N'-dimethylurea is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 50% by weight. This suspension is sprayed into the fluidized-bed granulator by means of atomization gas. The granulation takes place under the conditions indicated hereinafter.

Fluidizing gas:	Nitrogen Gas throughput 127 kg/h Entry temperature 35° C. Exit temperature 40° C.
Classifying gas:	Nitrogen Gas throughput 15.5 kg/h Gas temperature 40° C. Gas temperature 40° C.
Atomization gas:	Nitrogen Gas throughput 6 kg/h Gas temperature 20° C.
Drive gas (return):	Nitrogen Gas throughput 21 kg/h Gas temperature 35° C.
Granulation output:	1.3 kg/h

The result is a dust-free free-flowing granulate having a bulk density of 575 kg/m³. Mean particle size d₅₀=1,000 μm.

EXAMPLE 10

The apparatus mentioned in Example 4 is used to granulate an aqueous suspension (slurry).

First a pulverulent premix which contains 97.5% by weight of 4-amino-6-(1,1-dimethylethyl)-3-methylthio-

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1,2,4-triazin-5(4H)-one is mixed with stirring with sufficient water that the result is an aqueous suspension having a solids content of 50% by weight. This suspension is sprayed into the fluidized-bed granulator by means of atomization gas. The granulation takes place under the conditions indicated hereinafter

Fluidizing gas:	Nitrogen Gas throughput 127 kg/h Entry temperature 100° C. Exit temperature 40° C.
Classifying gas:	Nitrogen Gas throughput 11.5 kg/h Gas temperature 40° C.
Atomization gas:	Nitrogen Gas throughput 6.6 kg/h Gas temperature 20° C.
Drive gas (return):	Nitrogen Gas throughput 14.5 kg/h Gas temperature 40° C.
Granulation output:	4.3 kg/h

The result is a dust-free free-flowing granulate having a bulk density of 530 kg/m³. Means particle size d₅₀=450 μm.

What is claimed is:

1. A process for the continuous preparation of granules having a narrow grain size distribution and which grow in a shell-like fashion, comprising
 - (a) upwardly spraying a feed forming product to be granulated in liquid form into a fluidized bed of such granules, the feed consisting essentially of a liquid form, the bed being established within a vessel having an outflow bottom for the passage of granules,
 - (b) maintaining a flow of fluidizing gas such that fine material escaping from the fluidized bed in an off-gas is separated from the off-gas and is returned to the fluidized bed as nuclei for granule formation,
 - (c) forming granules of a predetermined size solely by means of setting a classifying gas flow, and
 - (d) removing the completed granules solely by way of at least one countercurrent gravity classifier disposed in the outflow bottom of the vessel.
2. A process according to claim 1, wherein the product to be granulated is a liquid which contains at least one active component selected from the group consisting of an agrochemical active substance, an active substance for combating pests in the domestic and hygiene areas, a pharmacologically active substance, a nutrient, a sweetener and a dyestuff.
3. A process according to claim 1, wherein the proportion of fine material which escapes from the fluidized bed is continuously cyclone separated from the off-gas and returned to the fluidized bed.
4. A process according to claim 1, wherein the proportion of fine material which escapes from the fluidized bed is continuously filtered out of the off-gas and returned to the fluidized bed.
5. A process according to claim 1, wherein the granules to be discharged are made to travel in a zig-zag path of adjustable length and cross-section, said zig-zag path formed by a plurality of straight rectangular channels which meet at an angle of about 120° .

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Bogotá, D.C.,

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Doctora:
Alicia Lloreda Ricaurte
Apoderada

Oficio N°: 11272

ASUNTO:

Radicación PCT N°	03-78286
Trámite	011
Evento	379
Actuación	440
Folios	011

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 Luis Fernando Rincón Cuellar, 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 Única 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, 18 FEB. 2005.

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