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www.cavelier.com
cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 No. 7
BOGOTÁ 8, COLOMBIA

Teléfono: (57-1) 347 3611

Teléfono: (57-1) 347 3611

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-049473- -00005-0000

Fecha: 2010-03-08 16:34:35 Dep: 2020 DIR.NULVASCR
Tra: 11 PATENTELIYII Lve: 3/3 FASELNACIONAL
Act: 444 RESPULSTARLOUL Fotos: 13

Señora Directora
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 06049473
Asunto : Solicitud de patente para: **PROCEDIMIENTO PARA LA APRODUCCIÓN DE UNA COMPOSICIÓN FARMACÉUTICA SÓLIDA DE ADMINISTRACIÓN ORAL**
Solicitante : BAYER HEALTHCARE AG
Clase : A61K 009/020, A61K 031/5377, A61K 9/20, A61P 007/002
Fecha solicitud: 23 de mayo de 2006

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, de acuerdo con la sustitución del poder a mí otorgada por el doctor Emilio Ferrero, me refiero al oficio No. 202 notificado por fijación en lista del 08 de enero de 2010

2. Mediante oficio No. 202 se puso en conocimiento del solicitante el informe que contiene la solicitud hecha por su Despacho para la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1 Presentación de documentos solicitados

Mediante oficio No. 202 y de acuerdo con las disposiciones del Artículo 46 de la Decisión 486 su Despacho solicita los siguientes documentos:

2.1.1 Lerk, Lagas, Fell, Nauta. (July 1978). "Effect of hydrophilization of hydrophobic drugs on release rate from capsules". *Journal of Pharmaceutical Sciences*. 67(7). 935-939

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- 2.1.2 Lerk, Lagas, Lie-A-Huen, Broersma, Zuurman. (May 1979). "In vitro and in vivo availability of hydrophilized phenytoin from capsules". *Journal of Pharmaceutical Sciences*. 68(5). 634-638.

Con el fin de atender a dicha solicitud, se presenta junto con este memorial copia de los documentos mencionados.

3. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

4. ANEXOS

- Copia del documento Lerk, Lagas, Fell, Nauta. (July 1978). "Effect of hydrophilization of hydrophobic drugs on release rate from capsules". *Journal of Pharmaceutical Sciences*. 67(7). 935-939
- Copia del documento Lerk, Lagas, Lie-A-Huen, Broersma, Zuurman. (May 1979). "In vitro and in vivo availability of hydrophilized phenytoin from capsules". *Journal of Pharmaceutical Sciences*. 68(5). 634-638.
- Copia auténtica de la sustitución de poder efectuada a mi favor por el Doctor Emilio FERRERO.

Señora Directora,

LUZ CLEMENCIA DE PAEZ
LUZ CLEMENCIA DE PAEZ

CC. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-14033-841-024-8

JMS\JMS\ID-166871\WPC14033

No. M-2010-166871\JMS

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WEB SITE: www.cavelier.com
E-MAIL: cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Poderdante : **BAYER HEALTHCARE AG**

Poder conferido el : 06/07/2005

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

Señora Jefe,



EMILIO FERRERO

T.P.A. N° 31.929

C.C. N° 438.019 de Usaquén

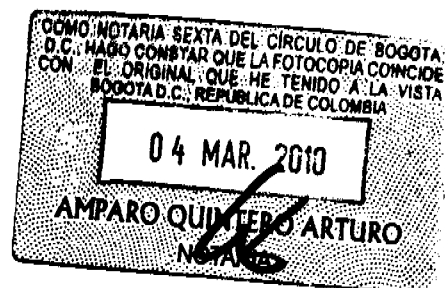
Acepto:



LUZ CLEMENCIA DE PAEZ

T.P.A. N° 23.555

C.C. No. 35.456.344 de Usaquén



NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D.C.

Ante mí AMPARO QUINTERO ARZUZO

22 OCT 2009

NOTARIA SEXTA DEL CÍRCULO DE
BOGOTÁ, D.C.

Comparecido(eron)

Emilio Ferrero
Williamsen y Luz Clemente
Sobres de Rueda

Quien(es) exhibió(aron) la(s) C.C.

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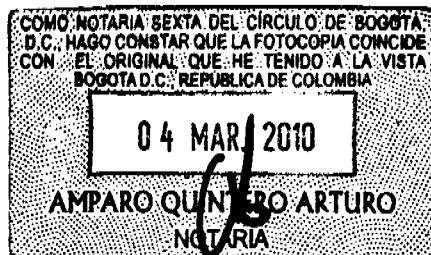
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Y declaró(aron) que la(s) firma(s) que aparece(n)
en el presente documento es(son) la(s) suya(s) y
que el contenido del mismo es cierto.

En constancia se firma esta diligencia.

Emilio Ferrero
Luz Clemente Sobres



Effect of Hydrophilization of Hydrophobic Drugs on Release Rate from Capsules

C. F. LERK*, M. LAGAS, J. T. FELL*, and P. NAUTA

Received May 16, 1977, from the Laboratory for Pharmaceutical Technology, University of Groningen, Antonius Deusinglaan 2, 9713 AW Groningen, The Netherlands. Accepted for publication October 19, 1977. *Present address: Department of Pharmacy, University of Manchester, Manchester M13 9PL, England.

Abstract □ The release of poorly soluble hydrophobic drugs from capsules can be improved significantly by the creation of a hydrophilic surface by intensive mixing of the hydrophobic drug with a small amount of a solution of a hydrophilic excipient. This technique was introduced previously for the production of microgranules. The data presented indicate that the hydrophilic material is mechanically distributed over the hydrophobic surface. The creation of hydrophilic capillaries in a capsule or tablet allowed the rapid penetration of the dissolution fluid, resulting in a dispersion of well-wetted particles, so that the maximum surface area of the powder was exposed to the dissolution medium. Moreover, hydrophilization of hydrophobic drugs has the important benefit that the release rate from capsules is independent of the surface tension of the dissolution medium.

Keyphrases □ Hydrophobic drugs—release rate from capsules, effect of hydrophilization □ Drug release—hydrophobic drugs from capsules, effect of hydrophilization □ Hydrophilization—of hydrophobic drugs, effect on release from capsules

Several methods for increasing the dissolution rate of poorly water-soluble drugs are available (1-4). A common approach is to reduce the drug's particle size to expose a greater surface area to the dissolution medium. This approach is, however, not without difficulties. Reducing the particle size leads to increased particle-particle interactions, and the resulting agglomerates may have an effective surface area smaller than anticipated.

If the drug is hydrophobic, particle-size reduction may give greater problems with wetting and liquid penetration into tablets and capsules. Since liquid penetration is the first step in the disintegration and dissolution of tablets and capsules, the overall process may be penetration rate limited. To overcome these problems, diluents and disintegrants are employed (5, 6), or the fine material may be granulated, which will aid in its wetting and promote liquid penetration (7). However, this method apparently would defeat, to some extent, the original object of size reduction.

In an ideal situation, the drug would be released from the dosage form as discrete, well-wetted particles, so that the maximum surface area afforded by the powder would be exposed to the dissolution medium. For hydrophobic materials, such a situation may be difficult; but it may be possible to achieve if the surface properties of the material are changed from hydrophobic into hydrophilic by coating the hydrophobic particles with a hydrophilic material. Such a coating should aid in the penetration of fluid and the wetting of individual particles but should not unduly retard the dissolution rate of the drug.

Coating of particles may be achieved by fluidization techniques (8-11), but problems may arise if the powder is cohesive. In this study, a technique described by de Jong (12) was used, in which a powder and a small amount of binder solution are mixed intensively in a kneading machine or high-speed mixer. The rigorous mixing inhibits

agglomeration, resulting in a fine free-flowing powder. Although this method was originally developed for microgranule production, it is claimed that the powder is coated with the binding agent, so hydrophobic substances can be rendered hydrophilic. This study applied this technique to increase the dissolution rate of a hydrophobic, relatively insoluble drug from hard gelatin capsules.

EXPERIMENTAL

Materials—Hexobarbital¹ (Ph. Ned. grade) was chosen as the test drug because it is relatively insoluble in water and exhibits a high contact angle of 88° (13). Prior to use, it was ground in a rotor mill² with a 500-μm screen and passed through a centrifugal classifier³ to remove fines with a particle size under 10 μm. The binders chosen were methylcellulose⁴ and hydroxyethylcellulose⁵. Both binders are soluble in water but completely insoluble in alcohol. Hydroxyethylcellulose was passed through a rotor mill² fitted with a 200-μm screen. The milled and classified hexobarbital, methylcellulose, and milled hydroxyethylcellulose exhibited mean particle sizes, based on air permeability measurements⁶, of 17, 30, and 32 μm, respectively.

Methods—*Treatment of Powders*—Dispersion of the binder over the drug surface was carried out in a small high-speed mixer⁷. Hexobarbital (50 g) was placed in the mixer, 3 ml of an aqueous solution of the binder was added, and the mixer was run for either 2 or 4 min at ~9000 rpm. The mixing was interrupted every 0.5 min to mix, with a spatula, material from deadspots in the mixer.

The material was dried in a tray drier at 50° for 1 hr and screened through a 200-μm sieve. Dry-mixed powders of hexobarbital and binder were prepared using a tumbler mixer⁸, running at 90 rpm for 30 min. Hexobarbital was blended with the same amount of methylcellulose or

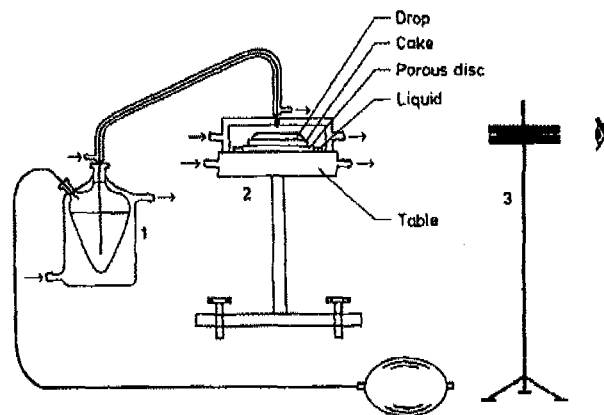


Figure 1—Schematic diagram of the setup for the contact angle measurement. Key: 1, liquid reservoir water jacketed at 23 and 37°; 2, environmental chamber for drop formation; and 3, cathetometer.

¹ Brocacef B. V., Maarsse, The Netherlands.

² Pulverisette 14002, Fritsch, Idar-Oberstein, West Germany.

³ Multiplex 100 MZR, Alpine AG, Augsburg, West Germany.

⁴ Celacel M20, British Celanese Ltd., Derby, England.

⁵ Natrosol 250L, Hercules Inc., Wilmington, Del.

⁶ Model 95, Fisher Scientific Co., Pittsburgh, Pa.

⁷ MX 32, Braun AG, Frankfurt/M., West Germany.

⁸ Turbula, W. A. Bachoven, Basel, Switzerland.

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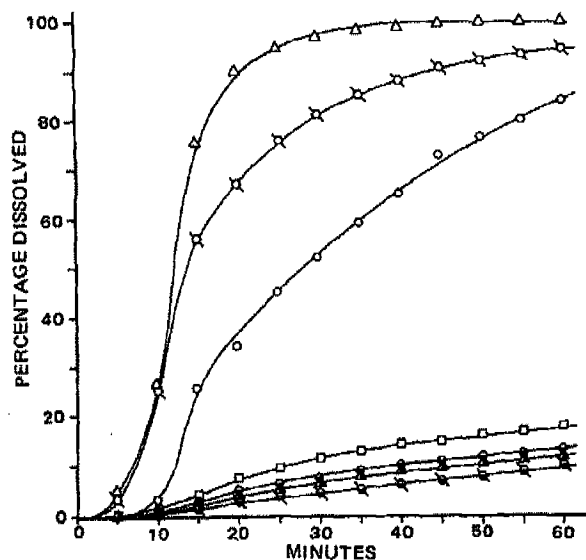


Figure 2—Release from hard gelatin capsules of hexobarbital, untreated, treated, and mixed with methylcellulose. Key: □, untreated; ●, 0.06% physical mix; ▲, 0.18% physical mix; ×, 0.30% physical mix; and ○, △, and ◇, treated for 2 min with 1, 3, and 5% binder solutions, respectively.

hydroxyethylcellulose as was used for the coating procedure of the drug.

Capsule Filling and Dissolution—The pure drug, the treated drug, or the physical mixes of drug and binder were loosely packed by hand (250 mg) into No. 1 hard gelatin capsules⁹, using a manually operated capsule-filling machine¹⁰. No compression of the powder was made.

Dissolution was carried out in a water-jacketed 1-liter beaker containing 900 ml of distilled water maintained at 37°. The capsule was held in a spiral of stainless steel wire, located centrally, 2 cm above the bottom of the beaker. Stirring was achieved with a 5-cm diameter, three-bladed, right-hand propeller, rotating clockwise at 100 ± 1 rpm 3.5 cm above the capsule.

Samples were taken at 5-min time intervals through membrane filters

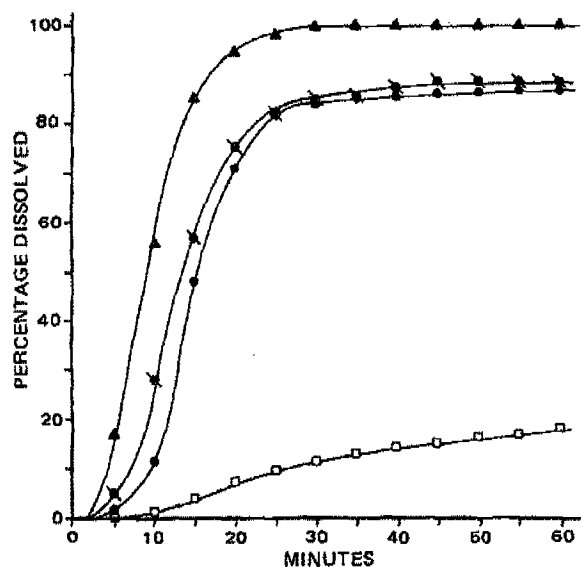


Figure 3—Release from hard gelatin capsules of hexobarbital, untreated and treated with methylcellulose. Key: □, untreated; and ●, ▲, and ×, treated for 4 min with 1, 3, and 5% binder solutions, respectively.

⁹ Snap-fit, Capsugel AG, Basel, Switzerland.
¹⁰ Tevopharm, Schiedam, The Netherlands.

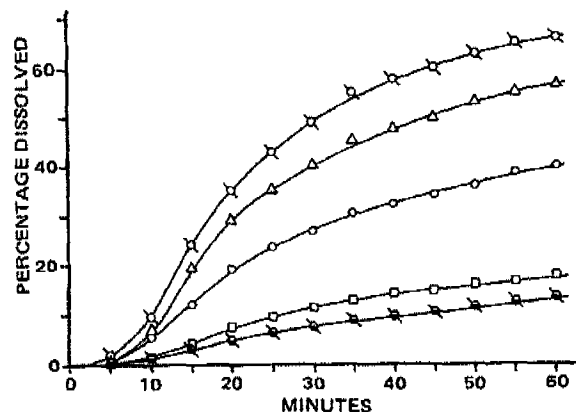


Figure 4—Release from hard gelatin capsules of hexobarbital, untreated, treated, and mixed with hydroxyethylcellulose. Key: □, untreated; ×, 0.30% physical mix; and ○, △, and ◇, treated for 2 min with 1, 3, and 5% binder solutions, respectively.

(0.8-μm pore diameter), diluted with pH 9.2 borate buffer to a buffer concentration of about 0.05 M, and analyzed spectrophotometrically¹¹ at 245 nm for hexobarbital. Corrections were applied for the samples removed. All release studies were based on six dissolution tests and were highly reproducible. Only average values are reported.

Intrinsic Dissolution Rates—Nondisintegrating disks, 13 mm in diameter, were prepared by compressing 500 mg of the powder at a load of 1500 kg for 5 min in a die and punch assembly. The die served as disk holder and allowed only one face of the disk to be exposed to the dissolution medium. The disk holder was attached to a shaft and was rotated at 100 ± 1 rpm in the center of a water-jacketed beaker containing 500 ml of ethanol maintained at 25°. Samples were taken at 10-min intervals, assayed for hexobarbital by dilution with a fivefold amount of 0.05 M borate buffer, and analyzed spectrophotometrically at 245 nm.

Wettability—The wettability of the different powders was characterized by contact angle determinations (13). For this purpose, compacts, 5 cm in diameter, were prepared by compressing about 5 g of the powder at 2000 kg in a die and punch assembly. The compacts were placed on a porous disk partly immersed in the test liquid to saturate the compact, but wetting of the compact surface was avoided (Fig. 1).

As soon as saturation was achieved, the test solution was slowly

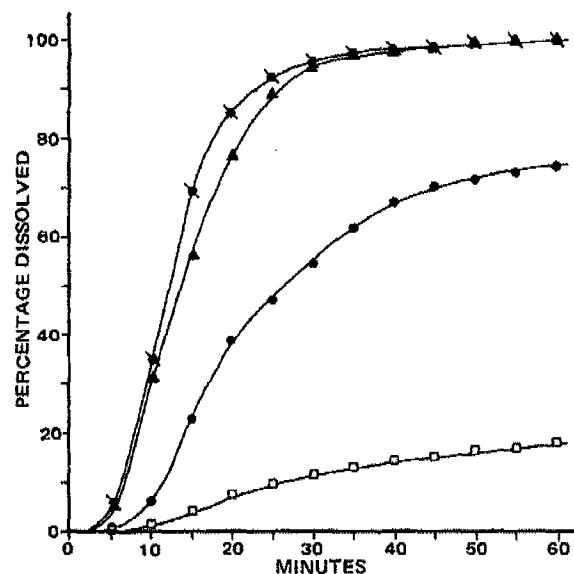


Figure 5—Release from hard gelatin capsules of hexobarbital, untreated and treated with hydroxyethylcellulose. Key: □, untreated; and ●, ▲, and ×, treated for 4 min with 1, 3, and 5% binder solutions, respectively.

¹¹ Model 25, Beckman Instruments Co., Fullerton, Calif.

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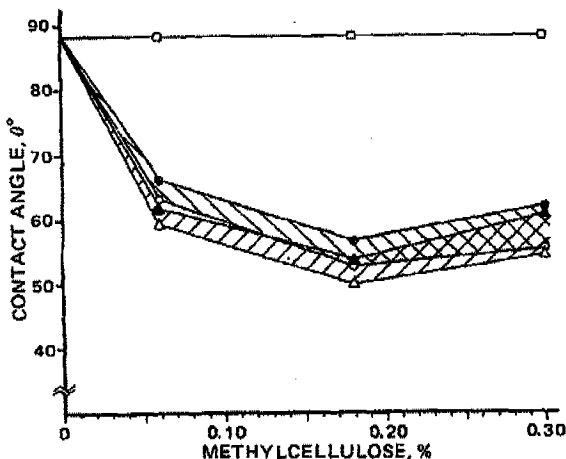


Figure 6—Relation between percentage of methylcellulose and contact angle of hexobarbital, physically mixed or treated with the binder. Key: □, physical mix; ○ and ●, treated for 2 min; △ and ▲, treated for 4 min; ○ and △, with $\gamma_{LV} = 72.4$ dynes/cm; and ● and ▲, with γ_{LV} as given in Table II.

dropped onto the compact surface; readings of the drop height were taken with a cathetometer¹² until additional drops caused no increase in height. The contact angle was then calculated from the appropriate equations as previously derived (14, 15), extended (16), and successfully adopted for pharmaceutical powders (13). All contact angle measurements were performed at least in duplicate. The reproducibility was better than 1° in each case.

Liquid and Solid Properties.—Densities and surface tensions of the liquids and densities of the solids were determined by a balance¹³, a tensiometer¹⁴, and an air comparison pycnometer¹⁵, respectively.

RESULTS AND DISCUSSION

Figure 2 shows the effect of the distribution of methylcellulose over the surface of the hexobarbital powder on the release profile of the drug from hard gelatin capsules. Significantly higher release rates were found for the treated hexobarbital than for the pure drug. The hexobarbital treated with 5% methylcellulose solution released the drug slower than when treated with 3% methylcellulose solution. This effect might be due to a large increase in the viscosity of the binder solution with an increasing methylcellulose concentration but also may be caused by thermal gelation

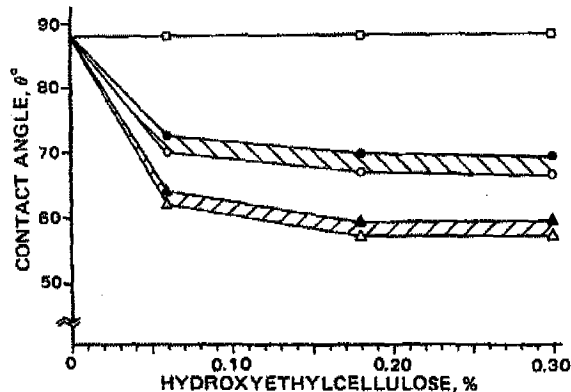


Figure 7—Relation between percentage of hydroxyethylcellulose and contact angle of hexobarbital, physically mixed or treated with the binder. Key: □, physical mix; ○ and ●, treated for 2 min; △ and ▲, treated for 4 min; ○ and △, with $\gamma_{LV} = 72.4$ dynes/cm; and ● and ▲, with γ_{LV} as given in Table II.

¹² Model 70000, Bouty, Paris, France.

¹³ Mohr, G. Kern, Ebingen, West Germany.

¹⁴ Du Nouty, 8800 EEE Krüss, Hamburg, West Germany.

¹⁵ Model 930, Beckman Instruments Ned. N.V., Amsterdam, The Netherlands.

Table I—Contact Angles of Cellulose Polymer Solutions on Hexobarbital Measured at 23°

Methylcellulose			Hydroxyethylcellulose		
Concentration, %	γ_{LV} , dynes/cm	θ , degrees	Concentration, %	γ_{LV} , dynes/cm	θ , degrees
0	72.4	88	0	72.4	88
1	45.6	76	1	62.7	87
3	44.6	76	3	62.5	86
5	44.6	76	5	62.3	86

of the methylcellulose at temperatures near 37° during dissolution (17).

The physical mixes exhibited release rates of the same order of magnitude as the pure drug and even showed a slight decrease in rate with an increasing amount of binder. These results indicate that the degree of distribution of a hydrophilic binder over the surface of a hydrophobic drug affects the release rate from capsules. This conclusion is supported by the results shown in Fig. 3. In this study, the hexobarbital powder was intensively mixed with the binder solutions for 8 × 0.5 min instead of 4 × 0.5 min. Comparison of Figs. 2 and 3 shows increased release rates for the drug treated for the longer period.

Distribution of hydroxyethylcellulose over the surface of the hexobarbital powder and blending of the dry binder with the drug resulted in the release rates from capsules shown in Figs. 4 and 5. The data show slightly lower release rates for the physical mixtures than for the pure drug. The release rate increased, over the range studied, with increasing concentrations of hydroxyethylcellulose and with an increasing degree of distribution.

To characterize the wettability of the pure drug by the binder solutions, contact angle measurements were made. Table I presents the contact angles between hexobarbital and solutions of different concentrations of methylcellulose or hydroxyethylcellulose. The results show a decrease in the contact angle from 88° for distilled water to 76° for solutions containing 1–5% methylcellulose. Almost no difference in contact angle was found over a concentration range of 0–5% for solutions of hydroxyethylcellulose. These results imply that neither binder solution would spread spontaneously on hexobarbital since both contact angles were high.

The input of energy from the mixer can, however, promote spreading of the liquid. The success of this operation depends first on factors affecting the spreading such as mixer efficiency, contact angle, and viscosity and second on whether the film is stable when formed and does not "dewet" from the surface (18). This latter factor may be a complex function of the contact angle and the viscosity of the liquid. These arguments are to some extent borne out by the finding that hydroxyethylcellulose, which exhibited higher contact angles and higher surface tensions than the methylcellulose, required greater mixing times to achieve equivalent effects.

To elucidate the mechanism of the change in release rate from capsules, the wettability of pure drug, treated drug, and physical mixtures of drug and binder was determined by contact angle measurement (Figs. 6 and 7). Both the pure drug and the physical mixtures exhibited contact angles of 88°. High-speed mixing of hexobarbital with methylcellulose or hydroxyethylcellulose solutions resulted in decreased contact angles. The contact angles given were calculated on the basis of the surface tension of distilled water and of the solution in the pores of the compact when the maximum amount of binder was dissolved completely from the drug surface (Table II).

As seen from Fig. 7, distribution of 3 ml of 3% methylcellulose over 50 g of hexobarbital powder, corresponding with a weight percentage of 0.18, decreased the contact angle of the drug from 88° to mean values of about 55 and 52° when treated for 4 × 0.5 and 8 × 0.5 min, respectively. Distribution of 3 ml of 5% methylcellulose over the drug resulted in contact

Table II—Surface Tensions of the Solutions in the Pores of the Compacts When the Binder Has Been Completely Dissolved from the Drug Surface

Weight Concentration of Binder on Drug, % ^a	Surface Tension, dynes/cm	
	Methylcellulose	Hydroxyethylcellulose
0	72.4	72.4
0.06	62.4	64.4
0.18	55.4	62.8
0.30	48.6	62.7

^a Values of 0.06, 0.18, and 0.30% correspond with treatment of 50 g of hexobarbital with 3 ml of 1, 3, and 5% of a binder solution, respectively.

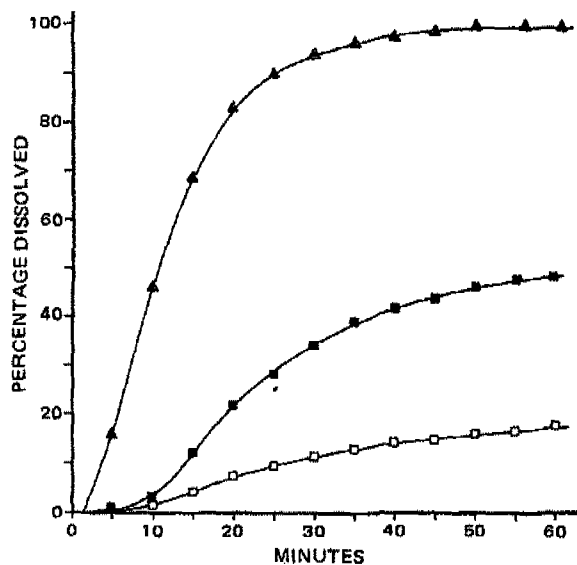


Figure 8—Release from hard gelatin capsules of pure hexobarbital and hexobarbital treated for 4 min with 3% methylcellulose. Key: $\square$, untreated drug in distilled water; $\blacksquare$, untreated drug in 0.14% methylcellulose; and $\blacktriangle$, treated drug in 0.14% methylcellulose.

angles of 59 and 58°, respectively. The slight increase in the contact angle found when the concentration of the methylcellulose solution was increased from 3 to 5% was possibly due to the increased viscosity of the binder solution.

Figure 7 shows the change in the contact angle when the drug was treated with hydroxyethylcellulose. The decrease in the contact angle was smaller, compared with a methylcellulose treatment, whereas the difference in contact angles between the powders treated for 4×0.5 and 8×0.5 min was more pronounced. This result was expected since the hydroxyethylcellulose solution exhibited higher surface tensions and higher contact angles on the drug than the corresponding methylcellulose solutions.

To prove that the increased penetration rates, resulting in increased release rates, were caused primarily by the decreased contact angle of the treated powder and not, or at most to a small extent, to dissolved binder in the pores of the capsule, release rates were measured from capsules filled with pure or treated hexobarbital immersed in water or binder solutions. The concentration of the binder solution was equal to the max-

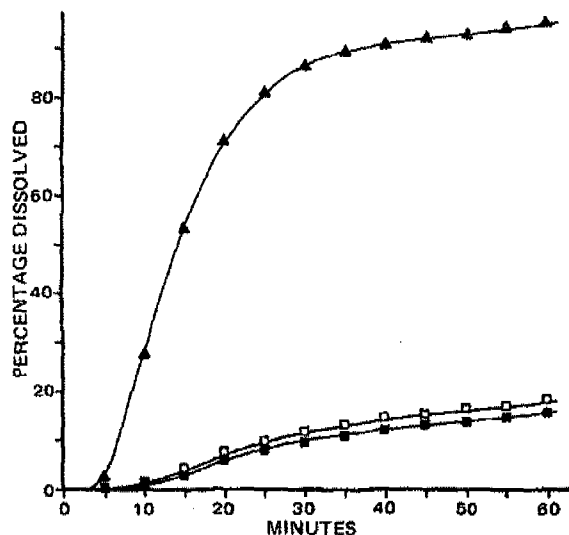


Figure 9—Release from hard gelatin capsules of pure hexobarbital and hexobarbital treated for 4 min with 3% hydroxyethylcellulose. Key: $\square$, untreated drug in distilled water; $\blacksquare$, untreated drug in 0.14% hydroxyethylcellulose; and $\blacktriangle$, treated drug in 0.14% hydroxyethylcellulose.

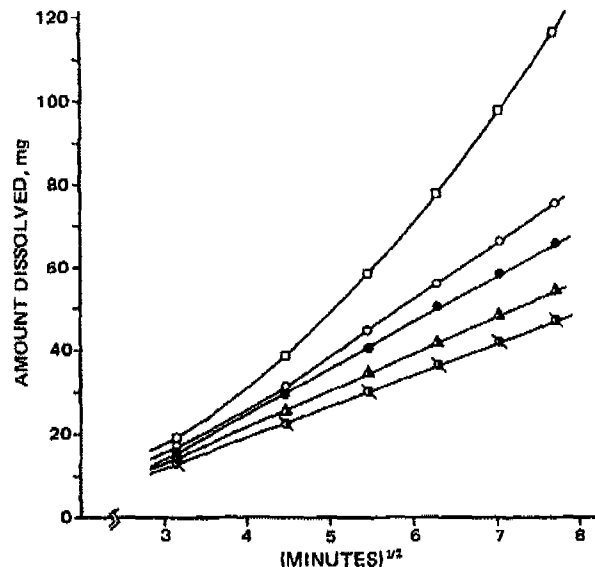


Figure 10—Dissolution in alcohol from rotating disks of hexobarbital, untreated and treated with hydroxyethylcellulose, as a function of the square root of time. Key: $\square$, untreated; $\circ$ and $\bullet$, treated with a 1% binder solution for 2 and 4 min, respectively; $\blacktriangle$, treated with a 3% binder solution for 2 and 4 min, respectively; and $\blacklozenge$, treated with a 5% binder solution for 2 and 4 min, respectively.

imum concentration of binder in the pores of the capsule if all binder had been dissolved from the surface of the treated drug (0.14%). As seen from Fig. 8, the release rate increased when the pure drug was immersed in the methylcellulose solution. The slight decrease in rate observed for the hydroxyethylcellulose solution (Fig. 9) may have been due to a slight increase in solution viscosity. A dramatic increase in release rate was found when the drug had been treated with the binder and immersed in the appropriate binder solution.

To demonstrate the degree of binder distribution over the drug, the intrinsic dissolution rates of the untreated and treated drugs were measured in ethanol to prevent binder dissolution.

The dissolution rates measured are presented in Fig. 10 as the amount dissolved versus the square root of time. The hexobarbital dissolution rates were significantly inhibited on treatment in a high-speed mixer with small amounts of hydroxyethylcellulose solutions. The dissolution rate decreased with increasing mixing times and increasing binder concentrations. A matrix of hydroxyethylcellulose was left when the drug leached out (Fig. 11). The existence of a matrix of hydroxyethylcellulose is consistent with the linear plots obtained when the amount of drug released was plotted as a function of the square root of time (Fig. 10).

The release rate of a strongly hydrophobic drug like hexobarbital from capsules thus can be increased considerably by rendering the hydrophobic surface of the drug hydrophilic. The release rate of a hydrophobic drug from a capsule, however, also can be increased by decreasing the surface tension of the dissolution medium (7). Figure 12 shows the release profiles of pure hexobarbital from capsules immersed in distilled water with varying concentrations of polysorbate 80¹⁶. As expected, increased release rates were obtained with decreasing surface tensions of the dissolution medium.

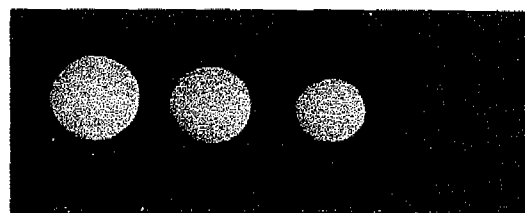


Figure 11—Photograph of a partly leached matrix of hydroxyethylcellulose.

¹⁶ Tween 80, Atlas Chemie, Essen, West Germany.

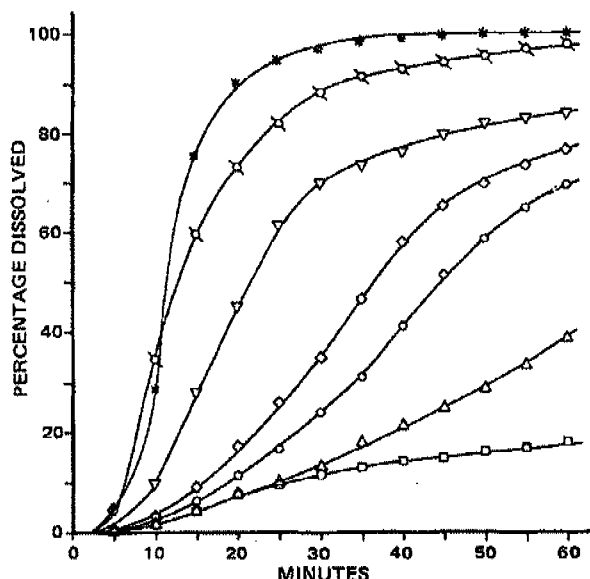


Figure 12—Release profiles of pure and methylcellulose-treated hexobarbital from hard gelatin capsules in water with varying concentrations of polysorbate 80 at 37°. Key: open symbols, untreated drug; □, 0% polysorbate 80 ($\gamma_{LV} = 70.1$ dynes/cm); Δ, 0.01% (45.4 dynes/cm); ○, 0.05% (42.7 dynes/cm); ◇, 0.1% (41.4 dynes/cm); ▽, 0.2% (39.3 dynes/cm); ◻, 0.5% (37.7 dynes/cm); and *, 0.18% binder-treated drug in solutions with 0–0.5% polysorbate 80.

According to Finholt and Solvang (19), the surface tension of human gastric juice is nearly independent of pH and secretion rate, having a value between 35 and 50 dynes/cm. Therefore, a mean surface tension of human gastric juice of 43 dynes/cm would require a concentration of 0.05% polysorbate 80. To compare the release rates of pure and treated drug, the release profiles from capsules of hexobarbital, treated as described with a 3% methylcellulose solution and immersed in dissolution media of varying surface tension, are incorporated in Fig. 12. The results show the

release rate of the treated drug to be independent of the surface tension of the dissolution medium. Because of the aforementioned differences in the surface tension of human gastric juice, the realization of a release rate from capsules that is independent of the surface tension of the medium is of practical importance, especially where absorption is dissolution rate limited.

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ACKNOWLEDGMENTS

The authors thank Mrs. P. Broersma and Mr. K. Zuurman for technical assistance.

Kinetics of Aggregation of Human Platelets

ANWAR B. BIKHAZI** and GHASSAN E. AYYUB

Received May 25, 1977, from the School of Pharmacy, American University of Beirut, Beirut, Lebanon. Accepted for publication November 1, 1977. *Present address: Department of Physiology, School of Medicine, American University of Beirut, Beirut, Lebanon.

Abstract □ A study of the aggregation kinetics of human platelets using an electronic counting device is reported. The experimental data were analyzed quantitatively by a physical model, which assumed that the initial disappearance rate of single platelets *versus* time fitted a second-order type of aggregation with respect to platelet number. The mechanism of aggregation was surface barrier controlled. Thus, the aggregation rate constants in different adenosine diphosphate concentrations (1.5–9.0 μg) were 10–100 times greater than the rate constant ($6.8325 \times 10^{-12} \text{ cm}^3/\text{sec}$) for a diffusion-controlled process as calculated from Smoluchowski's model. Also, the stability constant values, which were equal to unity in a fast diffusion-controlled mechanism, were smaller in the surface-barrier-controlled process and ranged from 0.00741 to 0.0467. The extent of aggregation was indicated by the calculation of a sticking probability constant as determined by the barrier. Adenosine

diphosphate induced a rapid aggregating effect. Prostaglandin E_1 produced the most drastic deaggregating effect as compared to dinoprostone (prostaglandin E_2) and dinoprost (prostaglandin $\text{F}_{2\alpha}$). Aspirin completely blocked the aggregating effect of arachidonic acid.

Keyphrases □ Aggregation, platelet—kinetic study, effect of adenosine diphosphate, various prostaglandins, and arachidonic acid □ Kinetics—human platelet aggregation, effect of adenosine diphosphate, various prostaglandins, and arachidonic acid □ Adenosine diphosphate—effect on human platelet aggregation with and without various prostaglandins, kinetic study □ Prostaglandins, various—effect on human platelet aggregation with and without adenosine diphosphate, kinetic study □ Arachidonic acid—effect on human platelet aggregation with and without aspirin, kinetic study

The origin, morphology, chemical composition, lifespan, and role of some endogenous substances on blood coagulation and platelet aggregation have been reported (1–13).

Nevertheless, very few quantitative and mechanistic studies have been conducted on human platelet aggregation. The present study was an attempt to develop exper-

In Vitro and In Vivo Availability of Hydrophilized Phenytoin from Capsules

C. F. LERK*, M. LAGAS, L. LIE-A-HUEN, P. BROERSMA, and K. ZUURMAN

Received July 31, 1978, from the Laboratory for Pharmaceutical Technology, University of Groningen, Antonius Deusinglaan 2, 9713 AW Groningen, The Netherlands. Accepted for publication November 9, 1978.

Abstract □ The effect of phenytoin hydrophilization on the liquid penetration rate into prepared plugs, on the disintegration time, on the *in vitro* release rate, and on *in vivo* absorption in humans was studied. Hydrophilization was performed by intensive mixing of the hydrophobic drug with a small amount of methylcellulose solution. Liquid penetration into the treated plugs was independent of the liquid wetting potency and extremely high compared to the pure drug plugs. Analogous results were obtained for the disintegration time and *in vitro* release rates from capsules loaded with pure and treated drug. A bioavailability study in seven healthy volunteers showed immediate absorption of the treated drug but a 1-hr absorption lag time for the pure drug.

Keyphrases □ Phenytoin, hydrophilized—*in vitro* and *in vivo* availability from capsules □ Bioavailability—hydrophilized phenytoin, capsule formulation, *in vitro* release rates □ Anticonvulsants—phenytoin, effect of hydrophilization, *in vitro* and *in vivo* availability

When a disintegratable tablet or capsule is administered orally to humans, gastric fluid must penetrate the porous mass before disintegration and absorption can occur. Any factor influencing the penetration rate may influence the absorption rate.

The liquid penetration rate into a porous mass is given by the Washburn (1) equation:

$$\frac{dl}{dt} = \frac{m\gamma \cos \theta}{2l\eta} \quad (\text{Eq. 1})$$

where l is the penetrated length at time t , m is the hydraulic pore radius, γ is the penetrating liquid surface tension, θ is the contact angle between solid and liquid, and η is the liquid viscosity. The penetration rate is strongly dependent on the solid contact angle.

In earlier studies on pharmaceutical powder wettability (2, 3), reported contact angles varied from 0° for dicalcium phosphate dihydrate up to 125° for chloramphenicol palmitate. Recently (4), the effect on the capsule release rate of surface hydrophilic binder distribution over a hydrophobic drug was studied. The increased hydrophilized hexobarbital release rate was independent of the dissolution medium wetting potency, in contrast to the untreated drug.

The purpose of this investigation was to examine the penetration rate effect on the *in vitro* and *in vivo* availability of poorly soluble, hydrophobic drugs from capsules. Phenytoin was selected as a prototype drug, exhibiting a contact angle of 102°. Phenytoin bioavailability is important because of the closeness of the therapeutic and toxic levels. Marked bioavailability differences between different products have been reported (5–9).

EXPERIMENTAL

Materials—Phenytoin¹ was NF grade. The mean particle size, based on air permeability measurement², was 5 µm. Methylcellulose³, poly-

sorbate⁴, β-glucuronidase⁵ (purified lyophilized powder, 5 × 10⁶ units/g), 5-(*p*-methylphenyl)-5-phenylhydantoin⁶, and 5-(*p*-hydroxyphenyl)-5-phenylhydantoin⁶ were used as received. Trimethylanilinium hydroxide⁷ was used as a 0.1 M solution in methanol, and tetramethylammonium hydroxide⁸ was used as a 25% solution in water.

All solvents and other chemicals were analytical grade, except *n*-heptane which was spectrophotometric grade⁹. The methylene chloride used as a mobile phase component in the high-pressure liquid chromatographic (HPLC) procedure was freshly distilled and 50% saturated with water before use.

Methods—Treatment of Drug—Methylcellulose dispersion over the phenytoin surface was carried out in a small high-speed mixer¹⁰. The drug (20 g) was placed in the mixer, 6 ml of a 3% aqueous binder solution was added, and the mixer was run for 6 min at ~9000 rpm. The mixing was interrupted every 0.5 min to mix, with a spatula, material from dead spots in the mixer. The material was dried in a tray drier at 40° for 1 hr and

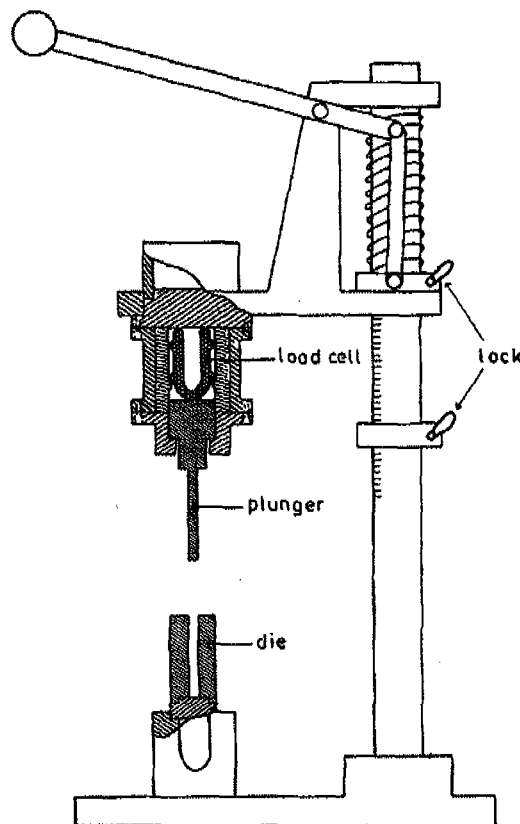


Figure 1—Die and plunger assembly for the plug preparation.

⁴ Tween 80, Atlas Chemie, Essen, West Germany.

⁵ Sigma, St. Louis, Mo.

⁶ Aldrich Europe, Beerse, Belgium.

⁷ B.D.H., Poole, England.

⁸ Serva, Heidelberg, West Germany.

⁹ Merck AG, Darmstadt, West Germany.

¹⁰ MX 32, Braun AG, Frankfurt/M., West Germany.

¹ Parke-Davis, Mijdrecht, The Netherlands.

² Model 93, Fisher Scientific Co., Pittsburgh, Pa.

³ Celacel M20, British Celanese Ltd., Derby, England.

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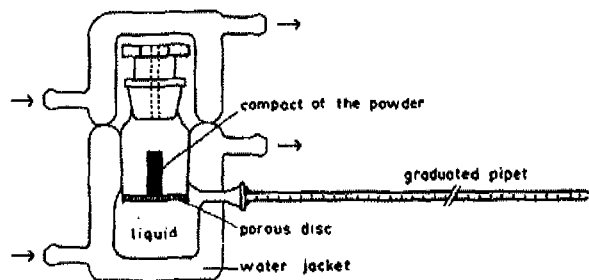


Figure 2—Thermostated apparatus for measuring unidimensional liquid penetration into the plugs.

screened through an 80- μ m sieve. Treated drug particle-size determination (measured value of 6 μ m) and electron micrographs of the untreated and treated powder showed that no milling and hardly any granulation had occurred during preparation.

Wettability.—Pure and hydrophilized phenytoin wettability was characterized by contact angle determination as described previously (4).

Plug Preparation.—Most commercial capsules are filled by compressing the powder and loading it into the capsule body. To reproduce this process, the pure and treated drugs were compressed with a 120 ± 5 N force to 300-mg plugs (1.8-cm length $\times$ 0.6-cm diameter) using a special die and plunger assembly (Fig. 1). The plunger was connected to a load cell for compression force registration.

Capsule Filling.—Prepared plugs were manually loaded into No. 1 hard gelatin capsules¹¹ for the disintegration measurements, the *in vitro* release studies, and the *in vivo* availability studies.

Liquid Penetration.—The unidimensional liquid penetration rate into the phenytoin plugs was measured by placing the plug on a modified thermostated apparatus glass filter plate (Fig. 2) (10). The liquid uptake rate was read from the graduated pipet. The penetrations were carried out at $37 \pm 0.2^\circ$ with distilled water or water to which different amounts of polysorbate had been added.

The all-side liquid penetration was measured at room temperature by registration of the phenytoin plug weight increase during penetration. The powder plug was placed in a small glass cylinder with a porous bottom and a gauze cover to prevent floating (Fig. 3). The whole was immersed in the penetrating liquid and connected to an electronic balance¹² with automatic recording. Unidimensional penetration measurements were made four times and averaged. All-side penetrations were so re-

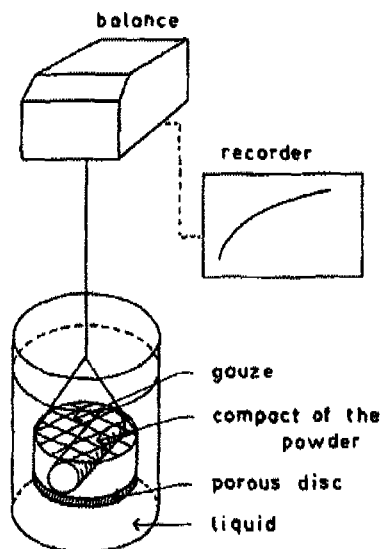


Figure 3—Schematic diagram of the setup for measuring all-side liquid penetration into the plugs.

¹¹ Snap-fit, Capsugel AG, Basel, Switzerland.

¹² PR 1200, Mettler, Greifensee-Zürich, Switzerland.

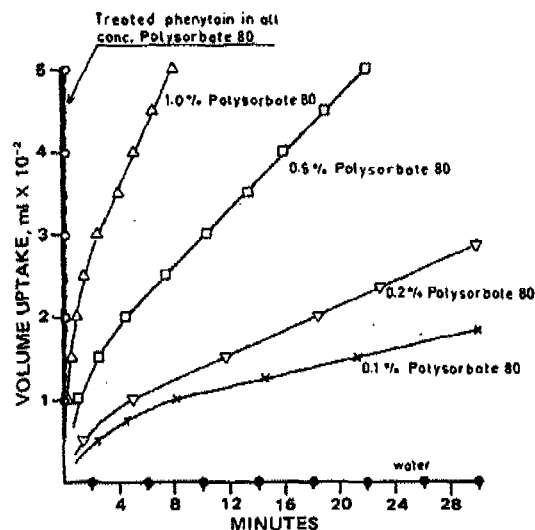


Figure 4—Unidimensional liquid penetration profiles as a function of the polysorbate concentration. Key: $\bullet$, $\times$, ∇ , $\square$, and Δ , penetration of water and 0.1, 0.2, 0.5, and 1.0% polysorbate into plugs of untreated phenytoin, respectively; and $\circ$, penetration of all concentrations of polysorbate into plugs of treated phenytoin.

producable that they were performed in duplicate only. No significant difference in experimental results was found when the penetrating liquid was presaturated with phenytoin.

Disintegration.—The capsule disintegration time was determined according to the BP 1973. Measurements were carried out without disks at $37 \pm 0.5^\circ$ in water with different polysorbate concentrations. Disintegration measurements were made eight times and averaged.

Dissolution and Solubility.—A water-jacketed 1-liter beaker containing the dissolution medium (900 ml) was maintained at $37 \pm 0.5^\circ$. The dissolution medium consisted of water with different polysorbate concentrations (pH < 5.5). The capsule was held in a stainless steel wire spiral located centrally 2 cm above the beaker bottom. Stirring was with a 5-cm diameter straight four-bladed impeller, rotated at 60 ± 1 rpm 3.5 cm above the capsule (11).

Samples were taken at convenient time intervals through membrane filters (0.8- μ m pore diameter) and analyzed by a modified UV spectrophotometric method (12). To a 4.0-ml sample (first diluted, if necessary, with water or the test medium) in a glass-stoppered 25-ml test tube were added 0.5 g of potassium permanganate and 8 ml of 8 N NaOH. After

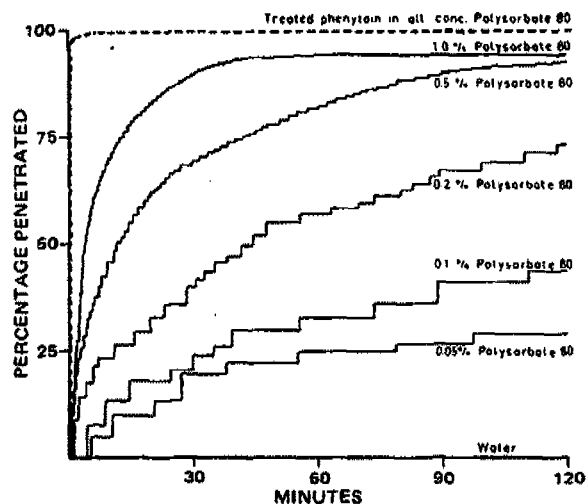


Figure 5—All-side liquid penetration profiles into plugs of treated and untreated phenytoin as function of the polysorbate concentration. Key: —, untreated phenytoin; and ---, treated phenytoin.

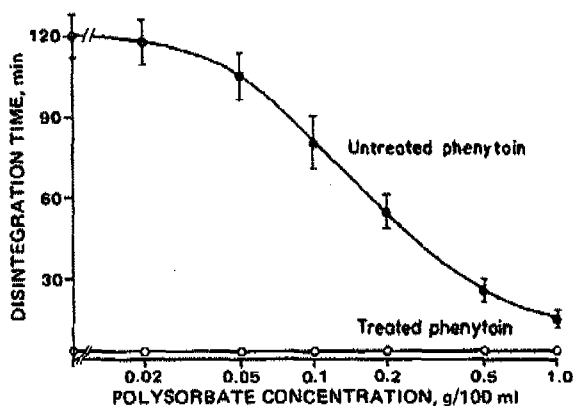


Figure 6—Untreated and treated phenytoin capsule disintegration time as a function of the polysorbate concentration. Key: ● and ○, untreated and treated phenytoin, respectively; and I, standard deviation.

being shaken for several minutes, the tubes were immersed in an 80° water bath for 30 min. The samples were allowed to cool to room temperature, and 5.0 ml of *n*-heptane was added. The mixture was shaken for an additional 15 min; after separation of the two layers, the heptane layer absorbance was measured¹³ at 247 nm against a suitable blank.

Calibration curves showed that Beer's law was obeyed with slopes of 0.017, 0.026, and 0.057 for water and 0.1 and 0.25% polysorbate, respectively. The correlation coefficients were at least 0.999. Each dissolution profile is the average of three to six determinations. The ranges are indicated in the graphs.

The saturated phenytoin solubility in the different solutions was determined by placing excess solute (about 300 mg) in glass vials filled with each test medium. The vials were closed and rotated at 25 ± 1 rpm in a

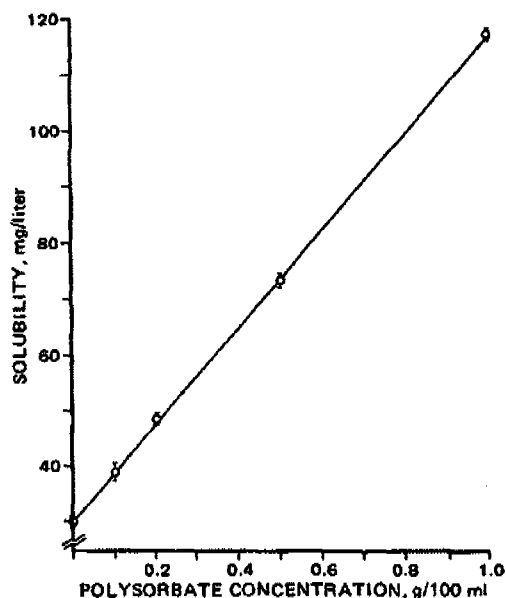


Figure 8—Phenytoin solubility as a function of the polysorbate concentration (I = standard deviation).

water bath at 37 ± 0.5° until no increase in the amount dissolved could be measured. Samples were taken at convenient time intervals through membrane filters and analyzed as described for the dissolution study.

For the dissolution and solubility studies, all glass syringes, pipets, and the filter apparatus were prewarmed to prevent drug precipitation.

Absorption—Absorption studies were carried out with nine healthy

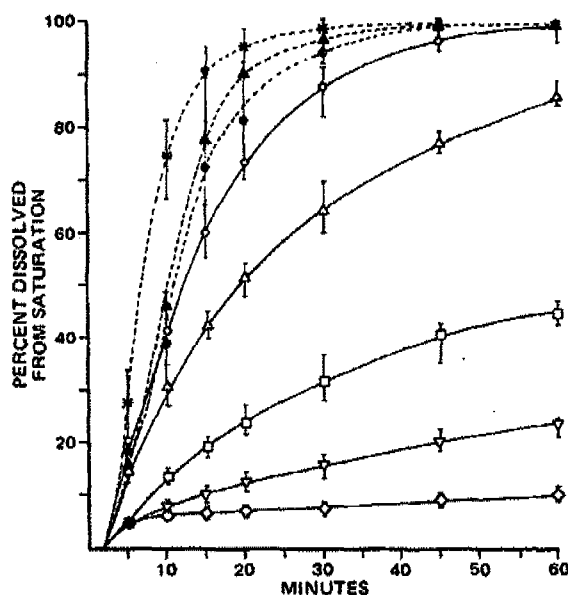


Figure 7—Treated and untreated phenytoin capsule release profiles as a function of the polysorbate concentration. Open symbols are for untreated phenytoin, and solid symbols are for treated drug. Key: ○, 0% polysorbate 80 ($\gamma_{LV} = 70.1$ dynes/cm); ▽, 0.1% polysorbate 80 (39.9 dynes/cm); □, 0.2% polysorbate 80 (38.9 dynes/cm); △, 0.5% polysorbate 80 (37.8 dynes/cm); ○, 1.0% polysorbate 80 (37.7 dynes/cm); *, polysorbate solutions with 0–0.2% polysorbate 80; ▲, polysorbate solution with 0.5% polysorbate 80; ●, polysorbate solutions with 1.0% polysorbate 80; and I, intercapsule variation.

¹³ Model 25 UV spectrophotometer, Beckman Instruments Co., Fullerton, Calif.

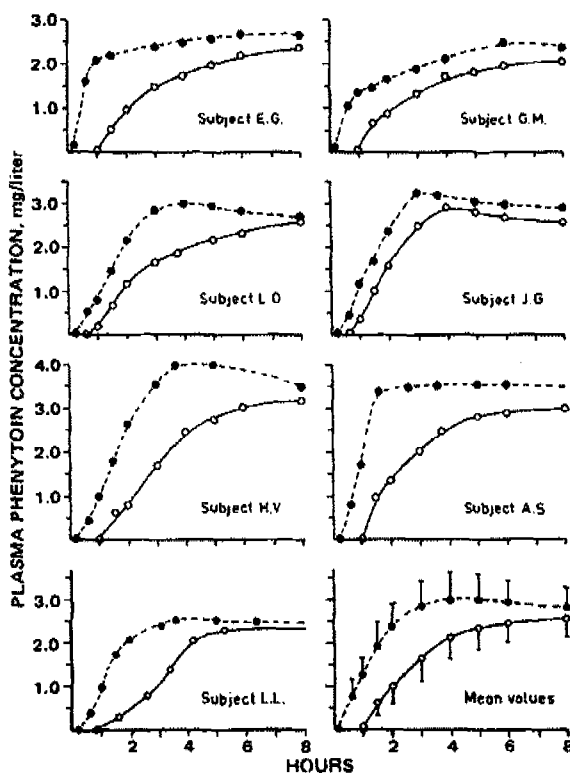


Figure 9—Plasma phenytoin concentration-time curves following oral administration of capsules loaded with 300-mg plugs of treated and untreated drug. Key: ● and ○, treated and untreated phenytoin, respectively; and I, standard deviation.

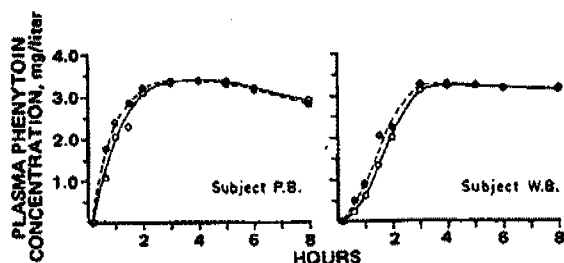


Figure 10—Plasma phenytoin concentration-time curves following oral administration of a capsule loaded with a plug of 300 mg of treated drug and of a suspension of 300 mg of phenytoin in water. Key: ●, capsule; and ○, suspension.

volunteers (66–87 kg, 21–28 years of age). Seven subjects received one capsule (300 mg) of pure phenytoin or one capsule of hydrophilized phenytoin. The two administrations were at least 2 weeks apart. The capsules were taken with 200 ml of water after an overnight fast, and no food was allowed for 4 hr after administration. Two subjects received one capsule with 300 mg of hydrophilized phenytoin; 2 weeks later, they received 300 mg of phenytoin dispersed in water.

Blood samples (8 ml) were taken from a forearm vein at 10, 40, 60, and 90 min and 2, 3, 4, 5, 6, 8, 12, 24, 30, and 48 hr. The heparinized blood samples were centrifuged, and the plasma was stored in a refrigerator until analyzed. Urine was collected at (convenient) time intervals over 48 hr. Volumes were recorded, and samples were refrigerated until assayed.

The plasma phenytoin levels were measured by HPLC¹⁴ according to a method developed for carbamazepine (13). The column was 15 cm × 3 mm (i.d.) stainless steel, packed by a balanced-density slurry technique (14) with 5-μm porous particle silicic acid¹⁵. The solvent system was 5% tetrahydrofuran in methylene chloride. The flow rate was 1.2 ml/min, and the pressure required was ~10 MPa (1500 psi). Nitrazepam was the internal standard. The absorbance¹⁶ was measured at 254 nm. The mean recovery from plasma was 95% with a relative standard deviation of ±2.5% (*n* = 32). The relative standard deviation of the calibration graph data down to 0.4-μg of phenytoin/ml of plasma did not exceed ±3% (*n* = 7).

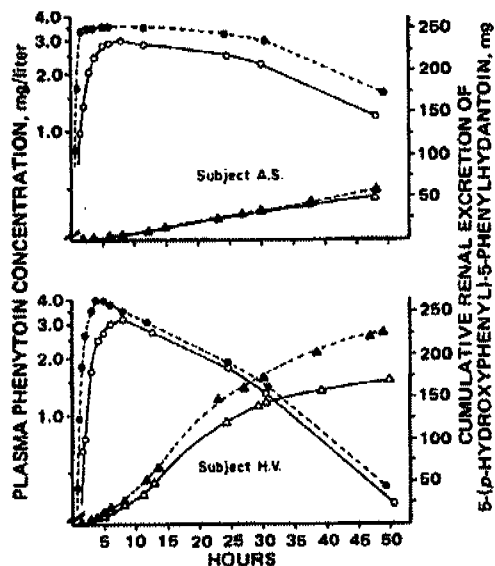


Figure 11—Plasma phenytoin concentration-time curves and cumulative renal excretion of the total amount of 5-(p-hydroxyphenyl)-5-phenylhydantoin following oral administration of 300-mg treated and untreated phenytoin capsules. Key: ● and ▲, plasma and urine after the treated drug, respectively; and ○ and △, plasma and urine after the untreated drug, respectively.

¹⁴ Model M-6000 B, Waters Associates, Milford, Mass.

¹⁵ Partail, Chrompack, Middelburg, The Netherlands.

¹⁶ Model 440, Waters Associates, Milford, Mass.

5-(p-Hydroxyphenyl)-5-phenylhydantoin and its conjugate, the main phenytoin metabolite in humans (15, 16), were assayed in the urine by a modified GLC method (17). To 1.0 ml of urine were added 0.5 ml of 0.066 M phosphate buffer (pH 6.9) and 250 units of β-glucuronidase. The samples were incubated for 15 hr at 37°. To the hydrolyzed samples were added 100 μl of an internal standard solution [50 μg/ml of 5-(p-methylphenyl)-5-phenylhydantoin in 0.01 N NaOH] and 1 ml of 3 M phosphate buffer (pH 4.5). After extraction with 8 ml of ether for 15 min and centrifugation, 7 ml of the organic phase was transferred to another test tube. Then 40 μl of 0.1 M trimethylanilinium hydroxide dissolved in methanol and 40 μl of 0.54 M tetramethylammonium hydroxide dissolved in water were added, and the tube was shaken for 10 min.

After centrifugation, 1 μl of the lower phase was injected into a gas chromatograph¹⁷ equipped with a flame-ionization detector. The coiled glass tubing column, 1.5 m long × 2.2 mm i.d., was packed with 3% OV-17 on 80–100-mesh Chromosorb G.H.P. Operating conditions were: injection port, 300°; column oven, 240°; and detector, 275°. The nitrogen flow rate was 20 ml/min. Hydrogen and compressed air flow rates were adjusted to give maximum response. The relative standard deviation of the calibration graph data down to 15 μg of 5-(p-hydroxyphenyl)-5-phenylhydantoin/ml of urine did not exceed ±4% (*n* = 9).

All plasma and urine samples were analyzed in duplicate.

Liquid Properties—Liquid surface tensions and viscosities were determined with a tensiometer¹⁸ and a capillary tube viscometer¹⁹.

RESULTS AND DISCUSSION

In Fig. 4, the distilled water and polysorbate 80 solution uptakes into pure and hydrophilized phenytoin plugs are graphed against penetration time. As expected, no distilled water penetration into plugs of nontreated drug could be detected because of the strongly hydrophobic nature of the solid and the distilled water surface tension (70.1 dynes/cm at 37°). Addition of 0.1% polysorbate 80 to the penetrating liquid produced a measurable volume uptake. The penetration rate increased with increasing surfactant, decreasing the penetrating liquid surface tension to 37.7 dynes/cm at a 1% concentration.

The wetting of a powder mass by a liquid containing a surfactant is a dynamic process during which surfactant monomers are adsorbed on the substrate. The surfactant micelles are broken down to monomers, which diffuse to the liquid-solid interfaces. During the dynamic penetration process, the micelle breakdown in the capillaries may result in a micelle diffusion from the bulk of the solution into the pores of the mass. In this case, the wetting potency is not limited by the critical micelle concentration [polysorbate 80 = 0.04% (w/v) at 37°]. This is consistent with the theory (18) that micelle diffusion and breakdown will be the rate-limiting steps.

Since the penetration rate into a porous mass is, according to the Washburn equation, strongly dependent on the contact angle of the solid, the extremely hydrophobic phenytoin, exhibiting a contact angle of 102°, was hydrophilized by hydrophilic binder distribution over the solid surface. Methylcellulose treatment decreased the contact angle to 51°. The penetration rate into the hydrophilized phenytoin plugs was strongly increased (Fig. 4). The extremely fast penetration rate was independent of the penetrating liquid wetting potency.

The all-side penetration profiles are represented in Fig. 5. Again no penetration of distilled water into pure phenytoin plugs could be detected. Addition of polysorbate 80 to distilled water resulted in penetrations that increased with increasing surfactant concentrations. The steps in the recorded curves were caused by air bubbles escaping from the porous mass. The hydrophilized phenytoin plugs exhibited instant uptake, which was again independent of the penetrating liquid wetting potency.

The effect of drug hydrophilization on the disintegration of capsules loaded with 300-mg plugs of phenytoin is shown in Fig. 6. The untreated drug capsule disintegration time was 2 hr in distilled water. The disintegration time decreased with increasing surfactant concentration down to 15 min at 1% polysorbate 80. The hydrophilized phenytoin capsules all exhibited, independent of the polysorbate 80 concentration, disintegration times of 3 min, corresponding with the time in which enough of the gelatin had dissolved to open the capsule shell completely.

Analogous results were obtained for the hydrophilization effect on the *in vitro* phenytoin release rate from the different capsules (Fig. 7). The results are expressed as the percentage dissolved from saturation against time. A strong increase in the percentage dissolved for the nontreated

¹⁷ Model 5750, Hewlett-Packard, Avondale, Pa.

¹⁸ Du Nöuy, 8600 EE, Krüss, Hamburg, West Germany.

¹⁹ Type Ubbelohde, Tamson, Zoetermeer, The Netherlands.

Table I—Area under the Curves for Seven Volunteers after Administration of Capsules Loaded with 300-mg Plugs of Pure or Hydrophilized Phenytoin

Subject	AUC, mg min/ liter, 0-8 hr		AUC, mg min/ liter, 0-48 hr	
	Untreated Drug	Treated Drug	Untreated Drug	Treated Drug
A.S.	995	1337	6336	8452
G.M.	873	905	4760	6075
J.G.	991	1192	4184	5324
L.O.	781	1109	4833	5103
E.G.	713	1098	4187	4783
H.V.	943	1447	4821	5661
L.L.	693	1096	—	5194
Mean	827	1169	4853	5900
SD	145	178	787	1328
p ^a	<0.001		<0.01	

^a Evaluated with the Student test for paired observations.

drug was found, along with a slight decrease for the treated drug with increasing surfactant concentrations. The slight decrease in the percentage dissolved from saturation corresponds with an absolute increase in the amount dissolved because of the increased phenytoin solubility with an increasing polysorbate 80 concentration. The latter was due to the strongly solubilizing surfactant (Fig. 8).

Comparative absorption studies were performed in humans. In Fig. 9, all of the individual and the mean plasma curves are given for two capsule preparations loaded with 300 mg of either pure or hydrophilized phenytoin. The plasma levels for all individuals were significantly higher for the treated phenytoin than for the pure drug. Moreover, phenytoin absorption from capsules with untreated drug showed an ~1-hr lag time whereas the hydrophilized drug was absorbed immediately. The area under the plasma level-time curve, evaluated by the trapezoidal rule from 0 to 8 and 0 to 48 hr, showed higher values for the hydrophilized powder than for the pure drug (Table I) ($p < 0.01$).

In two subjects, absorption profiles were compared following oral administration of a 300-mg hydrophilized drug capsule and of a 300-mg phenytoin/200 ml of water suspension (Fig. 10). Nearly identical plasma curves were obtained. The areas under the plasma concentration-time curves from 0 to 8 hr for the capsule and the suspension were 1394 and 1357 mg min/liter for one subject and 1251 and 1244 mg min/liter for the other, respectively. Differences between the areas from 0 to 48 hr after administration were similar.

The total amount of the hydroxylated phenytoin metabolite in the urine over 48 hr is shown in Fig. 11 together with the plasma drug levels in two subjects after pure and hydrophilized drug administration. The results showed remarkable intersubject variation in excretion rates and could not be used to predict relative drug absorption rates from different preparations.

These availability studies are based only on a comparison of hydrophilized drug with pure strongly hydrophobic drug without any adjuvants (i.e., disintegrating agents).

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ACKNOWLEDGMENTS

The authors thank Parke-Davis for phenytoin. They thank Mr. P. Bouma, Laboratory of Hospital Pharmacy, Mr. J. Visser, Laboratory of Pharmacotherapy and Dispensing, and Mr. D. Smith, Laboratory of Pharmacognosy, for their technical advice. These laboratories of the University of Groningen are acknowledged for providing their facilities. The medical supervision in the *in vivo* experiments of Dr. Wesseling, Department of Clinical Pharmacology, State University, Groningen, The Netherlands, is also gratefully acknowledged.

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Señora Directora
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 06049473
Asunto : Solicitud de patente para: **PROCEDIMIENTO PARA LA APRODUCCIÓN DE UNA COMPOSICIÓN FARMACÉUTICA SÓLIDA DE ADMINISTRACIÓN ORAL**
Solicitante : BAYER HEALTHCARE AG
Clase : A61K 009/020, A61K 031/5377, A61K 9/20, A61P 007/002
Fecha solicitud: 23 de mayo de 2006

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, de acuerdo con la sustitución del poder a mí otorgada por el doctor Emilio Ferrero, me refiero al oficio No. **201** notificado por fijación en lista del 08 de enero de 2010.

2. Mediante oficio No. **201** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1 Excepciones a la patentabilidad y usos

El Examinador ha objetado las reivindicaciones 19 y 20 por encontrarse relacionadas con usos. Asimismo, ha objetado la reivindicación 21 por referirse a un procedimiento para la prevención o tratamiento de enfermedades tromboembólicas.

3. Con el fin de subsanar las objeciones expuestas, se desean presentar las siguientes modificaciones:

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3.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 18 reivindicaciones.

De esta manera, siguiendo las observaciones del Examinador, se han eliminado las reivindicaciones 19, 20 y 21 del pliego reivindicatorio.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. ANEXOS

- Nuevo pliego reivindicatorio conformado por 18 reivindicaciones
- Formulario de modificaciones en solicitud pendiente
- Recibo por concepto de presentación de ocho reivindicaciones adicionales a la décima por valor de \$208.000
- Copia auténtica de la sustitución de poder efectuada a mi favor por el Doctor Emilio FERRERO.

Señora Directora,

Luz Clemencia de Paéz
LUZ CLEMENCIA DE PAEZ

CC. 35.456.344 de Usaquén

T.P.A. No. 23.555



Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BAYER CROPSCIENCE AG Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Leverkusen 51368, Alemania Domicilio: Leverkusen, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: LUZ CLEMENCIA DE PÁEZ Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax: 211 86 50 E-mail: clientes@cavelier.com Domicilio: Bogotá, Colombia.	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>35.456.344</u> T. P. <u>23.555</u>
4	Número de expediente: <u>06.049.473</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 18 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.	
6	Comprobante de pago No. <u>10-16.032</u> Fecha: <u>1 de marzo de 2010</u> <u>10-16.811</u> <u>3 de marzo de 2010</u> <u>10-16.826</u> <u>3 de marzo de 2010</u>	
7	Anexos ☐ Comprobante de pago de la tasa por \$114.000, por concepto de modificaciones. ☒ Comprobante de pago por 8 reivindicaciones adicionales después de la décima reivindicación por \$208.000.00. ☐ Poderes, si fuere el caso ☒ Copia auténtica de la Sustitución del poder otorgada por el Doctor EMILIO FERRERO a mi favor, para lo cual solicito me sea reconocida personería y así continuar con el trámite de la presente solicitud de patente.	

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NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA: Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén T.P.A. 23.555

JMS

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CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

WEB SITE: www.cavelier.com
E-MAIL: cavelier@cavelier.com

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Poderdante : **BAYER HEALTHCARE AG**

Poder conferido el : 06/07/2005

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

Señora Jefe,



EMILIO FERRERO

T.P.A. N° 31.929

C.C. N° 438.019 de Usaquén

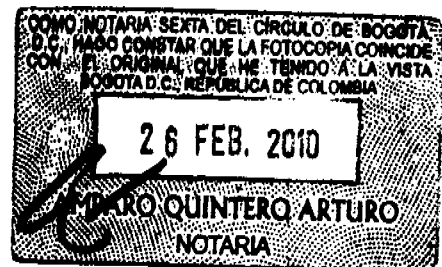
Acepto:



LUZ CLEMENCIA DE PAEZ

T.P.A. N° 23.555

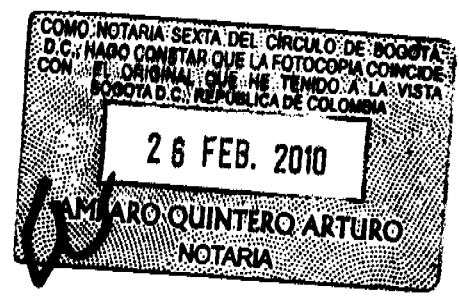
C.C. No. 35.456.344 de Usaquén



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NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. **22 OCT 2009**
Ante mí **AMPARO QUINTERO ARZUAGA**
NOTARIA SEXTA DEL CÍRCULO DE
BOGOTÁ, D.C.
Comparecieron **Emilio Ferrero**
Williams y Luz Clemencia
Sobres de Ríos
Quien(es) exhibió(aron) la(s) C.C.
CC 438019 TP 31929
CC 35456344 TP 23555
Y declaró(aron) que la(s) firma(s) que aparece(n)
en el presente documento es(son) la(s) suya(s) y
que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

Emilio Ferrero
Luz Clemencia Sobres



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REIVINDICACIONES

1. Un procedimiento para la producción de una composición farmacéutica sólida de administración oral que contiene 5-cloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida (I) en forma hidrofilizada, caracterizado porque
 - (a) en primer lugar se produce, mediante granulación húmeda, un granulado que contenga el principio activo (I) en forma hidrofilizada
 - (b) y luego, el granulado, dado el caso con adición de aditivos farmacéuticos adecuados, se transforma en la composición farmacéutica.
2. Un procedimiento según la reivindicación 1, caracterizado porque para el procedimiento para la granulación húmeda se utiliza la granulación en lecho fluidizado.
3. Un procedimiento según la reivindicación 1 ó 2, caracterizado porque el principio activo (I) se utiliza en forma cristalina.
4. Un procedimiento según la reivindicación 3, caracterizado porque el principio activo (I) se utiliza en forma micronizada.
5. Un procedimiento según una de las reivindicaciones de la 1 a la 4, caracterizado porque el principio activo (I) se incorpora en la granulación húmeda suspendido en el líquido de granulación.
6. Un procedimiento según una de las reivindicaciones de la 1 a la 5, caracterizado porque la composición farmacéutica es un comprimido de liberación rápida del principio activo (I).
7. Una composición farmacéutica sólida de administración oral que se produce mediante el procedimiento acorde a la reivindicación 1.
8. Una composición farmacéutica sólida de administración oral que contiene 5-cloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida (I) en forma hidrofilizada.
9. Una composición farmacéutica, según la reivindicación 8, que contiene el principio activo (I) en forma cristalina.
10. Una composición farmacéutica según la reivindicación 9, que contiene el principio activo (I) en forma micronizada.

11. Una composición farmacéutica según una de las reivindicaciones de la 7 a la 10, caracterizada porque el principio activo (I) está presente en una concentración del 1 al 60%, referida a la masa total de la formulación.
12. Una composición farmacéutica según una de las reivindicaciones de la 7 a la 11, que contiene laurilsulfato de sodio como humectante.
13. Una composición farmacéutica según la reivindicación 12, que contiene laurilsulfato de sodio en una concentración del 0,1 al 5%, referida a la masa total.
14. Una composición farmacéutica, según una de las reivindicaciones de la 7 a la 13, que contiene hidroxipropilmetil celulosa como aglutinante hidrófilo.
15. Una composición farmacéutica según la reivindicación 14, que contiene hidroxipropilmetil celulosa en una concentración del 1 al 15%, referida a la masa total.
16. Una composición farmacéutica según una de las reivindicaciones de la 7 a la 15, en forma de comprimido.
17. Una composición farmacéutica según la reivindicación 16, en forma de comprimido de liberación rápida.
18. Una composición farmacéutica según la reivindicación 16 ó 17, caracterizada porque la pastilla está recubierta con un esmalte.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 10 - 14,811
FECHA : MARZO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-049473- -00006-0000

Fecha: 2010-03-09 15:50:59 Dep: 2020 DIR NULVASCOR
Tra: 11 PATENTILYII Lve: 378 FASI NACIONAL
Act: 444 RLSPULSTARLQUE Folios: 9

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VAL. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062704387	176773822	03/03/2010	39,748,000.00

***** CONCEPTO *****

CANT.	PERIOTIDOS	CONCEPTO	TOTAL CONCEPTO
1	00005-01-09	OTROS SERVICIOS DE PROPIEDAD I	21 CERTIFICACIONES
			10,000.00
TOTAL :			10,000.00

SON: TRECE MIL PESOS

RESPONSABLE :

[Handwritten signature]

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

COLO : 14033 - 841 - 024 - 8