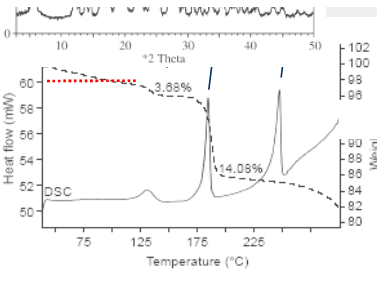

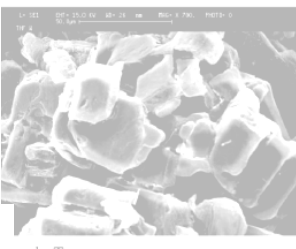




Patenteabilidade de Polimorfos: Algumas Questões Relevantes



Altivo Pitaluga Jr.
LAPOLC - Fortaleza
Outubro de 2007



nple T


Altivo Pitaluga Jr.


Os polimorfos são de grande valia para as empresas do setor farmacêutico, visto que eles podem possibilitar insumos com características diferenciadas, modificações no processo produtivo e medicamentos de melhor qualidade.


Altivo Pitaluga Jr.




OS POLIMORFOS:

Û SÃO FASES CRISTALINAS DISTINTAS DE
UMA SUBSTÂNCIA

POLIMORFISMO

Definição ICH

“ The occurrence of different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. ”

Specifications: Test Procedures & Acceptance
Criteria for New Drug Substances and New Drug
Products: Chemical Substances Q6A; ICH; 1999

ASPECTOS QUE DEVEM SER DISCUTIDOS PELOS SETORES INTERESSADOS NA ÁREA PATENTÁRIA

ü ECONÔMICOS

ASPECTOS ECONÔMICOS

ü Destaca-se o fato de que grande parte dos depósitos são realizados pela própria empresa detentora do registro do medicamento inovador, visando, principalmente, o bloqueio e o retardamento da entrada de medicamentos genéricos no mercado.

ü ...

ASPECTOS QUE DEVEM SER DISCUTIDOS PELOS SETORES INTERESSADOS NA ÁREA PATENTÁRIA

ü ECONÔMICOS

ü POLÍTICOS

ASPECTOS POLÍTICOS

ü Destaca-se o estabelecimento do nível de exigência das normas que regulam a área patentária do País, com base nas políticas e interesses nacionais.

ü ...

**ASPECTOS QUE DEVEM SER DISCUTIDOS
PELOS SETORES INTERESSADOS NA ÁREA
PATENTÁRIA**

ü ECONÔMICOS

ü POLÍTICOS

ü TÉCNICOS

SOCIAL



Altivo Pitaluga Jr.



**EM MUITAS OCASIÕES, OS DOCUMENTOS
DA ÁREA PATENTÁRIA QUE EXPLORAM
OS POLIMORFOS SÃO ESCRITOS
PRIVILEGIANDO A VISÃO DE UM QUÍMICO
SINTÉTICO, DEIXANDO EM SEGUNDO
PLANO AS INFORMAÇÕES PERTINENTES
AO ESTADO SÓLIDO DA MATÉRIA.**



Altivo Pitaluga Jr.



**É UM CONTRA-SENSO AS PATENTES QUE
VERSAM SOBRE O POLIMORFISMO NÃO
ABORDAREM O ESTADO SÓLIDO DA
MATÉRIA DE FORMA ADEQUADA, POIS OS
OBJETOS DAS INVENÇÕES SÃO
PROCESSOS E PRODUTOS RELACIONADOS
A ESTA ÁREA DA CIÊNCIA.**



Altivo Pitaluga Jr.



**EXISTEM DOCUMENTOS QUE NÃO
CARACTERIZAM OS SEUS PRODUTOS
DE FORMA ADEQUADA.**



Altivo Pitaluga Jr.



In accordance with the present invention, there is provided a novel crystalline form of efavirenz, designated as form H1, characterized by an x-ray powder diffraction spectrum

We claim:

12. A crystalline efavirenz form H1, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.4, 10.4, 11.6, 12.5, 15.3, 20.1, 20.8, 22.5, 23.1, 25.7, 27.9, 28.5, 28.8, 29.5, 30.2 and 38.2 degrees.
13. A crystalline efavirenz form H1 as defined in claim 12, further characterized by a x-ray powder diffraction spectrum as in figures 2.

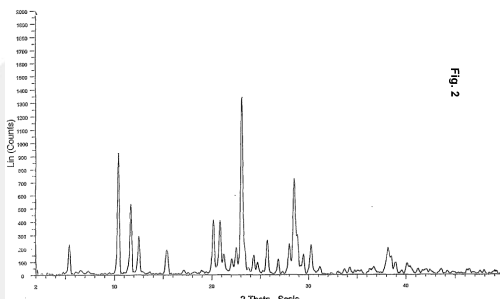


Fig. 2

WO 2006/018853



Altivo Pitaluga Jr.



Step D: (-)
6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726, Compound 37.2)

6-chloro-1-(1S)-camphanoyl-4-cyclopropylethynyl-4-trifluoromethyl-1,2-dihydro-4(H)-3,1-benzoxazin-2-one (7.50 g, 0.01512 mol) was dissolved in 150 mL of n-butanol at 60° C. under an atmosphere of argon. To this solution was added 10 mL of 1N HCl. This solution was maintained at 60° C. for 72 h. The mixture was neutralized with aqueous NaHCO₃ and the n-butanol was removed in vacuo. The residue was dissolved in 150 mL of THF and treated with 50 mL of 2N LiOH for 3 h at room temperature. This mixture was diluted with ethyl acetate and washed with two portions of water and one of brine. Drying (MgSO₄), filtration and removal of the solvent in vacuo gave a white solid. This material was recrystallized from hot hexane to give 3.43 g of (-) 6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as white crystals., m.p. 131°–132° C.; [α]_D²⁰ = -84.7° (CHCl₃, c=0.005 g mL⁻¹); ¹H-NMR (CDCl₃): 80.85 (m, 2H), 0.94 (m, 2H), 1.40 (m, 1H), 6.81 (d, J=8.5 Hz, 1H), 7.37 (dd, J=2.5, 8.5 Hz, 1H), 7.49 (d, J=2.5 Hz, 1H), 8.87 (br s, 1H).

crystal
branco

Caracterização:

- Ponto de fusão
- Rotação específica
- ¹H-RMN (CDCl₃)
sem apresentação do espectro

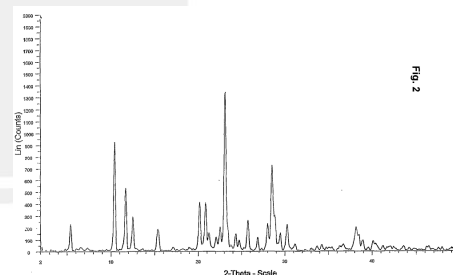


Fig. 2

US 5,519,021

WO 2006/018853



Altivo Pitaluga Jr.



Step D: (-)
6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-
1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726,
Compound 37.2)

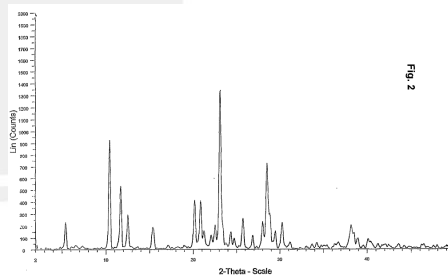
6-chloro-1-(1S)-camphanoyl-4-cyclopropylethynyl-4-trifluoromethyl-1,2-dihydro-4(H)-3,1-benzoxazin-2-one (7.50 g, 0.01512 mol) was dissolved in 150 mL of n-butanol at 60° C. under an atmosphere of argon. To this solution was added 10 mL of 1N HCl. This solution was maintained at 60° C. for 72 h. The mixture was neutralized with aqueous NaHCO₃ and the n-butanol was removed in vacuo. The residue was dissolved in 150 mL of THF and treated with 50 mL of 2N LiOH for 3 h at room temperature. This mixture was diluted with ethyl acetate and washed with two portions of water and one of brine. Drying (MgSO₄), filtration and removal of the solvent in vacuo gave a white solid. This material was recrystallized from hot hexane to give 3.43 g of (-) 6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as white crystals., m.p. 131°-132° C.; [α]_D²⁰ = -84.7° (CHCl₃, c=0.005 g mL⁻¹); ¹H-NMR (CDCl₃): δ 0.85 (m, 2H), 0.94 (m, 2H), 1.40 (m, 1H), 6.81 (d, J=8.5 Hz, 1H), 7.37 (dd, J=2.5, 8.5 Hz, 1H), 7.49 (d, J=2.5 Hz, 1H), 8.87 (br s, 1H).

cristal
branco

Caracterização:

- Ponto de fusão
- Rotação específica
- ¹H-RMN (CDCl₃)
sem apresentação
do espectro

QUAL A PUREZA QUÍMICA
DO PRODUTO?



US 5,519,021

WO 2006/018853



Altivo Pitaluga Jr.



A FALTA DE HARMONIZAÇÃO NA
NOMENCLATURA DE POLIMORFOS
PODEM PREJUDICAR OS EXAMES DOS
PEDIDOS DE PATENTE



Altivo Pitaluga Jr.





Do ponto de vista científico, os polimorfos sempre deveriam ser identificados a partir dos seus dados cristalográficos.

Mas a velocidade requerida nos trabalhos de P&D, aliado a outros fatores, muitas vezes impossibilitam esta abordagem.



Como não há regras estabelecidas para a nomenclatura de polimorfos, proteções múltiplas podem ser concedidas para um mesmo produto, em virtude da indefinição do objeto que está sendo reivindicado.

Table 1. Nomenclature of the Four CBZ Polymorphs^a

Year	Reference	Triclinic	Trigonal	P-Monoclinic	C-Monoclinic	Method of Confirmation
1968	13	I	—	III	—	Melting behavior
1975	14	C ₃	C ₂	C ₁	—	PXRD, IR
1981	15,16	—	—	Monoclinic	—	Crystal structure
1984	17	III	II	I	—	PXRD, DSC
1984	18	III	II	I	—	PXRD, DSC
1986	19	I	II, IV	III	—	PXRD, DSC
1986	20	α	—	β	—	PXRD, DSC
1987	21	I	—	III	II ^b	PXRD, DSC
1987	22	—	α, Trigonal	β	—	Trigonal structure, PXRD, DSC, IR
1991	24	I	—	III	—	DSC, preparation
1991	25	γ	α	β	—	Preparation
1992	26	I	—	III	—	IR, melting behavior
1996	27	I	—	III	—	PXRD
1997	28	Triclinic	—	—	—	Cell data, PXRD
2000	29	—	α	β	—	PXRD, SEM
2000	30	III	—	I	—	PXRD, DSC
2000	31	I	—	III	II ^b	PXRD, DSC, IR
2002	32	—	—	—	IV, C-Monoclinic	Crystal structure
	This study	I	II	III	IV	XRD, DSC, IR

2004 FDA article **b** — **a** —

Adaptado de Journal of Pharmaceutical Sciences, vol. 92, n. 11, p.2260, 2003

FDA article: Advanced Drug Delivery Reviews, 56, p.397, 2004



Altivo Pitaluga Jr.



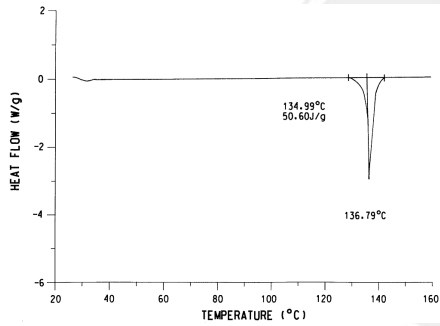
**EXISTEM DOCUMENTOS QUE NÃO
DESCREVEM AS CONDIÇÕES
EXPERIMENTAIS DOS ENSAIOS DE
CARACTERIZAÇÃO DE FORMA
ADEQUADA.**



Altivo Pitaluga Jr.



Samples were placed in sealed aluminum pans for analysis with an empty aluminum pan serving as the reference. Heating rates of 5 °C per minute or 10 °C per minute were employed over a temperature range of 25 °C to 200 °C. The instrument was calibrated with a indium standard.



No pedido de patente existem 5 curvas de DSC. Nenhuma delas informa qual a taxa de aquecimento utilizada.

WO 99/64405 A1

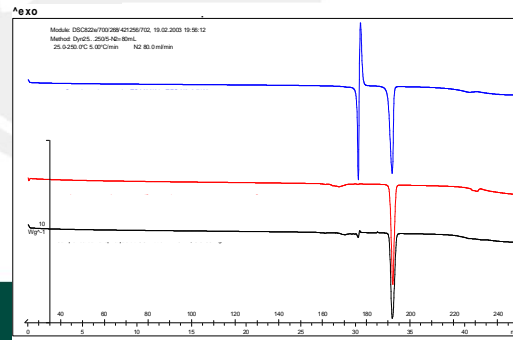
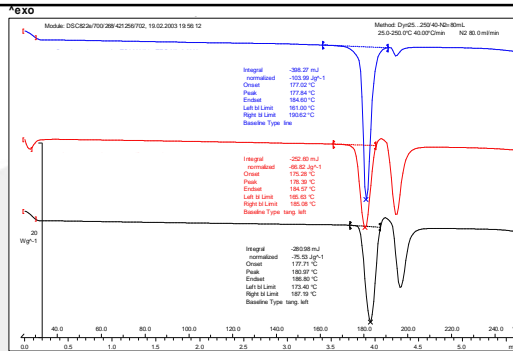


Altivo Pitaluga Jr.



taxa de aquecimento 40K/min

taxa de aquecimento 5K/min



EXISTEM DOCUMENTOS QUE
POSSUEM REIVINDICAÇÕES QUE NÃO
TÊM ATIVIDADE INVENTIVA.



WO 2006/030299

We Claim:

21. A process for the preparation of Form I of efavirenz, the process comprising:
- a) drying Form II under vacuum at a temperature from about 50°C or more, and obtaining Form I of efavirenz.

Form 1 is the most thermodynamically stable form.

It has a melting point of about 138 °C to about 140 °C, which is the highest of the four forms. Due to its increased stability, it is commonly used for drug formulation. All other forms may be converted into Form 1 during drying at about 60 °C to about 110 °C.

WO 99/64405

EXISTEM DOCUMENTOS QUE NÃO
DESCREVEM E/OU REIVINDICAM DE
FORMA ADEQUADA OS PROCESSOS
DE OBTENÇÃO DE POLIMORFOS.



Variáveis Importantes para os Processos de Cristalização

Table 1
Crystallization composition and processing variables [1,2,8]

Composition type	Process variables ^a					
	Polymorph/ solvates	Salts/ co-crystals	Thermal	Anti-solvent	Evaporation	Slurry conversion
■ Solvent/ solvent combinations	■ Counter-ion type	■ Heating rate	■ Anti-solvent type	■ Rate of evaporation	■ Solvent type	■ Mixing rate
■ Degree of supersaturation	■ Acid/base ratio	■ Cooling rate	■ Rate of anti- solvent addition	■ Evaporation time	■ Incubation temperature	■ Impeller design
■ Additive type	■ Solvent/ solvent combinations	■ Maximum temperature	■ Temperature of anti-solvent addition	■ Carrier gas	■ Incubation time	■ Crystallization vessel design (including capillaries, etc.)
■ Additive concentration	■ Degree of super-saturation	■ Incubation temperature(s)	■ Time of anti- solvent addition	■ Surface-volume ratio	■ Thermal cycling and gradients	
	■ Additive type and concentration	■ Incubation time				
	■ pH					
	■ Ionic strength					

^a Applicable to all types of screens.

Morissette *et al.*, *Advanced Drug Delivery Reviews*, 56, p.275, 2004

We Claim:

WO 2006/030299

1. A process for the preparation of Form II of efavirenz, the process comprising:
 - a) obtaining a solution of efavirenz in one or more organic solvents;
 - b) adding an anti-solvent to the solution; and
 - c) isolating the Form II of efavirenz by the removal of the solvents.
2. The process of claim 1, wherein the organic solvent comprises one or more of aromatic hydrocarbons, lower alkanols, chlorinated hydrocarbons, polar aprotic solvents, or mixtures thereof.
8. The process of claim 1, wherein the anti-solvent comprises one or more of C₆₋₈ straight or branched chain alkanes, petroleum ether, C₅₋₇ cycloalkanes, C₄₋₁₂ ethers, or mixtures thereof.
10. The process of claim 1, wherein removing the solvents comprises one or more of filtration, filtration under vacuum, decantation and centrifugation.
11. The process of claim 1, further comprising additional drying of the product obtained.

Solventes orgânicos:

**3 hidrocarbonetos aromáticos, 6 álcoois de baixo peso molecular,
3 hidrocarbonetos halogenados e 5 solventes polares apróticos.**



Altivo Pitaluga Jr.



**EXISTEM PRODUTOS QUE APESAR DE
SEREM PRODUZIDOS PELO HOMEM,
TAMBÉM PODEM SER GERADOS
ESPONTANEAMENTE EM CERTAS
CONDIÇÕES CLIMÁTICAS.**



Altivo Pitaluga Jr.



The district court found as a matter of fact that at some point, likely in late 1984, something occurred in SKB's laboratories that gave rise to two new phenomena simultaneously. SK II, 247 F. Supp. 2d at 1021-22. The first was a synthetic crystal later named paroxetine hemihydrate, id., ostensibly a patentable human-made invention under Chakrabarty. The second was a natural physical process whereby paroxetine anhydrate (a pre-existing synthetic crystal that today is in the public domain) could, under normal climactic conditions and with no human intervention, bond with water molecules and convert itself into paroxetine hemihydrate, SK II, 247 F. Supp. 2d at 1021-22, ostensibly an unpatentable, newly discovered natural process under Chakrabarty.

United States Court of Appeals for the Federal Circuit

SMITHKLINE BEECHAM CORPORATION
and BEECHAM GROUP, P.L.C.,

v.

APOTEX CORP., APOTEX, INC., and TORPHARM, INC.,

03-1285, -1313



Altivo Pitaluga Jr.



**OS EXEMPLOS APRESENTADOS NÃO
ESGOTAM AS QUESTÕES TÉCNICAS QUE
PODEM SER DISCUTIDAS NOS PEDIDOS DE
PATENTE E NAS PATENTES CONCEDIDAS
QUE ENVOLVEM O TEMA POLIMORFISMO.**



Altivo Pitaluga Jr.



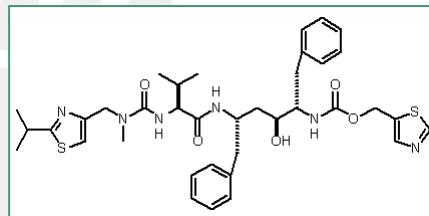


E PARA TERMINAR:

O caso Norvir®

Precipitação na parede interna da cápsula

Os resultados analíticos mostraram que o "pp" era um novo polimorfo, chamado de forma II



Perfil de solubilidade em várias soluções hidroalcoólicas (5°C)

Ethanol/Water	99/1	95/5	90/10	85/15	80/20	75/25
Form I	90 mg/mL	188	234	294	236	170
Form II	19 mg/mL	41	60	61	45	30

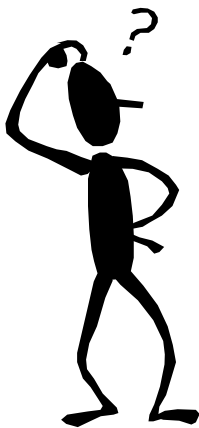
J. Bauer et al.; Pharmaceutical Research; vol. 18; n.6; 2001

O caso Norvir®

APENAS DEPOIS DESTE CASO QUE MUITAS
PESSOAS E INSTITUIÇÕES ATENTARAM PARA O
FATO DE QUE O POLIMORFISMO PODE SER
IMPORTANTE PARA TODAS AS APRESENTAÇÕES
FARMACÊUTICAS



Altivo Pitaluga Jr.



DO PONTO DE VISTA TÉCNICO, A
PATENTE DO SEGUNDO POLIMORFO
DO RITONAVIR PREJUDICA A ENTRADA
DE MEDICAMENTOS GENÉRICOS NO
MERCADO?

E SE O NORVIR® FOSSE UMA
APRESENTAÇÃO FARMACÊUTICA SÓLIDA?



Altivo Pitaluga Jr.



MAS DO PONTO DE VISTA ECONÔMICO...



Altivo Pitaluga Jr.



OBRIGADO POR SUA ATENÇÃO!

Altivo Pitaluga Jr.

pitaluga@far.fiocruz.br / pitalugajr@gmail.com



Altivo Pitaluga Jr.

