RIFAXIMIN BY FRIULCHEM

AN INNOVATIVE AND HELPFUL PRODUCT

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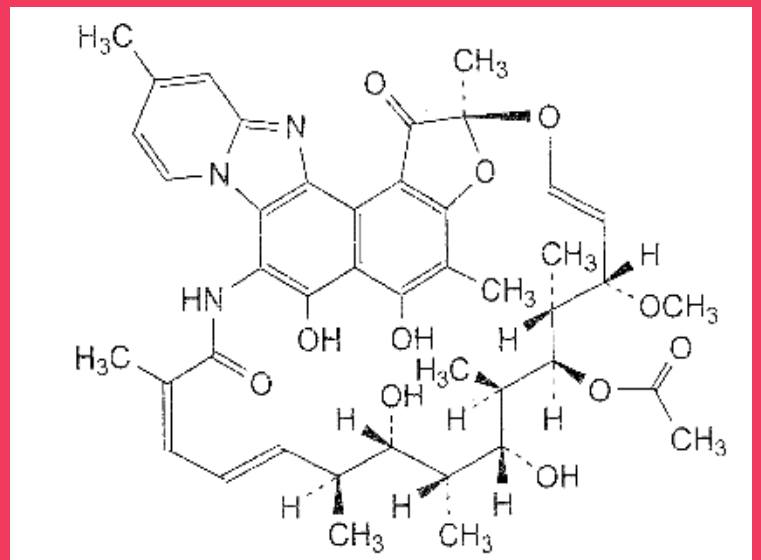
Rifaximin: existing patents and polymorph α



Semi-synthetic product derived from a fermentation product (Rifamycin).

Rifaximin shows many polymorphs, most of them are covered by Patent (α, β, γ, δ forms…).

Rifaximin is used in the treatment of traveller's diarrhoea and hepatic encephalopathy.

Polymorph α is the most active. It cannot be absorbed, so its intestinal action is local (covered by Alfa-Wasserman patent).

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Friulchem active ingredient

FC Rifaximin API is patented

Friulchem patented an own polymorph, a pseudo-crystalline solid form, derived from Rifamycin O.

Friulchem patent was filled in 2011, in Europe, Mexico, and USA. (PCT/EP2011/058171)

Friulchem patent has been granted in Europe and the USA.

Friulchem form is stable at different contents of water (%KF 2.00 - 4.45).

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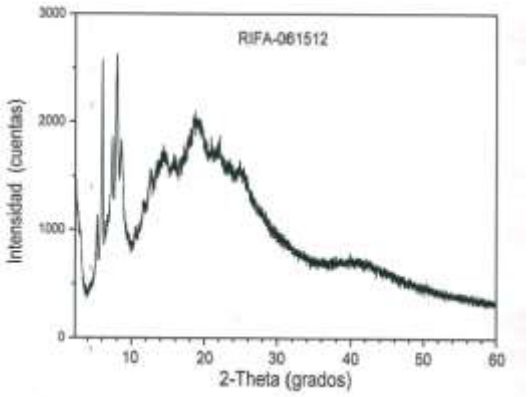
FC Rifaximin API quality

API is manufactured by Interquim Mexico.

Instituto de Física UNAM
Laboratorio de Refinamiento de Estructuras Cristalinas

Figura D-01



interquim Mexico

CERTIFICATE OF ANALYSIS

Product:	RIFAXIMIN	Batch:	RIFA-061512
		Amount:	165.0 Kg
Conforms to:	Eur. Ph. 8.0 Ed	Manufacturing Date:	December, 2015
Code:	1300	Retest Date:	December, 2017

TEST	SPECIFICATIONS	RESULTS
APPEARANCE	Red-orange, crystalline, hygroscopic powder.	Red-orange crystalline, hygroscopic powder.
SOLUBILITY	Practically insoluble in water, soluble in acetone and methanol.	Practically insoluble in water, soluble in acetone and methanol.
IDENTIFICATION A) I.R.	The spectrum obtained with the substance to be examined correspond with the spectrum obtained with the reference substance.	The spectrum obtained with the substance to be examined correspond with the spectrum obtained with the reference substance.
B) H.P.L.C.	The retention time for the sample of Rifaximin peak corresponds to the retention time of the standard.	The retention time for the sample of Rifaximin peak corresponds to the retention time of the standard.
HEAVY METALS	Maximum 20 ppm	< 20 ppm
WATER	Maximum 4.5%	1.5%
SULPHATED ASH	Maximum 0.1%	< 0.1%
RELATED SUBSTANCES		
- SUM OF IMPURITIES D+H	Not more than 0.5%	0.2%
- UNSPECIFIED IMPURITIES	Not more than 0.10%	0.10%
- TOTAL	Not more than 1.0%	0.4%

APPROVED: December, 2015 * Calculated on anhydrous basis

Marco Antonio Romero Salazar
Quality Control Manager

Marisol Rodríguez Hernández
Quality Assurance Manager

IEX-1471-GMA -This batch is approved and meets the stablished specifications. 1/2

interquim Mexico

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TEST	SPECIFICATIONS	RESULTS
RESIDUAL SOLVENTS	Not more than 5000 ppm of Ethanol Not more than 5000 ppm of Acetone Not more than 600 ppm of Dichloromethane	4093 ppm < 75 ppm < 92 ppm
ASSAY*	It contains not less than 97.0% and not more than 102.0%	99.0%

APPROVED: December, 2015 * Calculated on anhydrous basis

Marco Antonio Romero Salazar
Quality Control Manager

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IEX-1471-GMA -This batch is approved and meets the stablished specifications. 2/2

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FC Rifaximin is distinct from patented forms α, β and γ

X-RAY comparison with Rifaximin α, β and δ

Rifaximin[a]	Rif.	2θ	2θ	2θ	2θ	2θ	2θ	T, K and crystal system
Rifaximine α	1	5.78	6.55	7.29	7.92	8.92	8.47	295,monoclinic
Rifaximine α hemihydrate	1	5.80	6.50	7.28	7.83	8.74	8.26	295,monoclinic
Rifaximine δ dihydrate	1	5.64	6.72	7.14	8.00	8.74	8.61	295,monoclinic
Rifaximine α sesquihydrate	1	5.84	6.54	7.31	7.88	8.79	9.29	295,monoclinic
Rifaximine β trihydrate	1	5.33	6.41	6.93	7.80	8.87	9.28	295,monoclinic
Rifaximine β hydrate	1	5.39	6.43	7.01	7.83	8.94	9.38	295,monoclinic
Rifaximine tetrahydrate	2	5.28	6.38	6.91	7.78	8.91	9.30	295,monoclino
Rifa-061512	**Friulchem**	**5.35**	**6.86**	**7.86**	**8.54**	**9.35**	**9.63**	**298, orthorhombic**

For samples Rifa-061512 (FC Rifaximin) the intense low angle peaks (those below 10° 2q), lie near 5.40, 6.12, 7.48, 8.06 and 8.82°.

FC Rifaximin and α, β and δ-phase are distinct crystal phases.

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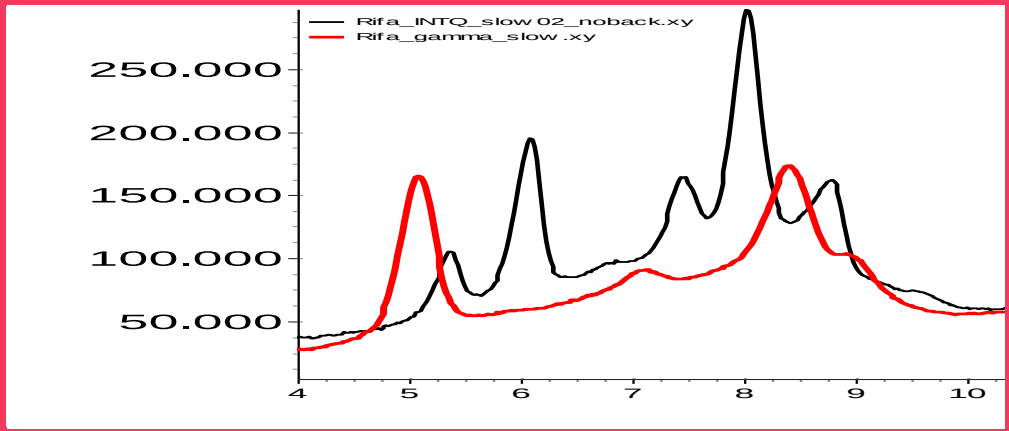
Are FC Rifaximin and γ-phase different?

X-RAY and 13C comparison with Rifaximin γ

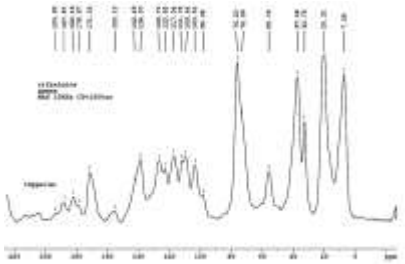
X-RAY

For comparison with Rifaximin γ (the most similar form) diffraction data were collected under the same experimental conditions.

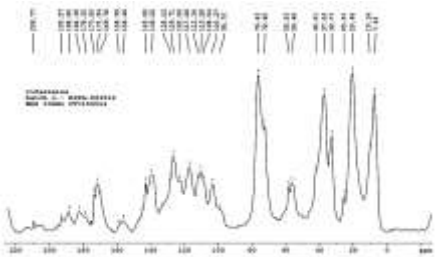
Rifa-061512 and γ-phase are distinct crystal phases. To support this claim, a further plot is hereafter proposed, with the two traces overlaid. Black: sample Rifa-061512; Red: γ-phase.



Solid-state 13C-NMR spectra (CP/MAS) were performed on two different samples of solid Rifaximin (γ-form and Rifa-061512).



γ-form



Rifa-061512

In "RIFA-06512" sample an additional more crystalline polymorph is present, as proved by several additional sharper resonances, not detected in rifaximin-gamma. Resonances at 25.5ppm, 58.2ppm, 143.0ppm and at 209.7ppm are particularly diagnostic for such additional crystalline form.

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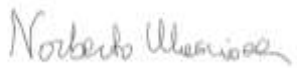
Direct comparison with existing patent

Synoptic comparison of the XRD peak positions reported in Patents US 7,902,206 B2; US 7,915,275 B2 and US 8,835,452 B2 (containing data on a, β and γ phases; assignee: *Alfa Wassermann*), with those of sample RIFA-061512 (*Friulchem*).

"On the basis of the peak positions, I can certify that, despite of the occasional similarity of a few values, the RIFA-061512 sample if manifestly different from any of the crystal forms reported in Patents US 7,902,206 B2; US 7,915,275 B2 and US 8,835,452 B2."



Prof. Norberto Maschiocchi - University of Insubria, Science and High Technology department

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Legal actions against FC-Rifaximin

Mexico

IMPI
INSTITUTO MEXICANO DE LA PROPIEDAD INDUSTRIAL

DIRECCIÓN DIVISIONAL DE PROTECCIÓN A LA PROPIEDAD INTELECTUAL.
SUBDIRECCIÓN DIVISIONAL DE MARCAS NOTORIAS; INVESTIGACIÓN; CONTROL Y PROCESAMIENTO DE DOCUMENTOS.
COORDINACIÓN DEPARTAMENTAL DE RESOLUCIONES DE MARCAS NOTORIAS.

ALFA WASSERMANN, S.P.A.
Vs
INTERQUIM, S.A. DE C.V.

INSTITUTO MEXICANO DE LA PROPIEDAD INDUSTRIAL
Dirección Divisional de Protección a la Propiedad Intelectual

Folio: 35033
Fecha: 31/AGO/2017 Hora: 20:46
Exped: P.C.1624/2015(M-54)13814
143548
PI/S/2017/035033

SE NIEGAN ADMINISTRATIVAMENTE LAS INFRACCIONES PREVISTAS EN EL ARTÍCULO 213 FRACCIONES I, XI Y XXX, ESTA ÚLTIMA EN RELACIÓN CON EL NUMERAL 25 FRACCIÓN I DE LA LEY DE LA PROPIEDAD INDUSTRIAL, RESPECTO DE LAS PATENTES 260156 "FORMAS POLIMORFICAS DE RIFAXIMINA COMO ANTIBIOTICOS", 276279 "FORMAS POLIMORFICAS DE RIFAXIMINA COMO ANTIBIOTICOS" y 290737 "NUEVAS FORMAS POLIMORFAS DE RIFAXIMINA, PROCEDIMIENTOS PARA SU PRODUCCIÓN Y USO DE LA MISMA EN PREPARACIONES MEDICINALES", POR PARTE DE INTERQUIM, S.A. DE C.V.

Korea

Case: Confirmation of Scope of Rights of Patent No. 855084 "Polymorphic forms of rifaximin, processes for production thereof, and use thereof as a medicinal product."

… … … … … …

CONCLUSION … As observed above, the invention in question is not within the scope of rights of the inventions of Claims 1 through 7, Claims 12 through 15, and Claims 18 through 20.

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Friulchem finished form

FC-Rifaximin 200 mg and 550 mg film-coated tablets for human use

Friulchem Tablet (test drug)

Originator Tablet (reference drug)

Pharmacokinetic studies were performed on **50 people over 19 years old.**

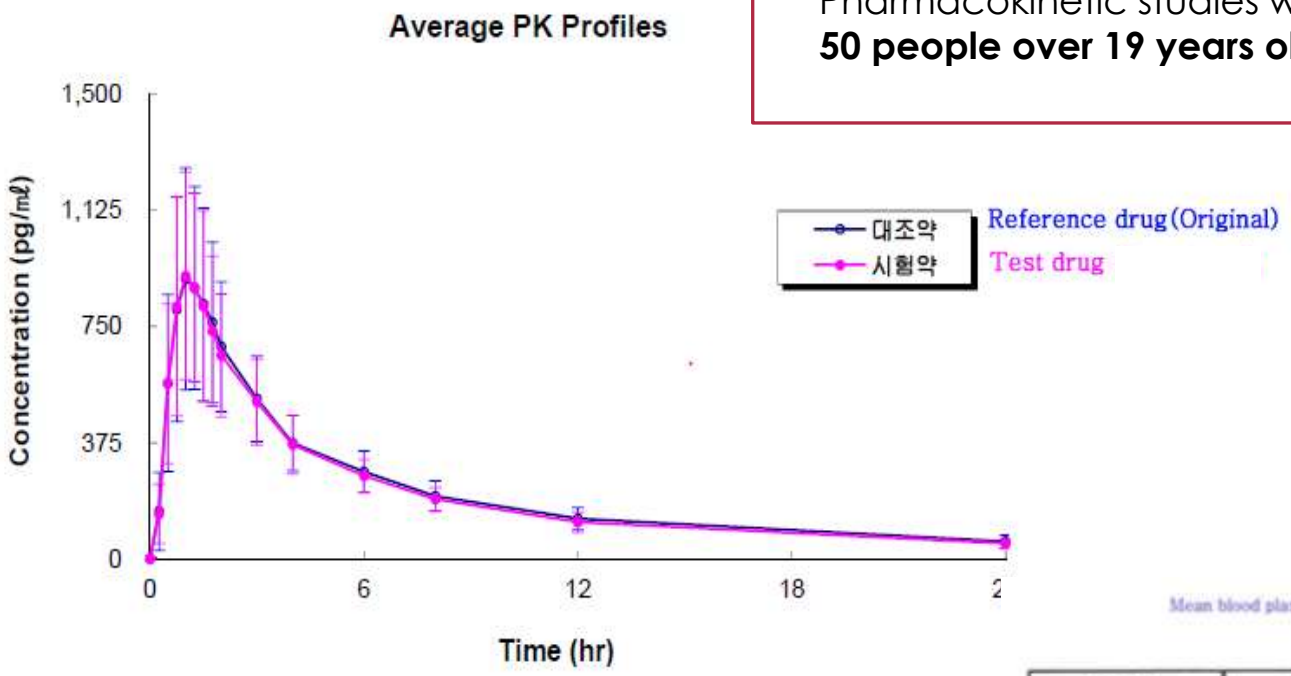

Fig. 60. 대조약과 시험약의 평균 혈장 중 Rifaximin 농도 추이

(n = 50, Mean ± SD)

Mean blood plasma concentration of Rifaximin

Rifaximin	AUC$_t$ (pg·hr/㎖)	C_{max} (pg/㎖)
대조약* Reference drug (Original)	5260.72 ± 1194.20	1012.57 ± 350.31
시험약* Test drug	5040.46 ± 1002.58	991.56 ± 351.15
90% 신뢰구간(ā)**	0.9176 ≤ ā ≤ 1.0164	0.8979 ≤ ā ≤ 1.0674

*Mean ± SD / **로그변환치임

FC-Rifaximin in FC-Cubes for veterinary application

Friulchem
FC-Cubes

Friulchem identified a different manufacturing method that allows reaching a chewable matrix with all the benefits presented for the drugs already on the market, but without the limit connected to production by extrusion.

Due to the high palatability showed in the preliminary tests performed, FC-cubes could be used to prepare formulations that can include different active pharmaceutical ingredients.

The matrix composition developed in Friulchem is 100% palatable and able to mask also active components that are particularly disliked by the animals.