



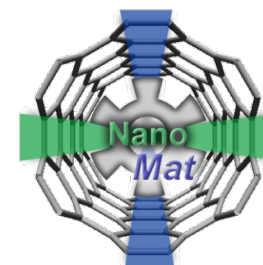
4. Estudio de Casos



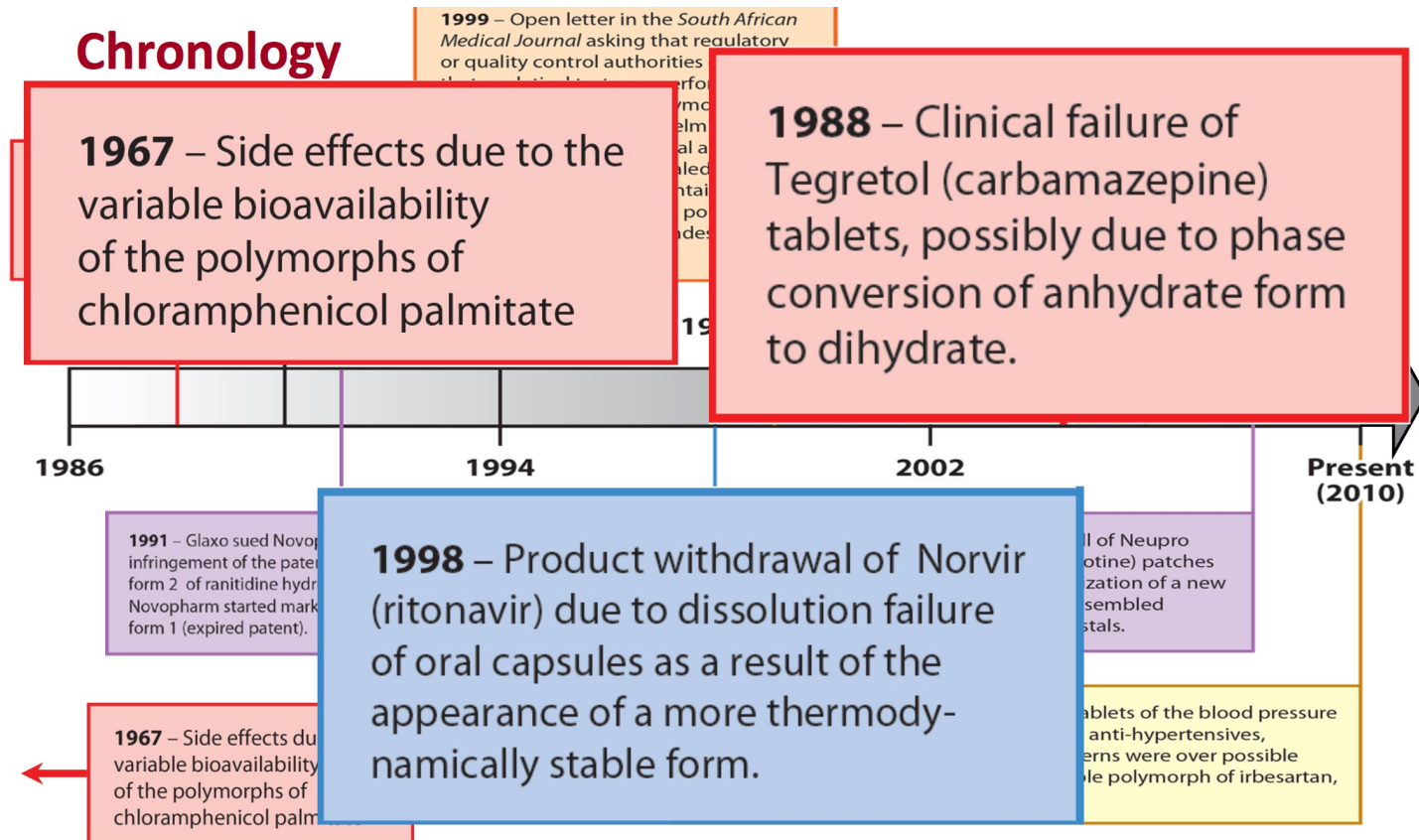
Dr. Ricardo Faccio



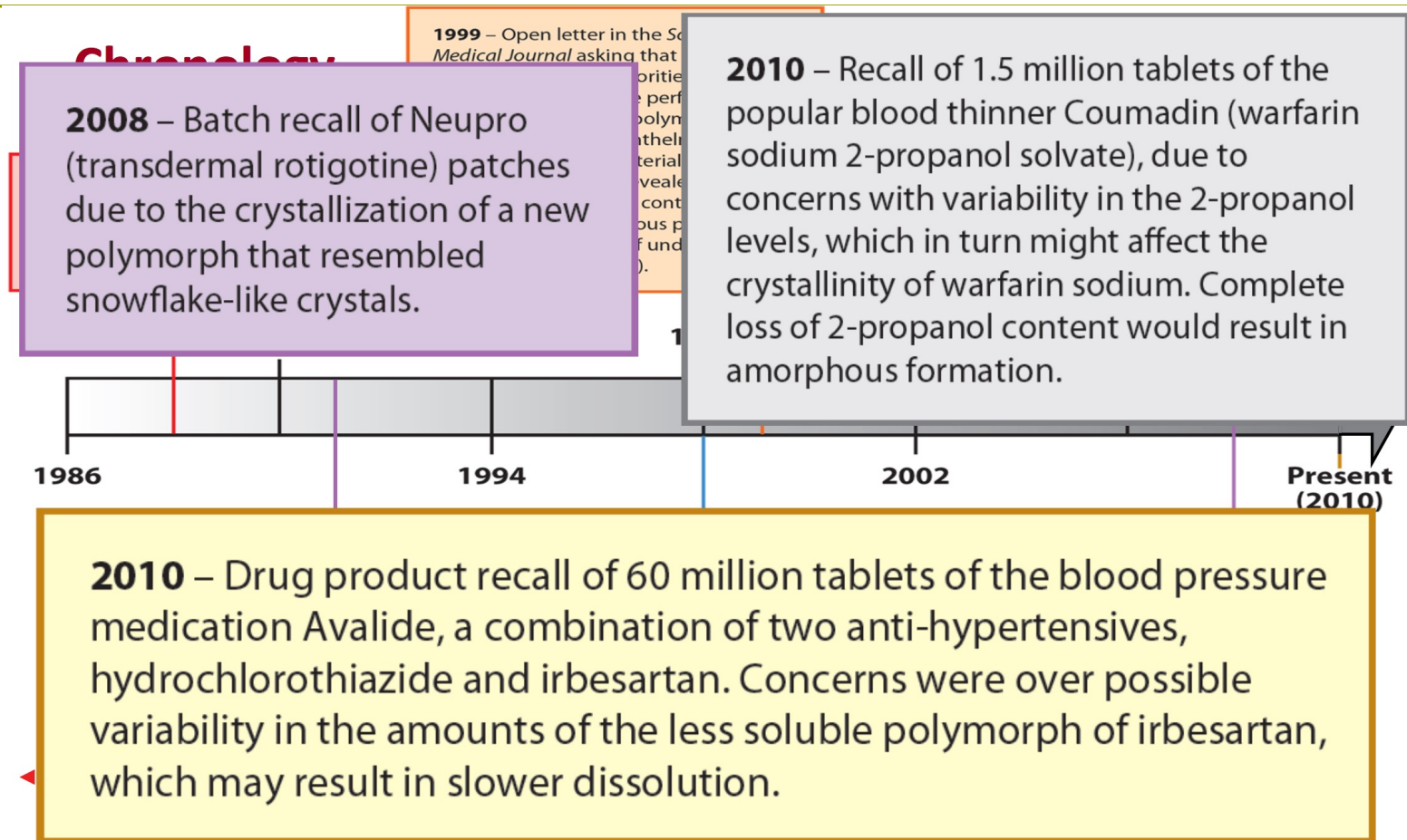
Centro NanoMat
Facultad de Química
Universidad de la República
rfaccio@fq.edu.uy



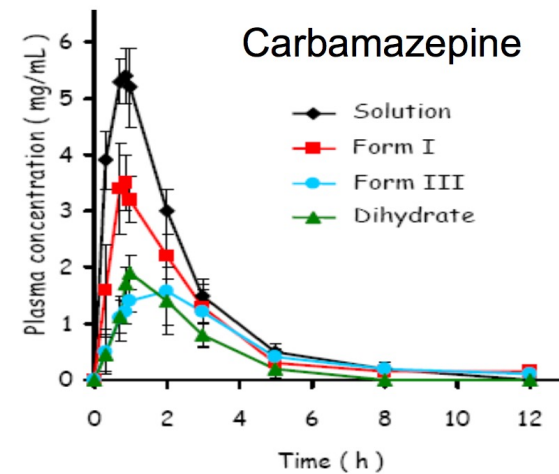
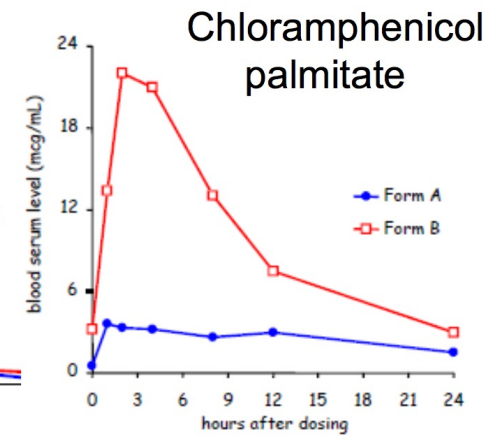
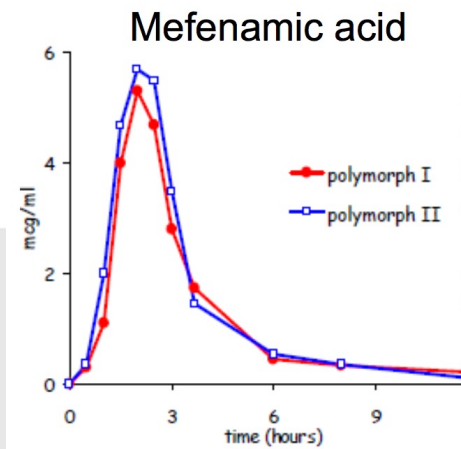
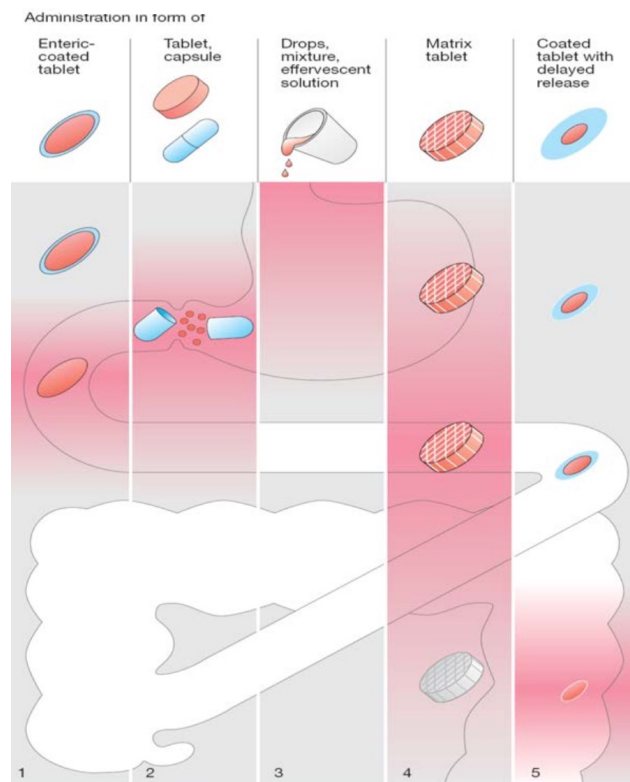
Introducción



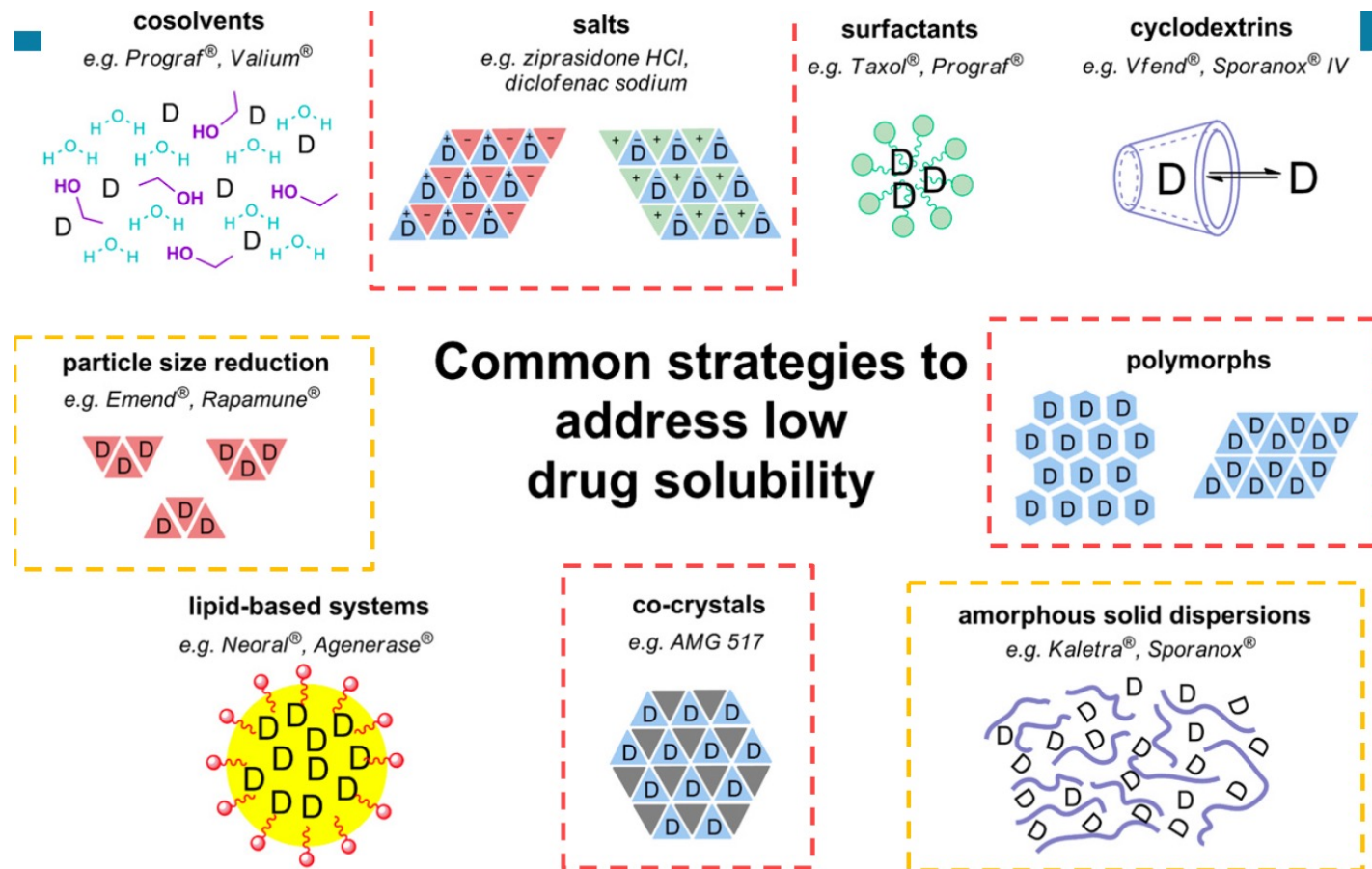
Introducción



Biodisponibilidad

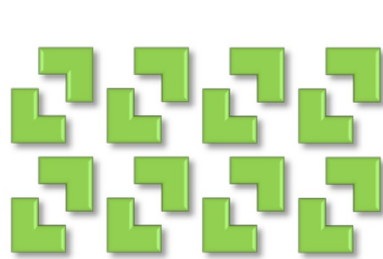


Baja Disolución: estrategias

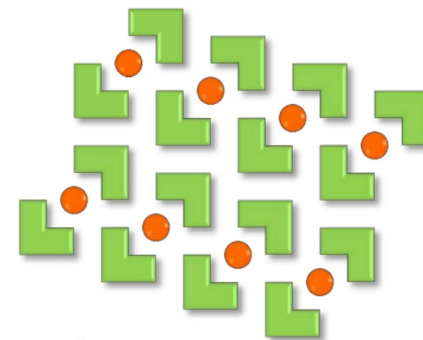


Polimorfismo: Definición

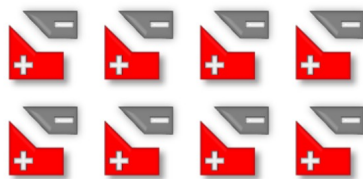
Polymorphism – is the ability of a substance to exist as two or more crystalline forms having different arrangements and/or conformations of the molecules in the crystalline lattice.



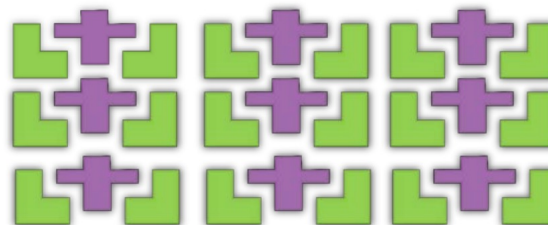
Polymorphs



Solvates



Salt



Cocrystal



Amorphous

Polimorfismo: Definición

European pharmacopoeia: <5.9> Polymorphism

Polymorphism (or crystal polymorphism) is a phenomenon related to the solid state; it is the ability of a compound in the solid state to exist in different crystalline forms having the same chemical composition. Substances that exist in a non-crystalline solid state are said to be amorphous.

Where a monograph indicates that a substance shows polymorphism, this may be true crystal polymorphism, occurrence of solvates, allotropy or occurrence of the amorphous form.

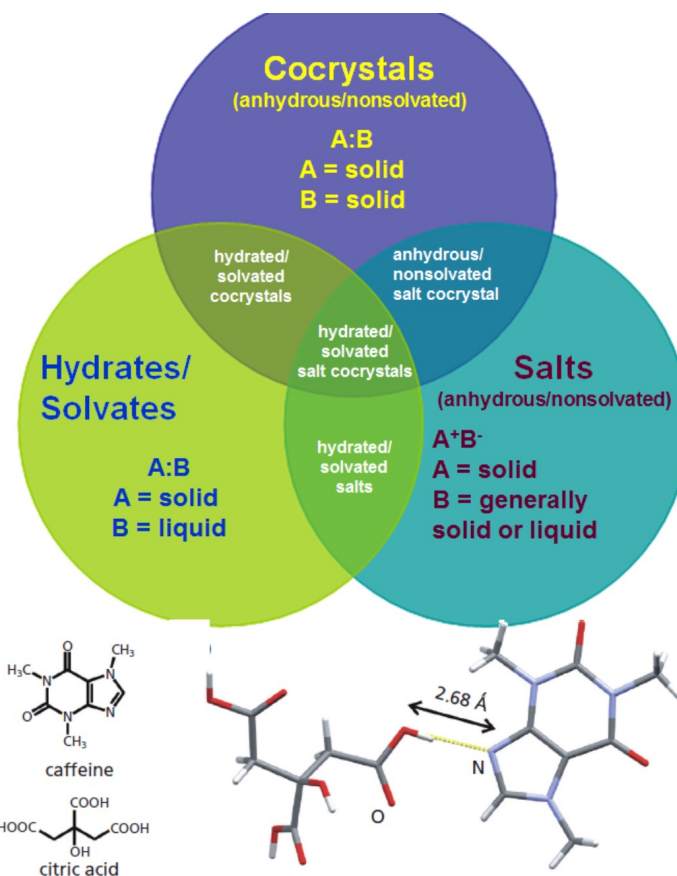
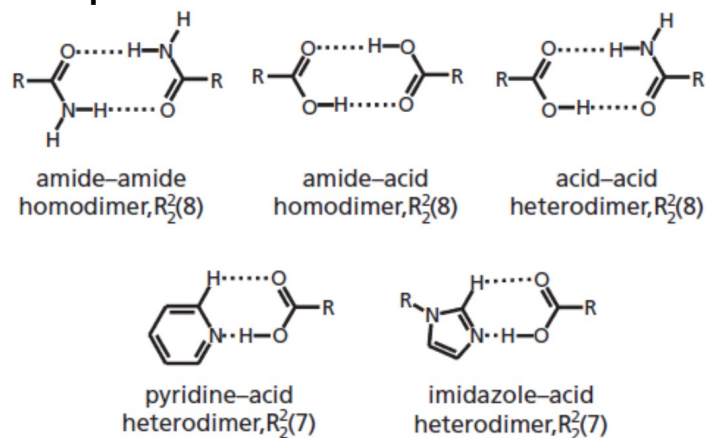
FDA: Guidance for Industry, ANDAS Pharmaceutical Solid Polymorphism

We recommend that ANDA applicants investigate whether the drug substance in question can exist in polymorphic forms. Polymorphic forms in the context of this guidance refer to crystalline and amorphous forms as well as solvate and hydrate forms, which are described below.⁸

When a drug substance exists in polymorphic forms, it is said to exhibit polymorphism.

Otras Estrategias: Cocristales

Cocrystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.



Aspectos Regulatorios



Guidance for Industry Regulatory Classification of Pharmaceutical Co-Crystals

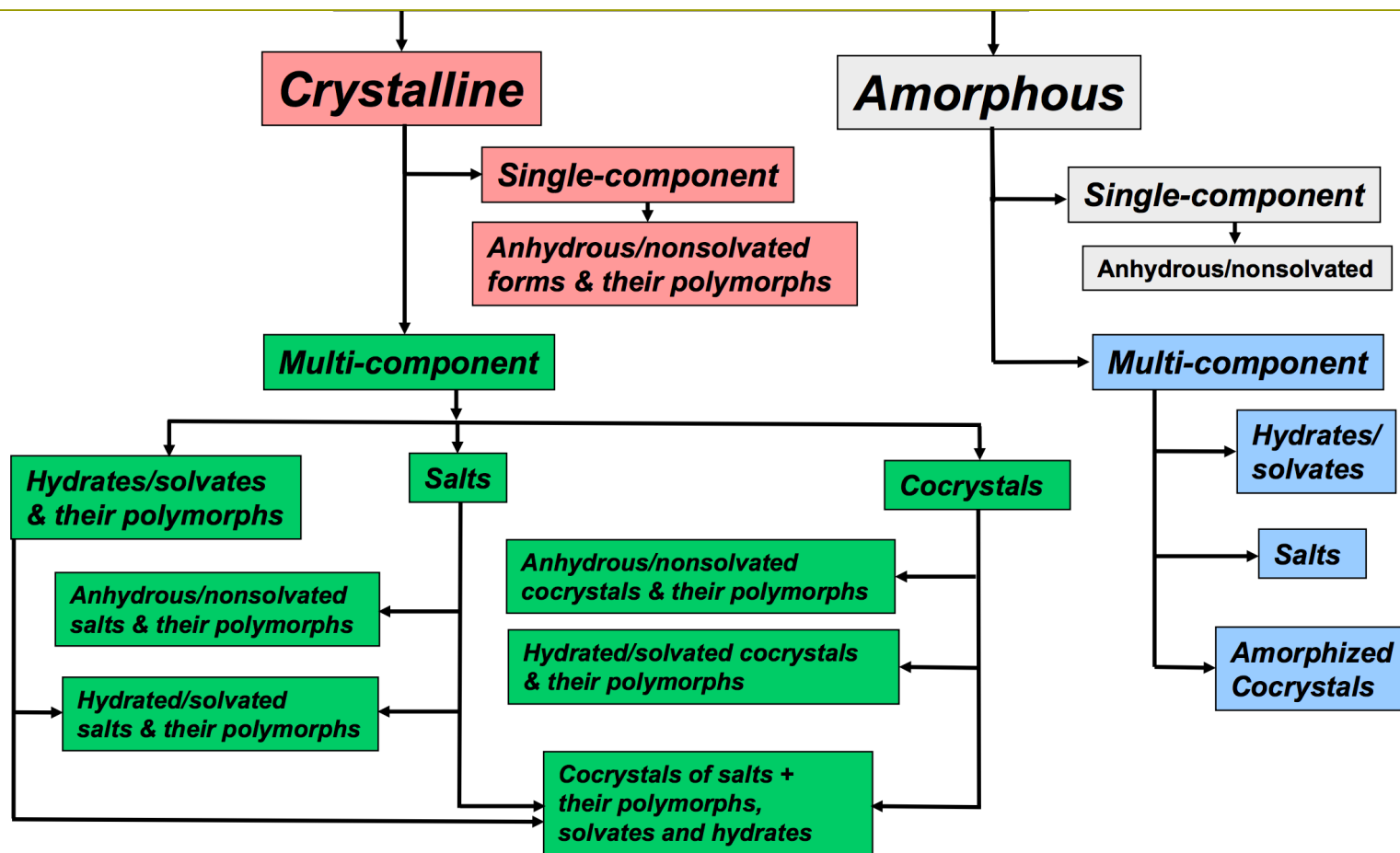
GLOSSARY

Co-crystals: Crystalline materials composed of two or more molecules within the same crystal lattice.

Polymorphs: Different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients. (See Guidance for Industry: *ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information*, July 2007.)

Salts: Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound. Per the current regulatory scheme, different salt forms of the same active moiety are considered different active ingredients. (See 21 CFR 314.108 and 21 CFR 320.1(c).)

API Solid Form



Polimorfismo en las Farmacopeas

Farmacopea	Ed.	Capítulo	Caracterización					Polimorfismo
			DR X	TA	IR	NIR	RS	
Brasileña	5			✓	✓			19
Argentina	8	✓		✓	✓			67
Británica	6	✓		✓	✓		✓	155
Japonesa	15		✓	✓	✓			0
Portuguesa	7			✓	✓		✓	69
Europea	5	✓		✓	✓	✓	✓	104
Estados Unidos	33		✓	✓	✓	✓	✓	*

XRD : X-ray diffraction

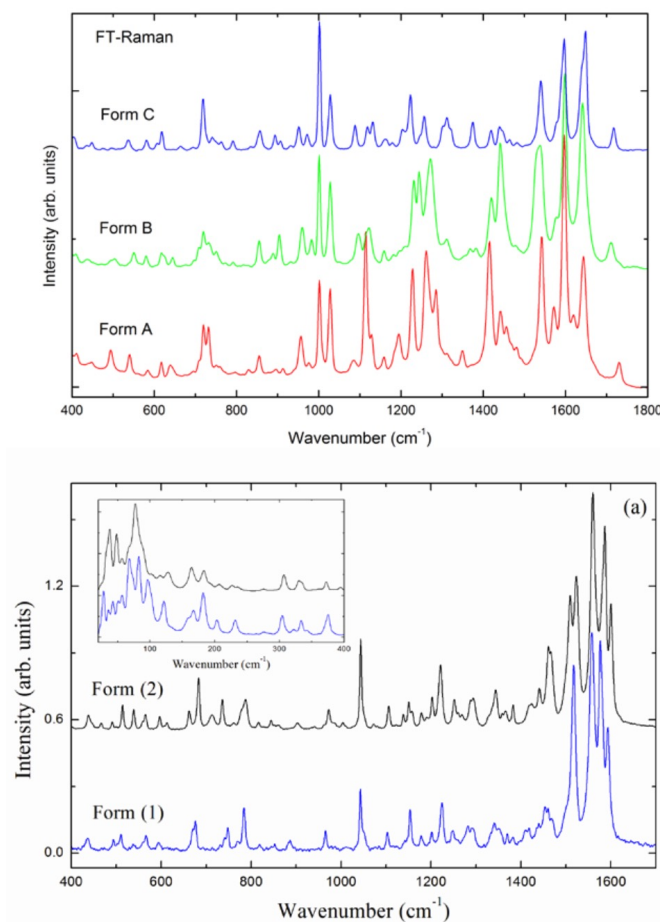
TA: Thermal analysis

IR: infrared absorption

NIR: near infrared absorption

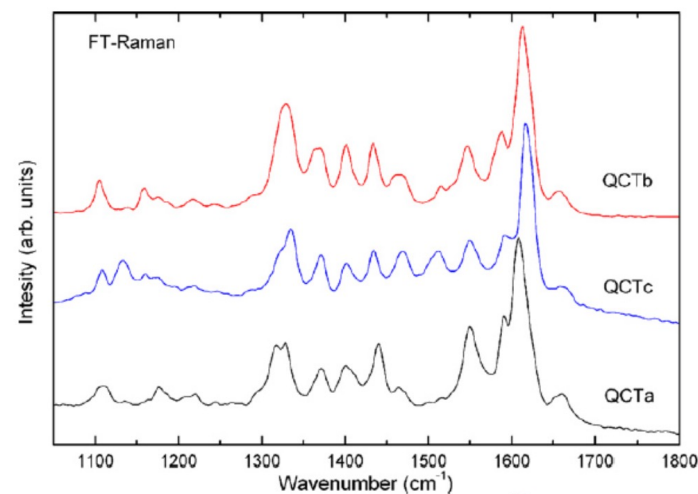
RS: Raman spectroscopy

Identificación de Polimorfos: Raman



Mebendazole

A. P. Ayala, et al. *J. Raman Spectrosc.* 39, 1150 (2008)



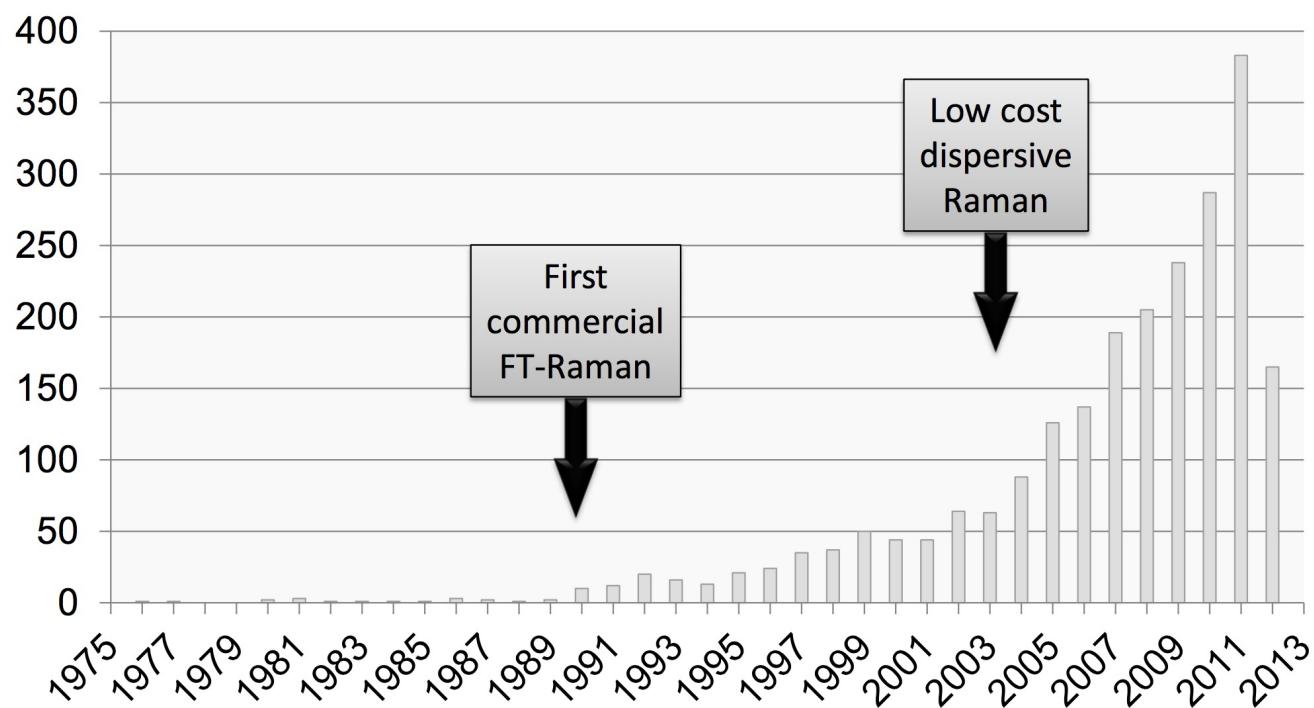
Quercetin

G.S. Borghetti, et al. *Thermochim. Acta.* 539, 109 (2012)

Olanzapine

A. P. Ayala, et al. *Int. J. Pharm.* 326, 69 (2006); 301, 33 (2005)

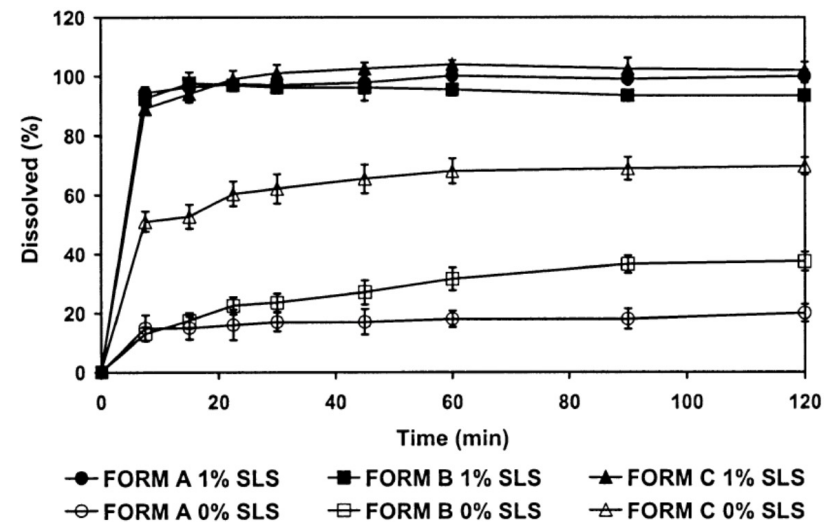
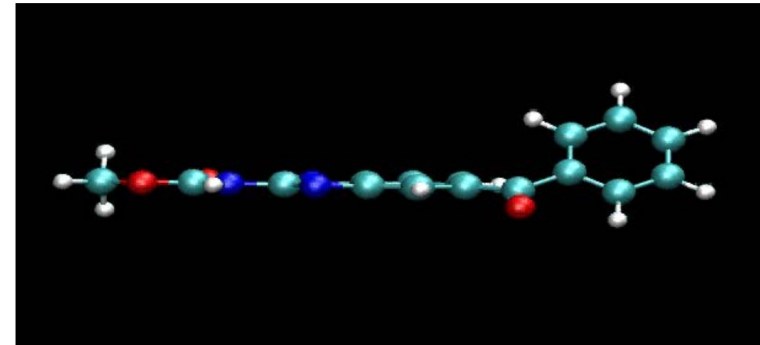
Publicaciones en Fármacos

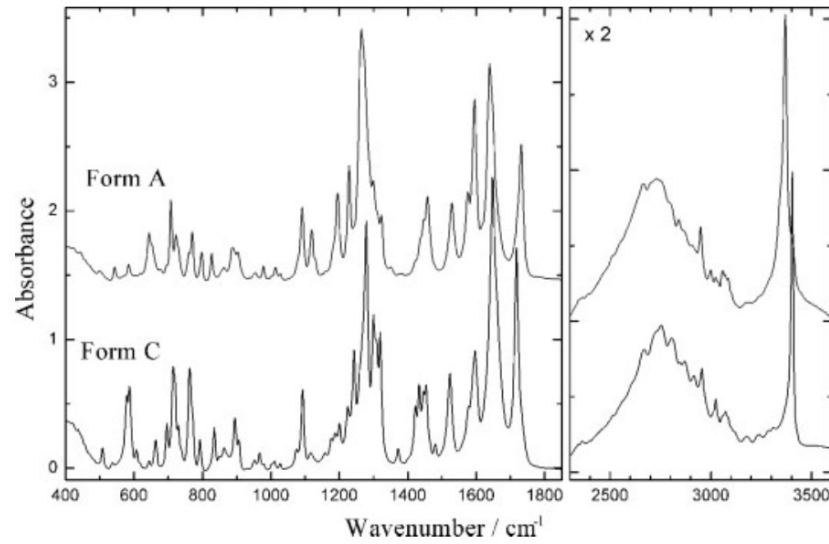


Ejemplo 1: Mebendazole

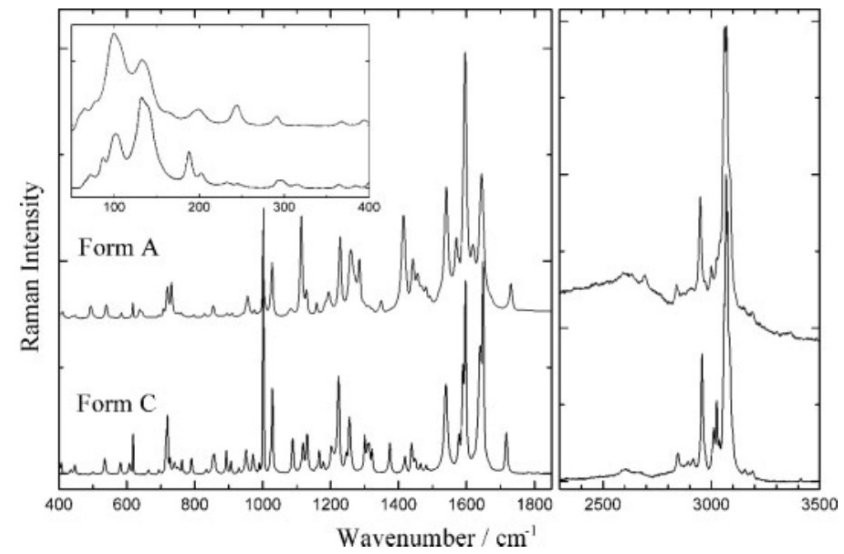
Propiedades generales:

- Tres polimorfos (A,B y C)
- Solubilidad $C > B > A$
- Forma B: posible toxicidad
- Forma A: posiblemente inactiva
- USP no distingue entre las formas A y C





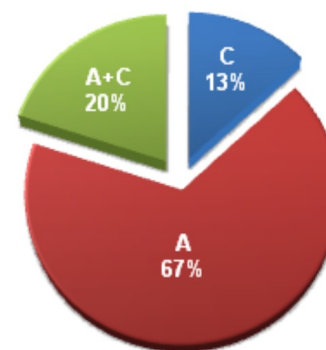
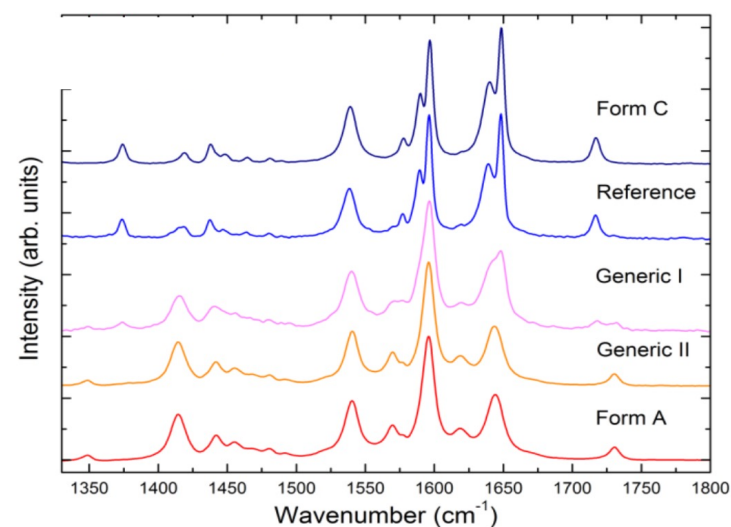
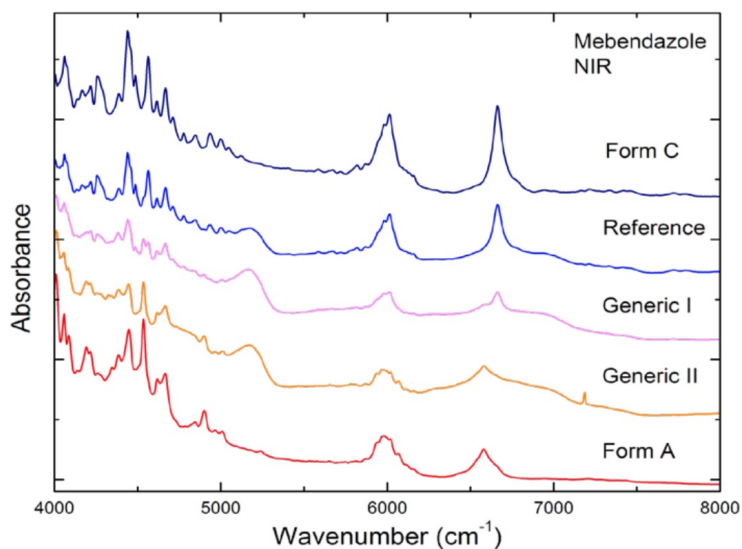
FT-IR spectra of the polymorphs A and C of mebendazole.



FT-Raman spectra of the polymorphs A and C of mebendazole.

Control de Calidad de Mebendazole

- ◆ More than a dozen of generic medications
- ◆ USP quality control norms are adopted: solubility test and infrared spectra after **recrystallization**



Octubre de 2023

Ayala et al. (2008), J. Raman Spectrosc. 39, 1150

Ejemplo 2: Chlorpropamide

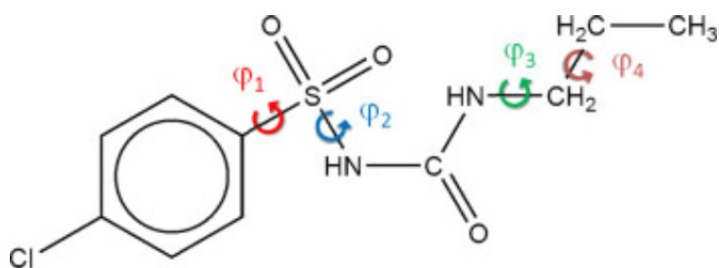
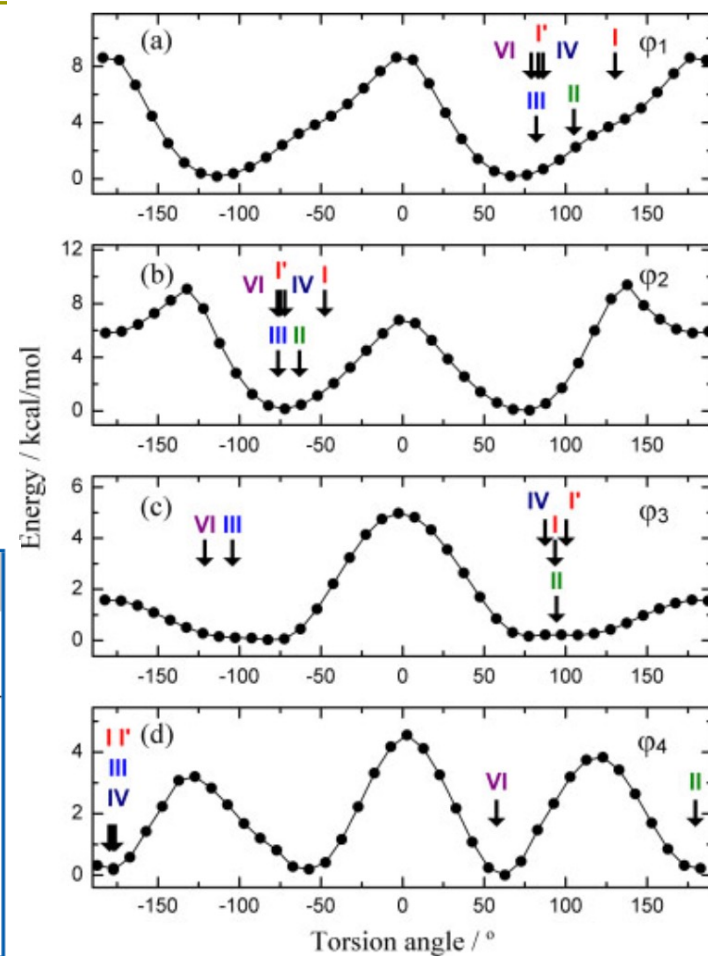


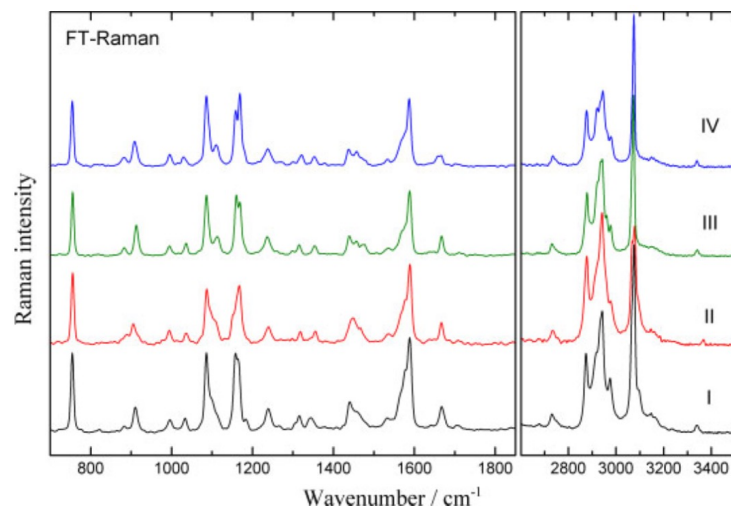
Figure 1. Scheme of the chlorpropamide molecule with φ_1 , φ_2 , φ_3 , and φ_4 indicating selected torsion angles.

Table 1. Backbone torsion angles of the chlorpropamide polymorphs

Form	CCSN (φ_1)	CSNC (φ_2)	SNCN	NCNC	CNCC (φ_3)	NCCC (φ_4)
I (ϵ)	130.48	-47.60	145.48	174.72	93.61	-179.35
II (β)	105.16	-62.97	168.79	178.59	94.55	179.72
III (α)	82.24	-76.20	170.22	175.30	-104.16	-176.05
IV (γ)	86.35	-72.10	173.22	-179.34	87.54	-177.17
VI (δ)	79.06	-76.55	168.07	179.42	-121.05	57.78
I' (ϵ')	83.48	-74.92	168.84	178.99	-100.42	-174.73

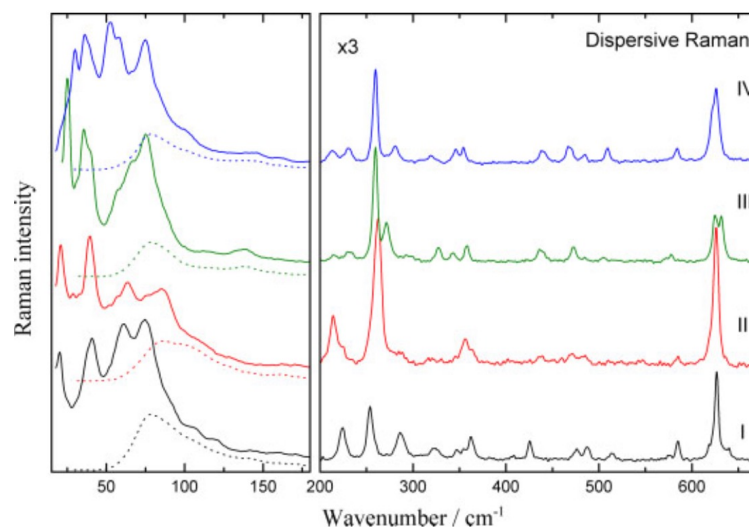


Ejemplo 2: Chlorpropamide



Conformational polymorphism is clearly identified by low wavenumber dispersive Raman scattering.

Raman spectra in the fingerprint region exhibit little dependence on the crystal structure because polymorphism in chlorpropamide is related to conformational changes.



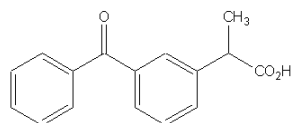
Caso 1



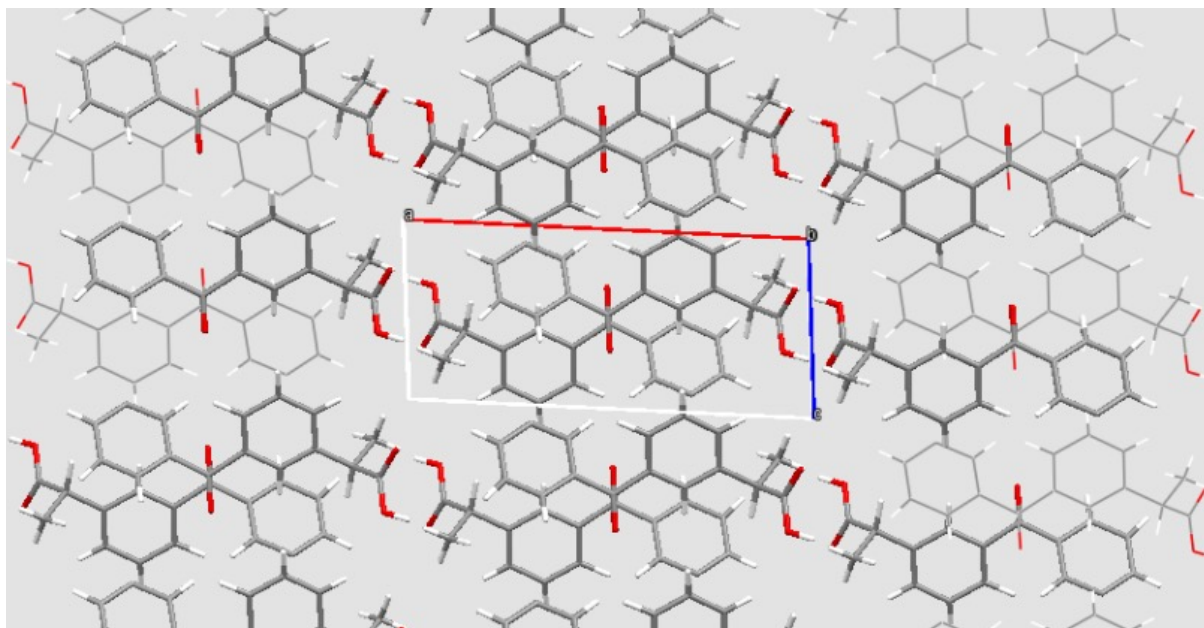
Granulados y Comprimidos de Ketoprofeno

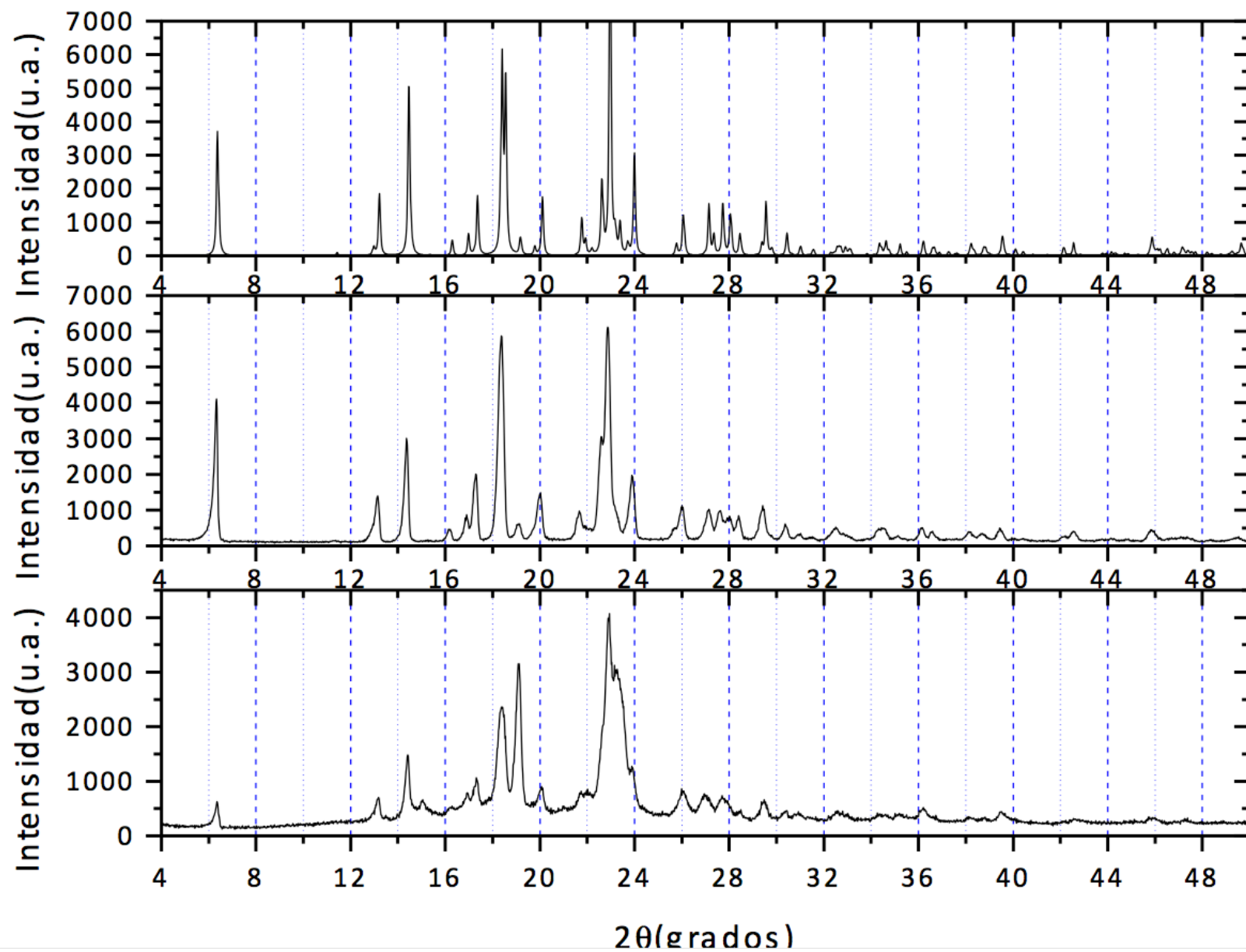
Ketoprofeno

■ Estructura Cristalina



Identifier	KEMRUP
Literature Reference	P.Briard, J.C.Rossi, <i>Acta Crystallogr., Sect. C: Cryst. Struct. Commun.</i> (1990), 46 , 1036
Formula	C ₁₆ H ₁₄ O ₃
Compound Name	2-(3-Benzoylphenyl)propionic acid
Synonym	Ketoprofen
Space Group	P -1
Cell Lengths	a 13.893(8) b 7.741(3) c 6.136(2)
Cell Angles	α 89.61(3) β 94.56(4) γ 88.78(4)
Cell Volume	657.639
Z, Z'	Z : 2 Z' : 0
R-Factor (%)	6.61
Disorder	





Ketoprofeno

La figura corresponde a una referencia de ketoprofeno, la figura 2 corresponde a granulado de ketoprofeno y la figura 3 corresponde a comprimido de ketoprofeno, que incluye excipientes.

Preguntas:

1. ¿El granulado demuestra tener el polimorfo de ketoprofeno según referencia?
2. ¿El comprimido demuestra tener el polimorfo de ketoprofeno según referencia?
3. Si no se tuviera la referencia de ketoprofeno, cuál sería el procedimiento para confirmar que se trata de una muestra monofásica.

Caso 2



Polimorfos de la Carbamazepina

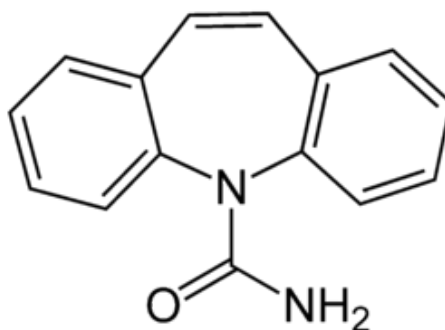
Carbamazepina

Comparison of the Four Anhydrous Polymorphs of Carbamazepine and the Crystal Structure of Form I

ADAM L. GRZESIAK, MEIDONG LANG, KIBUM KIM, ADAM J. MATZGER

Department of Chemistry and the Macromolecular Science and Engineering Program, The University of Michigan, Ann Arbor, Michigan 48109-1055

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 92, NO. 11, NOVEMBER 2003



Carbamazepina

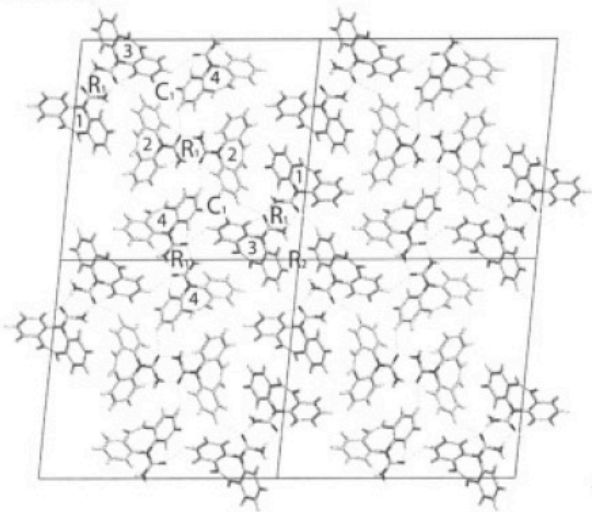
Table 1. Nomenclature of the Four CBZ Polymorphs^a

Year	Reference	Triclinic	Trigonal	<i>P</i> -Monoclinic	<i>C</i> -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	I	—	III	—	PXRD, DSC
2000	31	I	—	III	II ^b	PXRD, DSC, IR
2002	32	—	—	—	IV, <i>C</i> -Monoclinic	Crystal structure
	This study	I	II	III	IV	XRD, DSC, IR

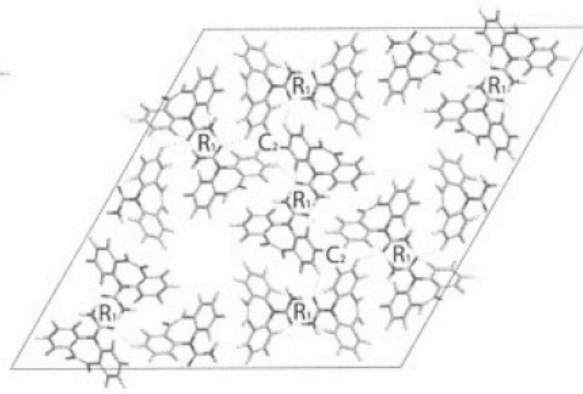
^aEach form was verified by the listed method as well as the method of preparation of each form.

^bThese forms are most similar to *C*-monoclinic CBZ, however, differences noted in the text exist.

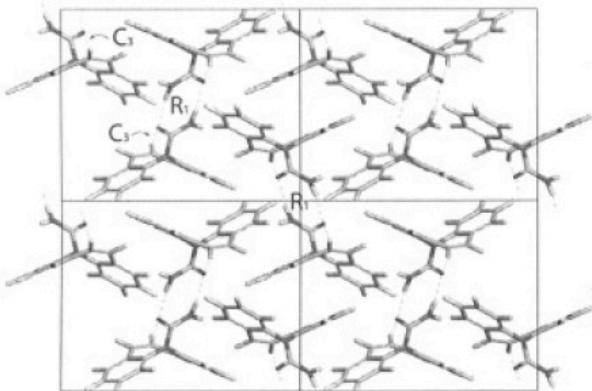
Triclinic
Form I



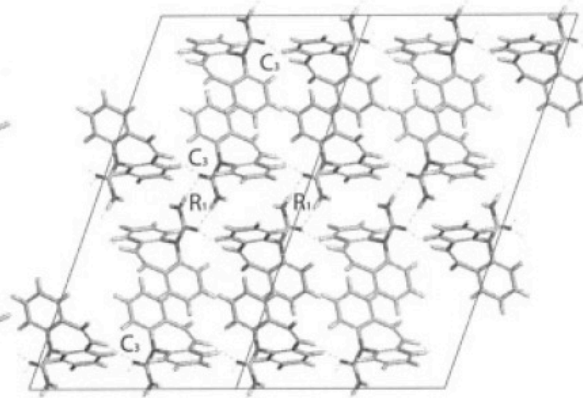
Trigonal
Form II



P-monoclinic
Form III



C-monoclinic
Form IV



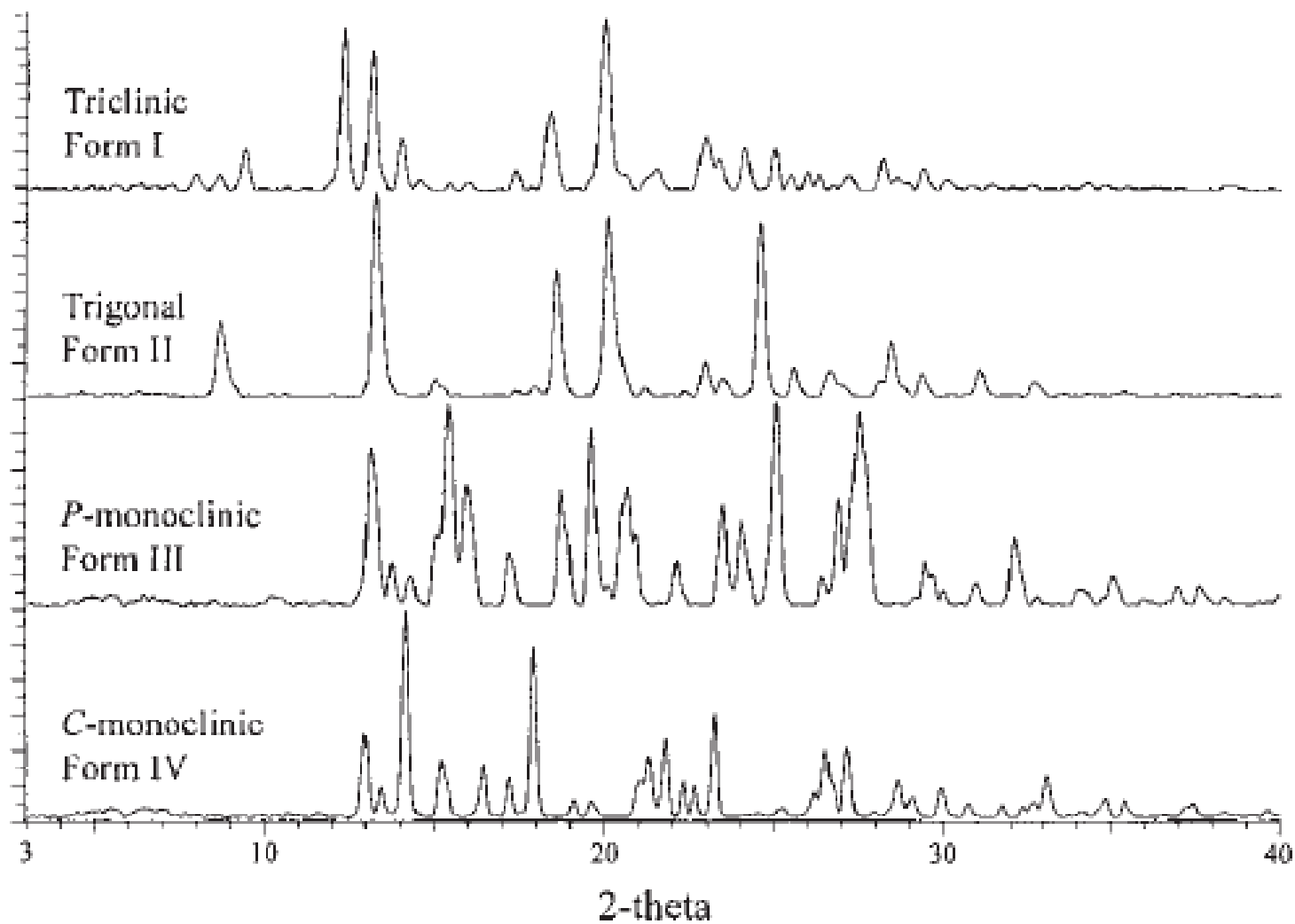
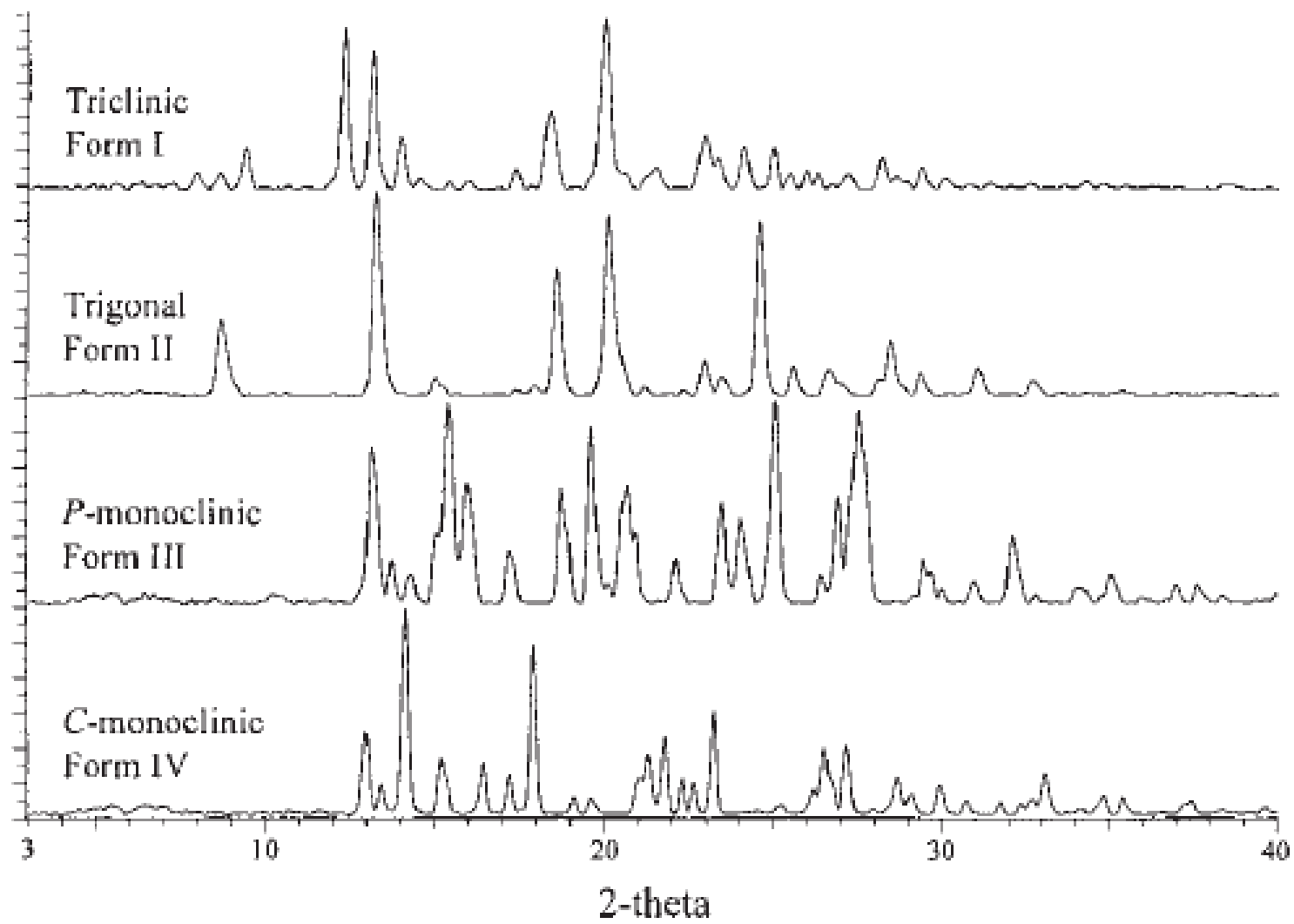


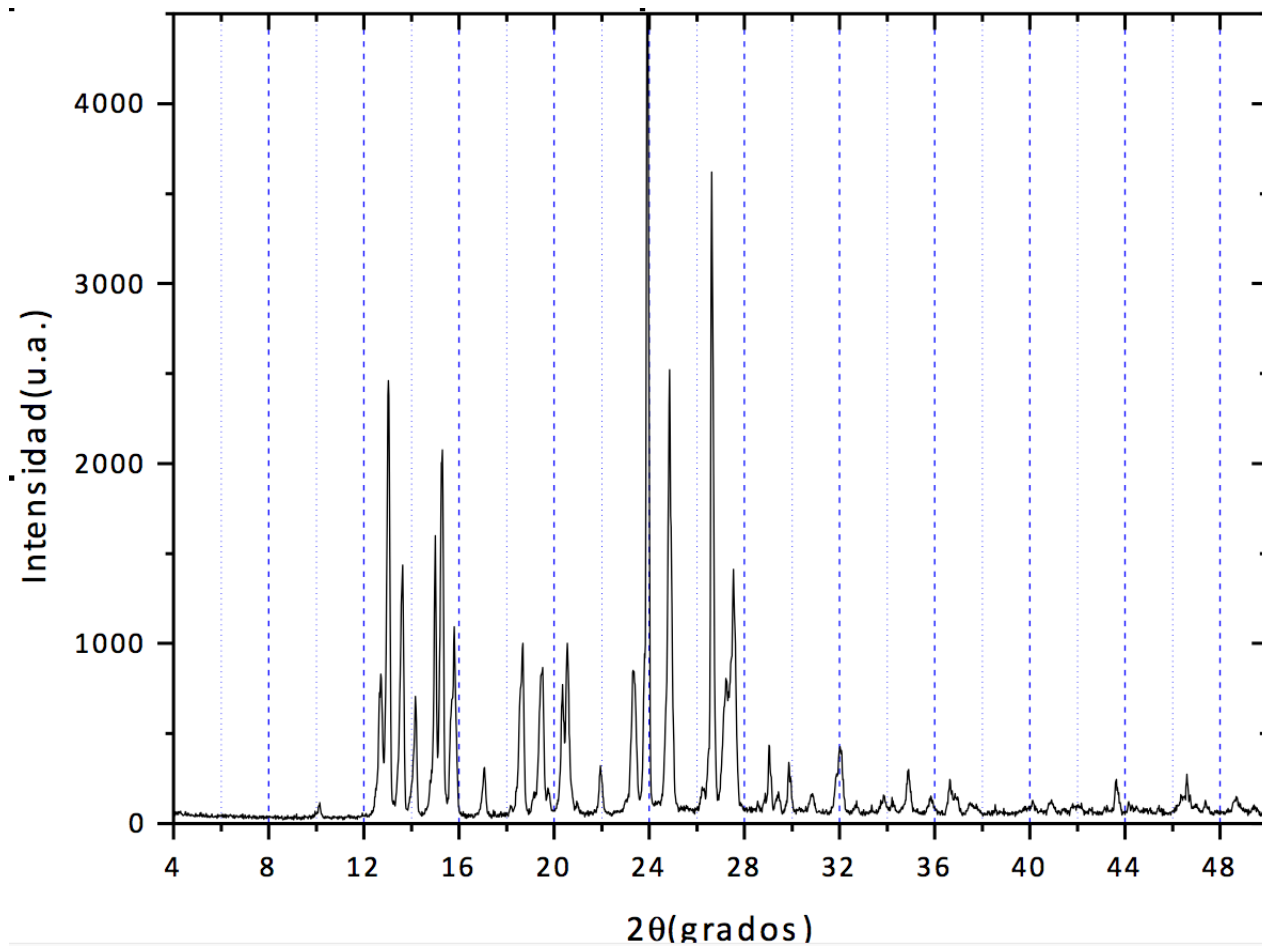
Tabla con Máximos de Difracción

Table 2. Powder X-ray Diffraction Peak Positions and Relative Intensities of the Four Anhydrous Polymorphs of CBZ

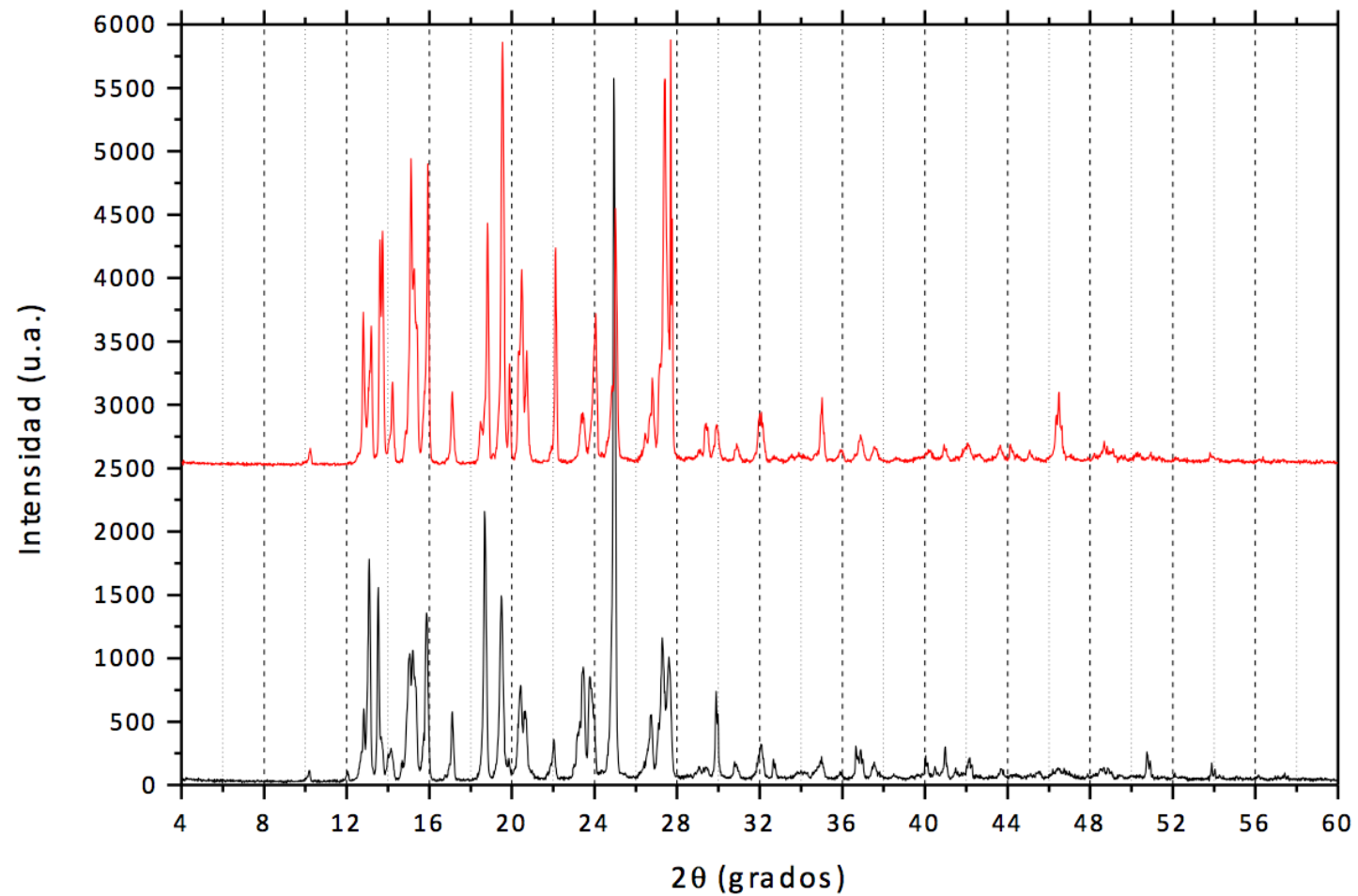
Triclinic (Form I)		Trigonal (Form II)		<i>P</i> -Monoclinic (Form III)		<i>C</i> -Monoclinic (Form IV)	
2θ (°)	Intensity (%)	2θ (°)	Intensity (%)	2θ (°)	Intensity (%)	2θ (°)	Intensity (%)
7.92	45	8.68	57	13.14	87	12.93	51
8.63	44	13.26	100	13.71	41	13.42	29
9.37	56	15.00	20	14.26	34	14.11	100
12.28	100	18.56	64	15.03	47	15.18	35
13.15	87	20.07	86	15.36	100	16.42	31
13.98	47	21.12	14	15.93	65	17.21	27
14.52	26	22.89	24	17.17	35	17.89	79
17.40	25	23.43	18	18.69	60	19.09	17
18.39	51	24.54	82	19.56	85	19.61	16
19.99	94	25.55	23	20.56	64	21.01	26
21.48	22	26.61	20	20.85	44	21.27	35
22.92	37	28.41	33	22.07	29	21.79	43
23.30	27	29.31	20	23.45	53	22.28	25
24.07	31	31.04	19	23.99	49	22.64	23
24.95	33	32.69	12	25.00	92	23.22	51
25.44	23			26.40	24	25.21	11
25.93	24			26.87	57	26.19	18
26.27	23			27.47	90	26.49	36
27.12	20			29.44	28	27.17	38
28.15	25			30.98	18	28.71	24
29.35	19			32.09	38	29.08	17
30.05	14			35.05	22	29.99	19
				36.98	17	30.77	12
				37.63	17	31.79	11
						32.41	11
						32.73	13
						33.11	24
						34.87	14
						35.44	13
						37.45	11



Muestra 1



Muestra 2



Preguntas:

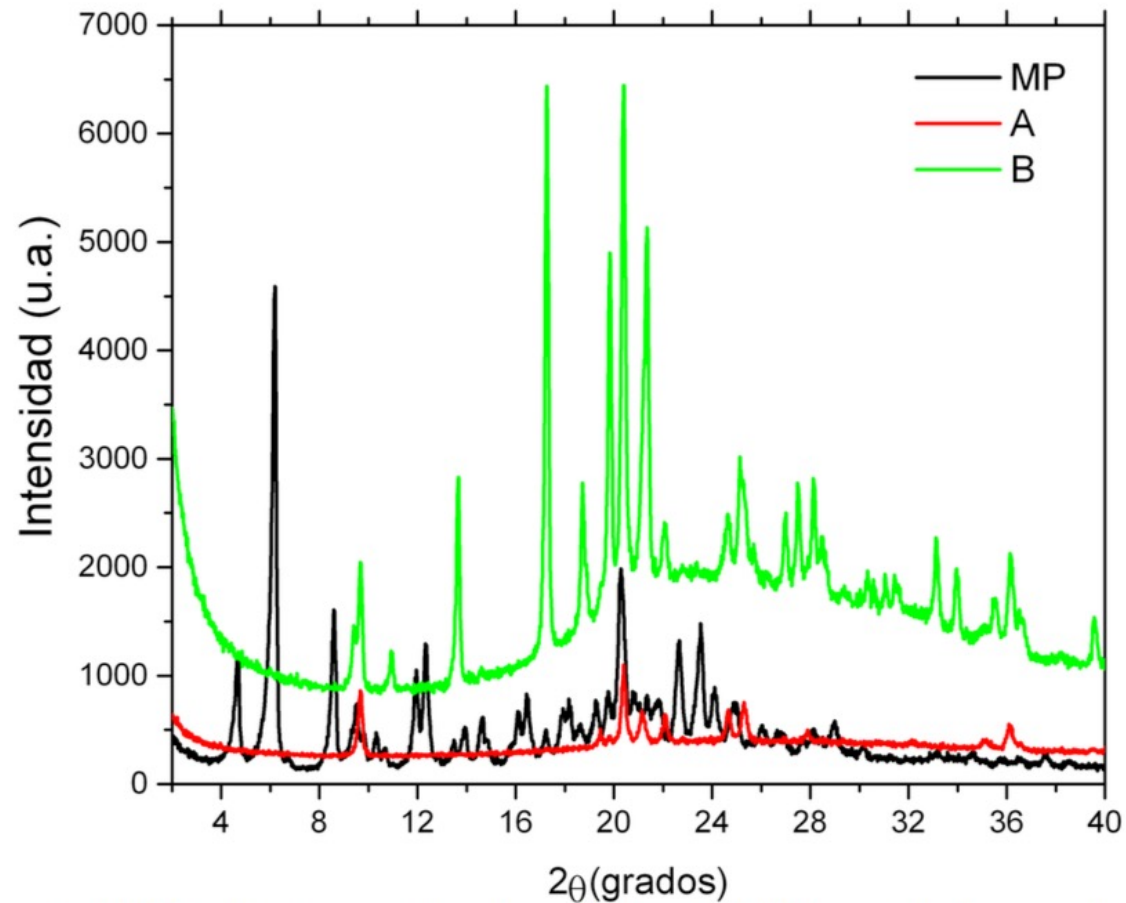
1. ¿Cuál es la forma cristalina que corresponde a la muestra 1 y la muestra 2?
2. ¿Qué diferencia observa en las muestras incluidas en la Figura de la muestra 2?
3. ¿Cuál puede ser el origen en dichas diferencias?
4. ¿Qué consecuencias puede tener en el análisis las diferencias encontradas?

Caso 3

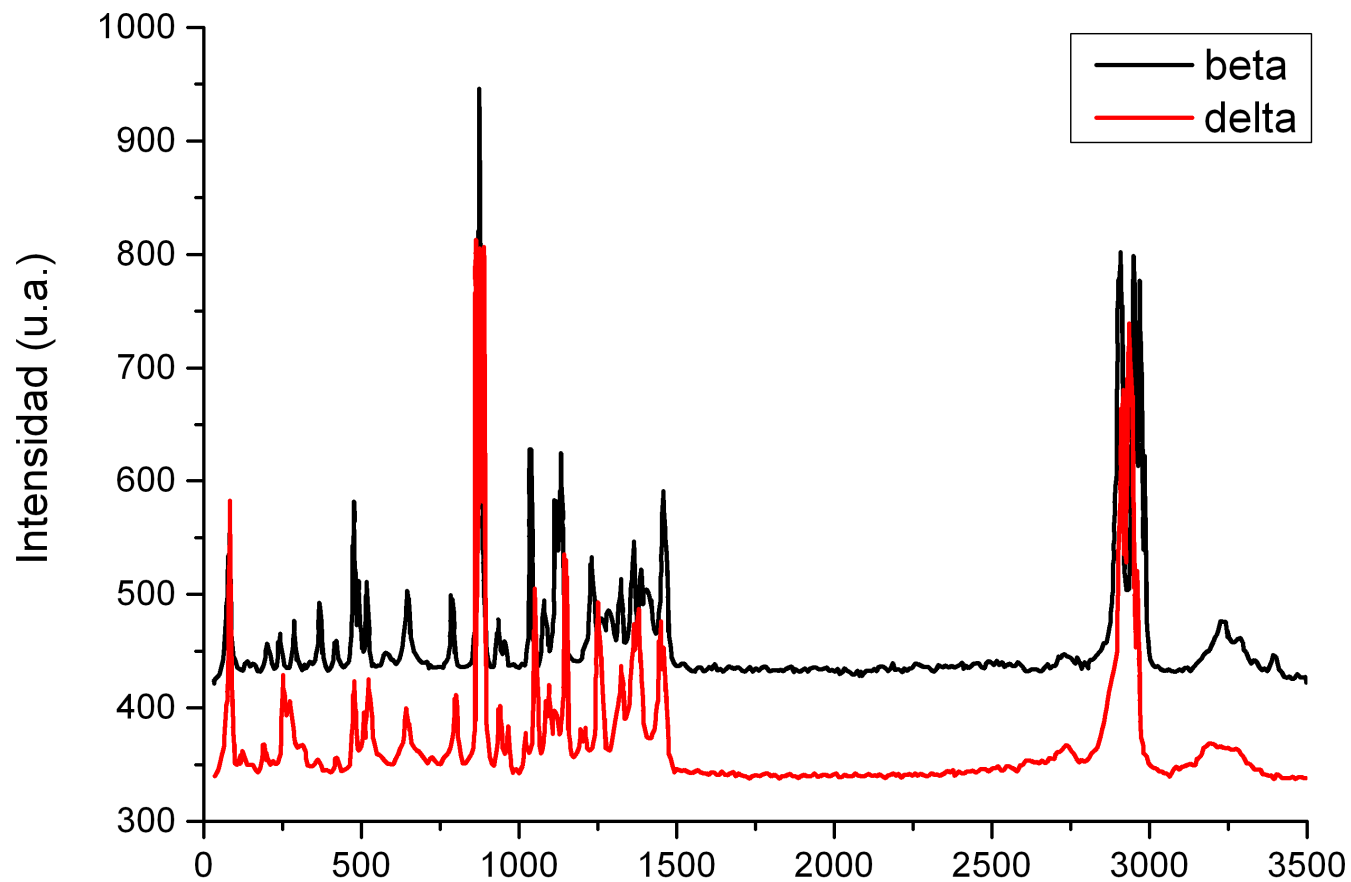


API amorfo en presencia de
excipiente cristalino

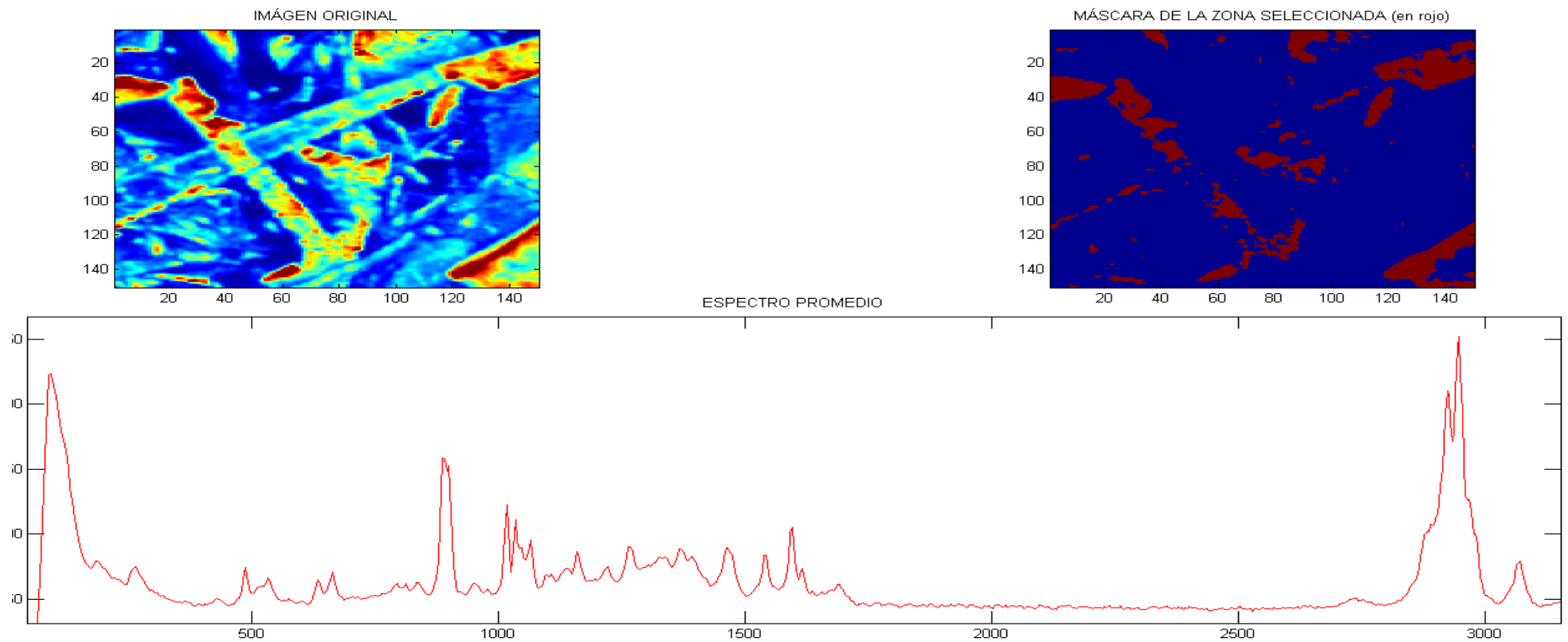
XRD: Muestra A, B y Materia Prima



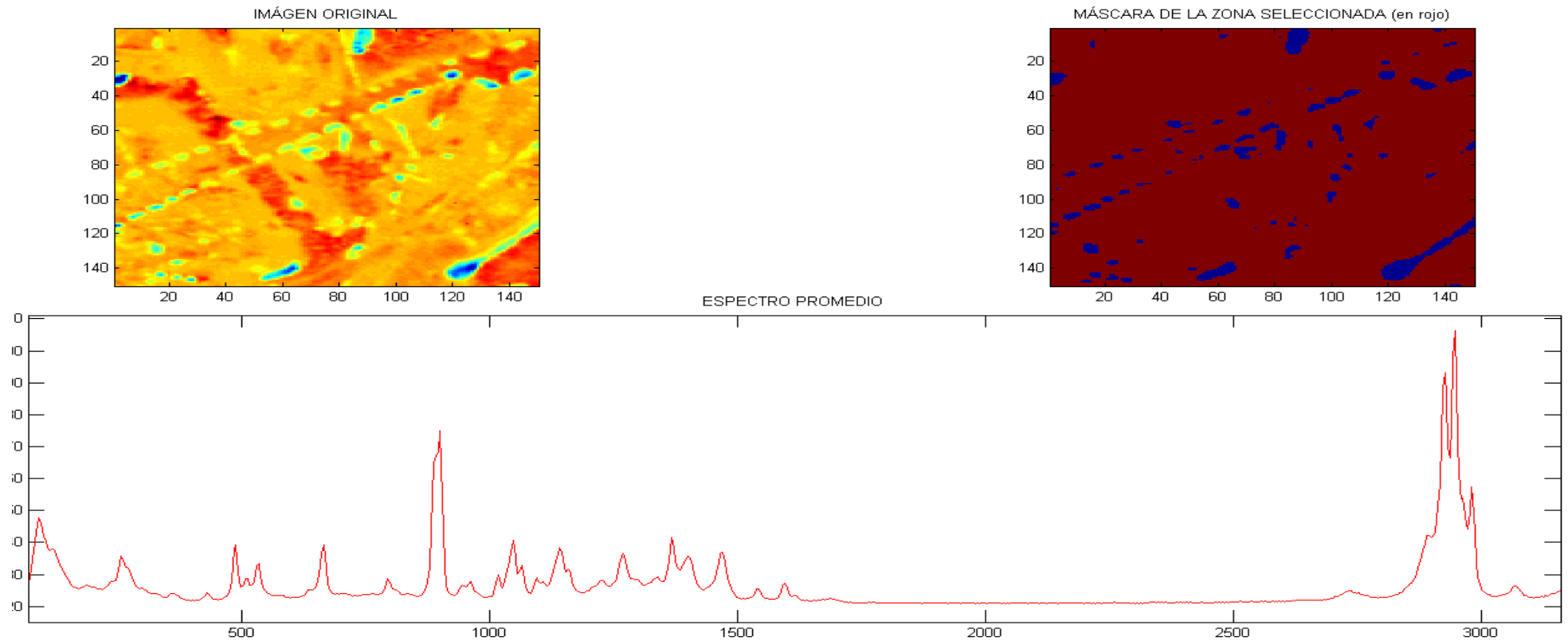
Espectros Raman de Mannitol



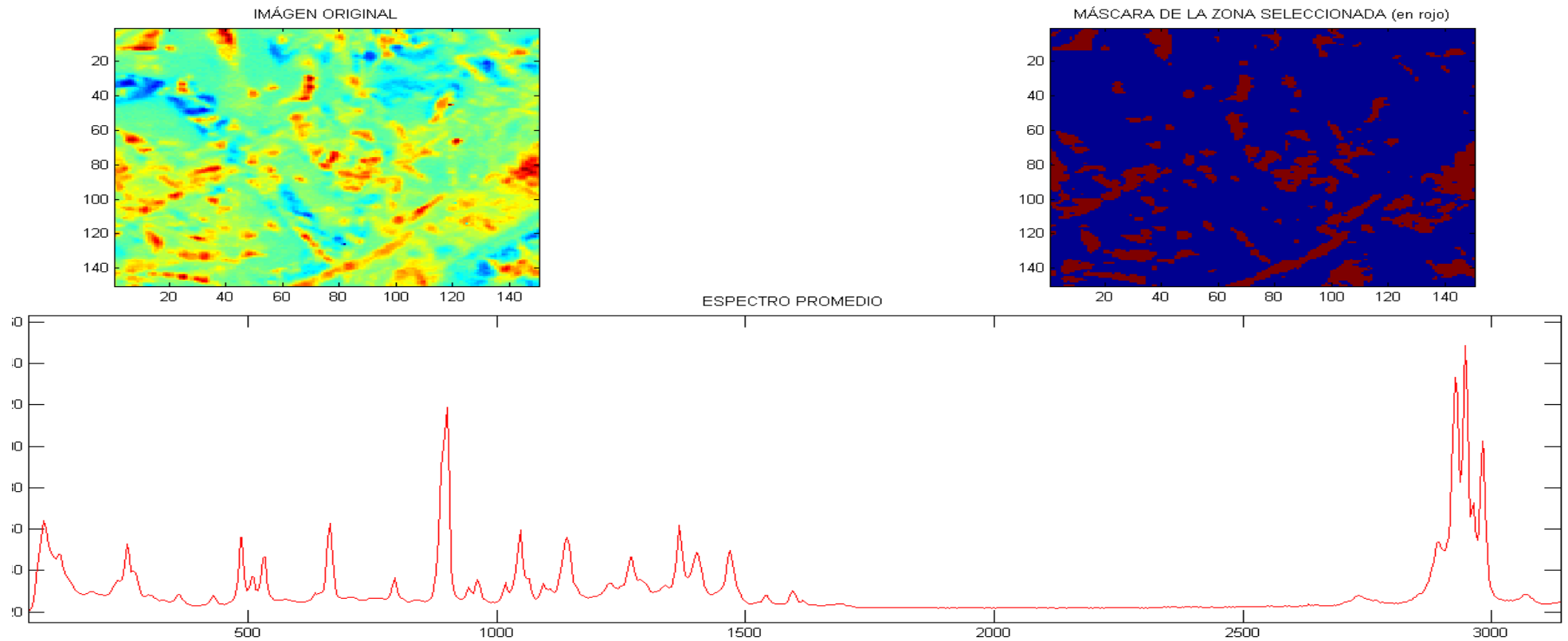
PCA: Componente 1



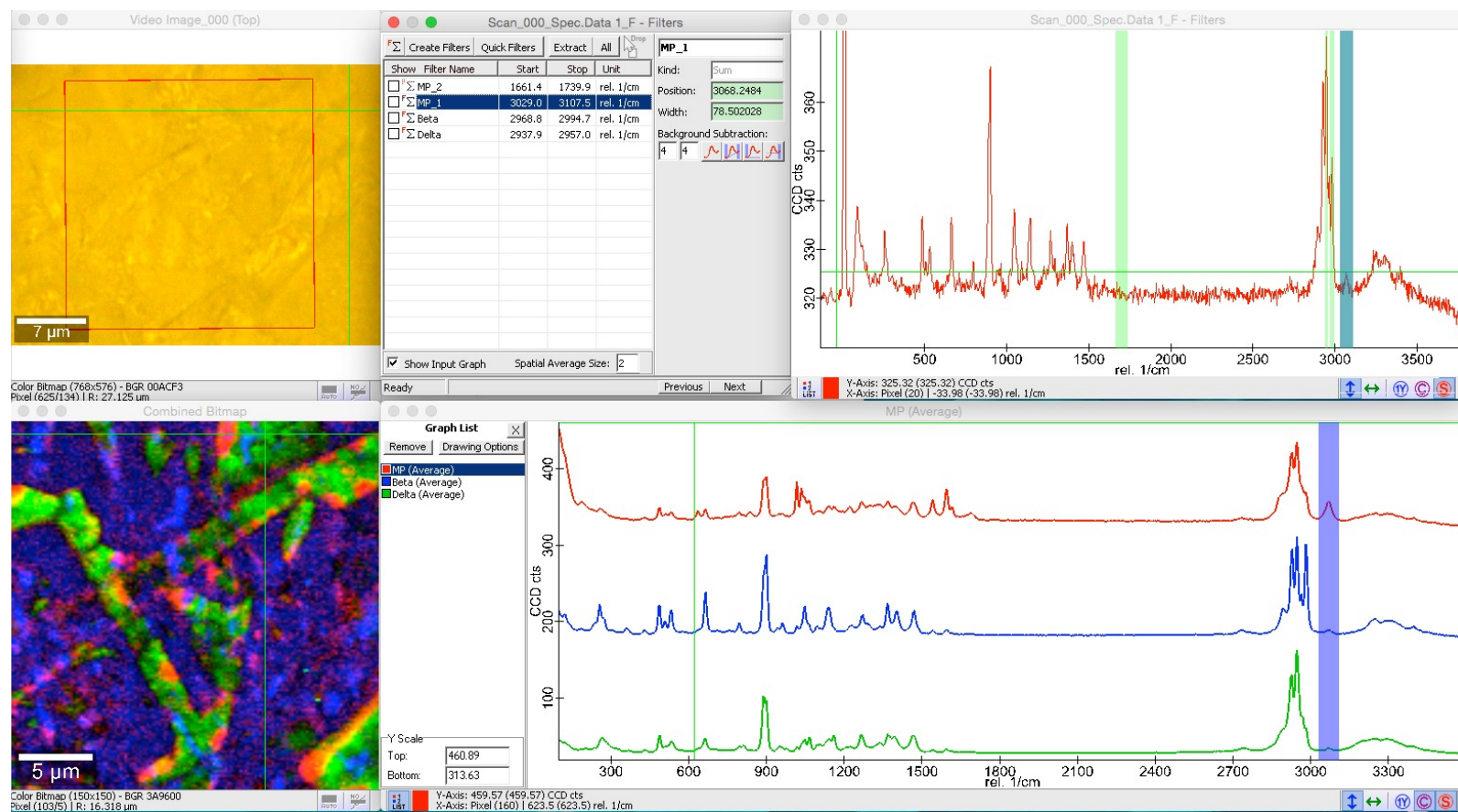
PCA: Componente 2



PCA: Componente 3

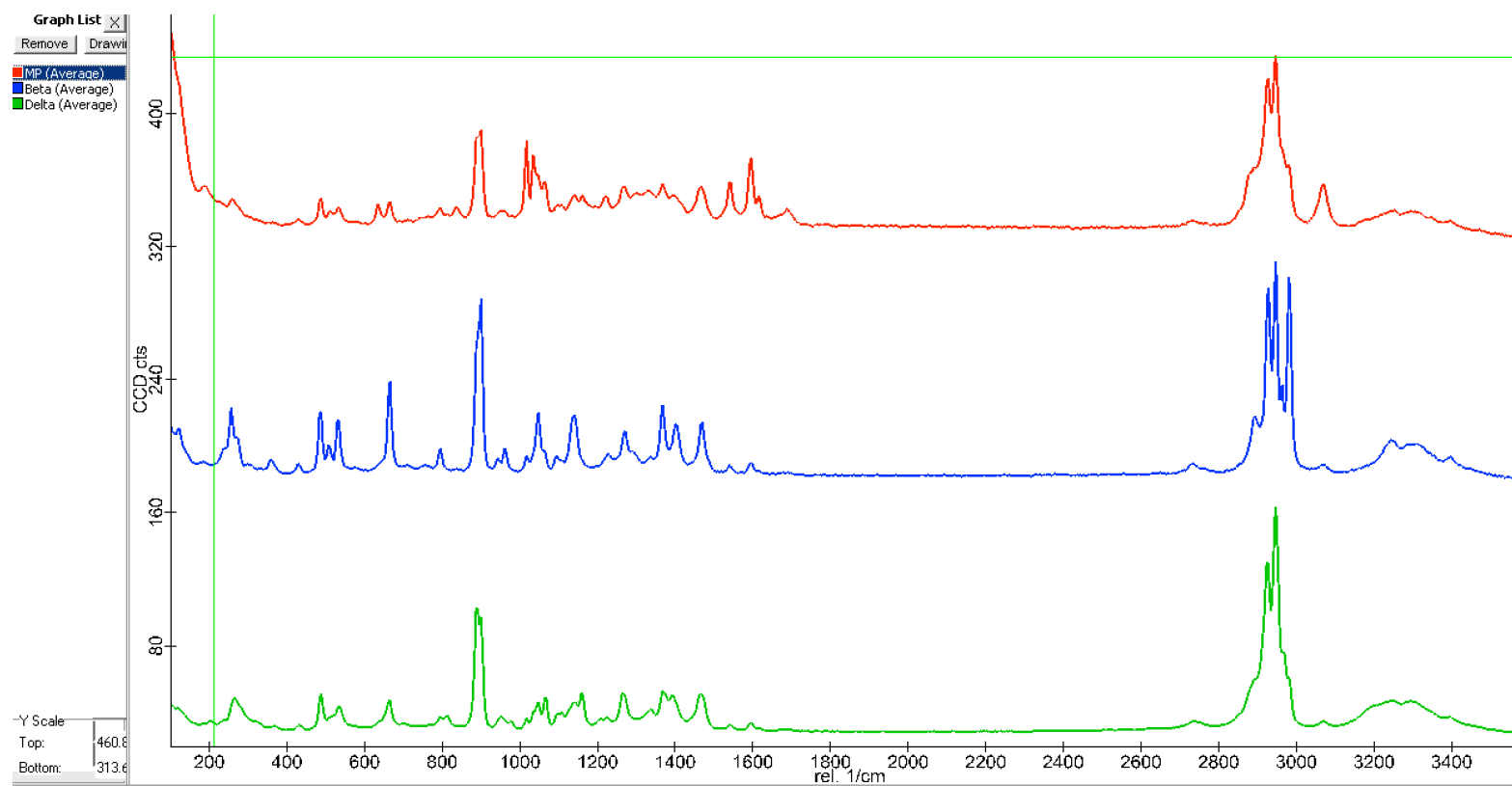


Formulaciones: Mannitol+ API



Octubre de 2023

Identificación de los 3 Componentes



Octubre de 2023