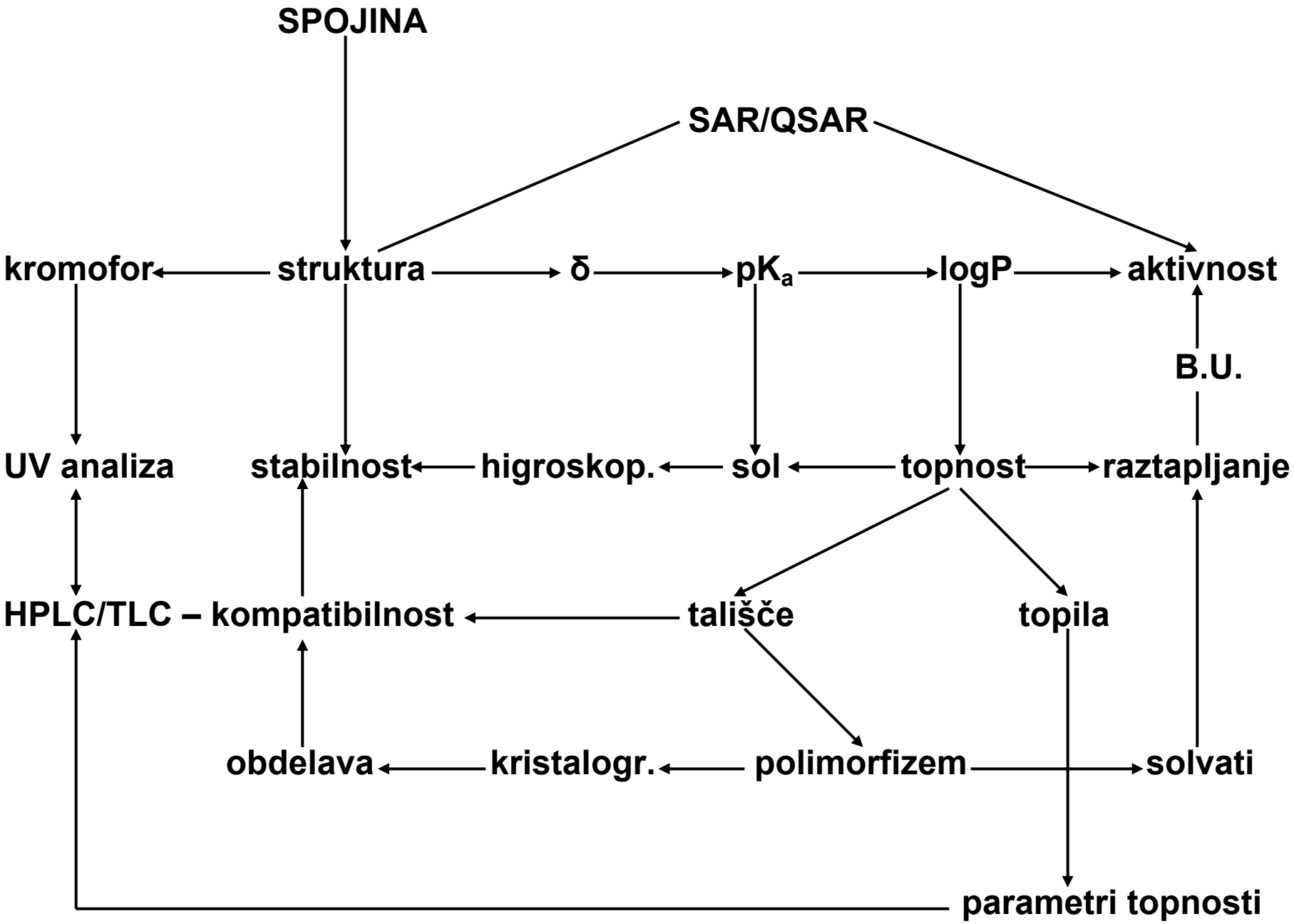

SPOJINA
SAR/QSAR
kromofor
struktura
δ
pKa
logP
aktivnost
B.U.
UV analiza
stabilnost
higroskop.
sol
topnost
raztapljanje
HPLC/TLC
kompatibilnost
tališče
topila
obdelava
kristalogr.
polimorfizem
solvati
parametri topnosti

Table 1: Predformulation drug characterization in a structured programme

Test	Method/function/ characterization	References
Fundamental		
(1) UV spectroscopy	Simple assay	Daglish (1969)
(2) Solubility	Phase solubility/purity	Mader (1954), Higuchi and Connors (1965)
Aqueous	Intrinsic and pH effects	
pK_a	Solubility control	
	Salt formation	Albert and Serjeant (1984)
Salts	Solubility, hydroscopicity and stability	Berge *et al.* (1977)
Solvents	Vehicles and extraction	Yalkowsky and Roseman (1981)
K_w^o	Lipophilicity, structure activity	Leo *et al.* (1971)
Dissolution	Biopharmacy	Swarbrick (1970)
(3) Melting point	DSC — polymorphism, hydrates and solvates	Wendlandt (1974), Haleblian (1975), Haleblian and McCrone (1969)
(4) Assay development	UV, HPLC and TLC	Jaffe and Orchin (1962), Bristow (1967)
(5) Stability	Thermal, hydrolysis, pH, oxidation, photolysis and metal ions	Mollica *et al.* (1978) Connors *et al.* (1979)
In solution		
In solid state		
Derived		
(6) Microscopy	Particle size and morphology	McCrone *et al.* (1978)
(7) Bulk density	Tablet and capsule formulation	Neumann (1967)
(8) Flow properties	Tablet and capsule formulation	Neumann (1967)
(9) Compression properties	Aid excipient choice	De Boer *et al.* (1978), Jones (1981)
(10) Excipient compatibility	Preliminary screen by DSC, confirmation by TLC	Smith (1982)

POLIMORFIZEM

1. Različna ureditev molekul
   - različno: tališče
     topnost
     gostota
     rast
     optične in električne lastnosti
     parni tlak
2. Termodinamika
   - metastabilno stanje v stabilno
3. Pogostnost
   - 63 % barbituratov
   - 67 % steroidov
   - 40 % sulfonamidov
4. Nomenklatura
   α, β, γ, δ; I., II., III., IV.

5. Pomen za oblikovanje

KARAKTERIZACIJE TRDNIH SPOJIN

Metoda	Vzorec
Mikroskopija	1 mg
Tališče (mikroskop)	1 mg
Termalne analize DSC – DTA	2,5 mg
IR – spektroskopija	2,2 mg
X – difrakcija	500,0 mg
Elektronska mikroskopija	2 mg
Termogravimetrična analiza	10 mg
Topnost – raztapljanje	1 mg – 1000 mg

KARAKTERISTIKE POLIMORFOV SULFOTIAZOLA

	oblike		
	I.	II.	III.
Tališče	200 – 202	200 – 202	200 – 202
Temp. prehoda v I.	–	173 – 175	173 – 175
Oblika	palice	prizme	plošče
Št. molekul	8	4	4
Gostota	1,5	1,55	1,57

POLIMORFIZEM SULFANILAMIDA

Polimorfinski sistem		*a*	*b*	*c* (10^{-10}*m*)	*kot* (º)	*v* (Å^3)
α	monoklinski	9,04	9,03	10,06	110º42’	821,2
β	monoklinski	8,95	9,06	9,96	110º	807,4
γ	monoklinski	7,78	12,84	7,95	106º1’	800,4
δ	ortorombični	14,81	5,65	18,46		777,3

HIDRATI – SOLVATI

1. Pogostnost
2. Odkrivanje: DSC, TGA, mikroskop
3. Vpliv na topnost in B.U.

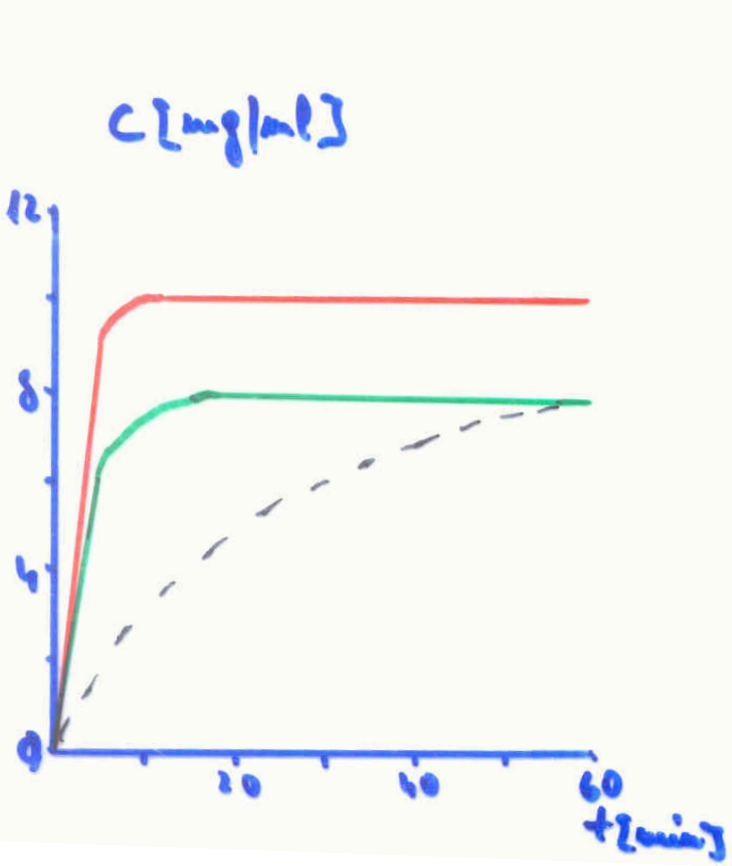
HIDRATI OUABAINA

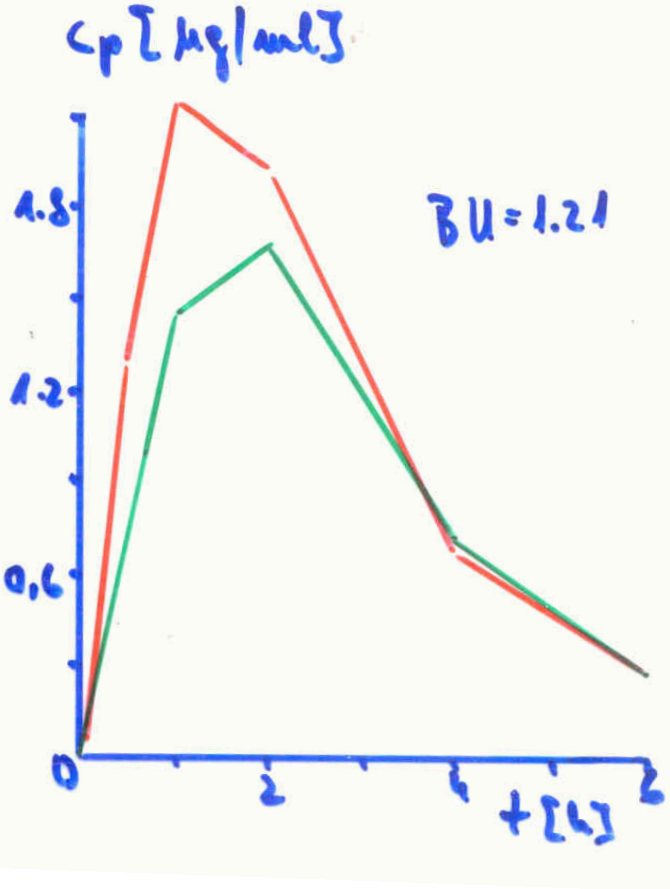
Hidrat	n H_2O	Izvor
di – hidrat	2	iz vode pri 50ºC
tri – hidrat	3	iz 94 % dioksana
tetra – hidrat	4	iz 97 % MeOH
4 (1/2) – hidrat	4 (1/2)	iz 95 % EtOH
okta – hidrat	8	iz vode pri 20ºC
nona – hidrat	9	iz vode pri 4ºC
anhidrid	–	iz EtOH pri 150ºC

VPLIV NA TOPNOST IN B.U.

Učinkovina	Tališče	Topnost
Ampicilin anhidrid	200,5ºC	10,1 mg/mL
Ampicilin trihidrat	203,0ºC	7,6 mg/mL
Glutetimid anhidrid	83,0ºC	0,42 mg/mL
Glutetimid hidrat	68,0ºC	0,26 mg/mL

Ampicilin
anhidrid
trihidrat





Oblika	Pogostnost (%)
Tablete	45,8
Kapsule	23,0
Raztopine or.	16,0
Injekcije	15,0
Mazila	3,0
Supozitorije	3,3
Aerosoli	1,2
Kapljice za oči	1,8
Ostalo	0,3

OSNOVNI LASTNOSTI NOVE SPOJINE:

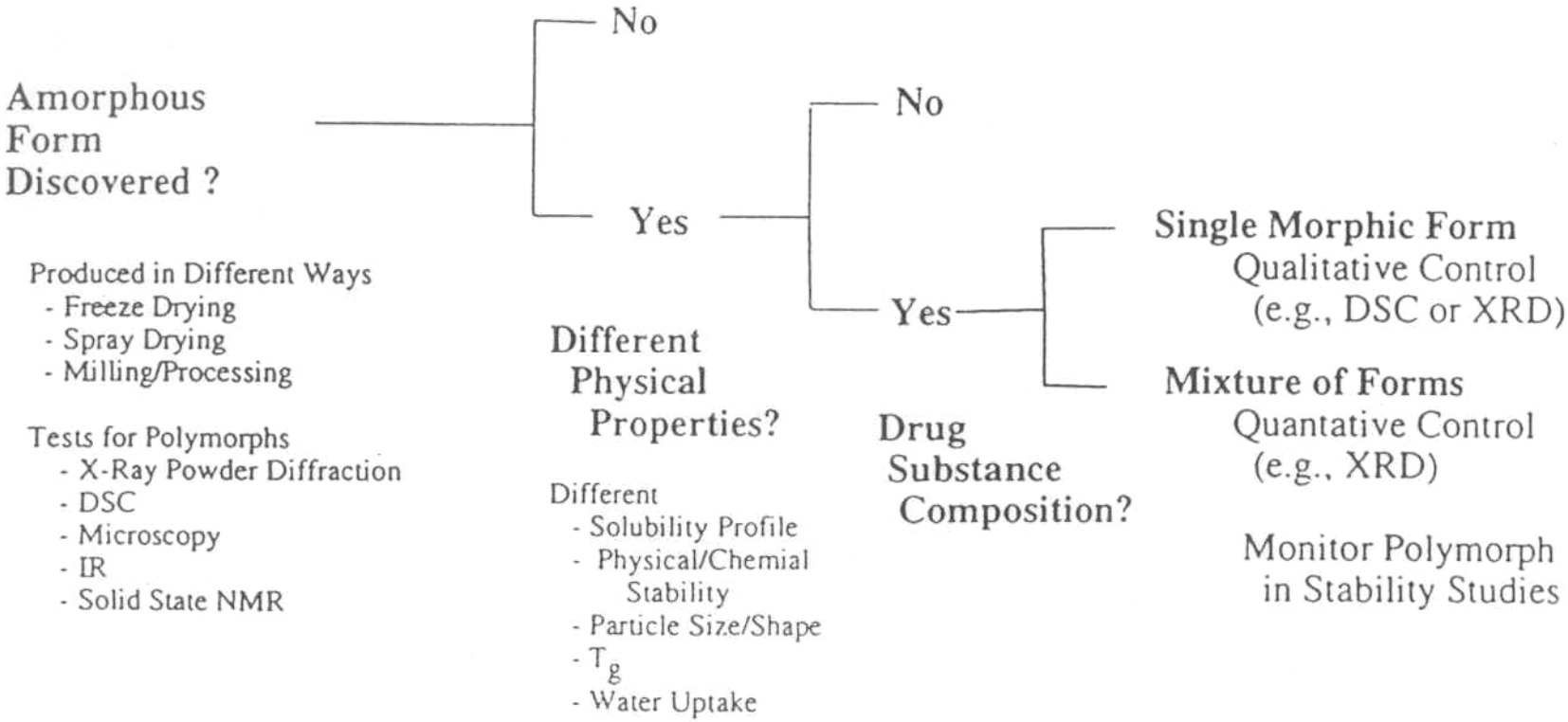
a) intrinzična topnost (c_0)

b) konstanta disociacije (pK_a)

J. I. Wells, Pharmaceutical preformulation: The Physicochemical Properties of Drug Substances

AMORPHOUS FORMS

Drug Substance

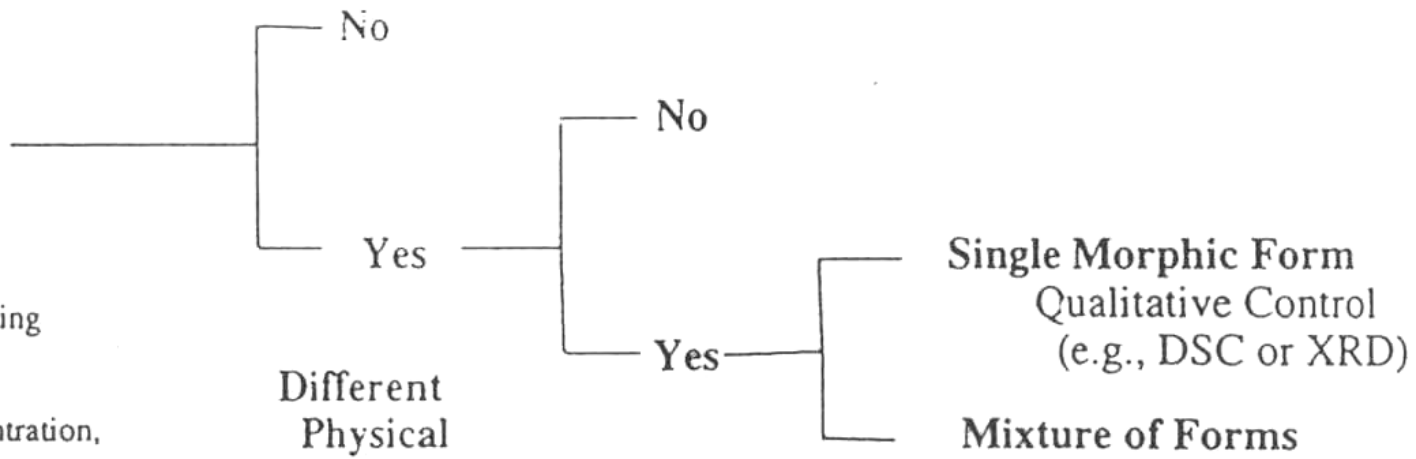


Does it Crystallize? How? When?

Flow chart for amorphous solids.

POLYMORPHS

Drug Substance



Different Recrystallizing Solvents (different polarity) - vary temperature, concentration, agitation, pH

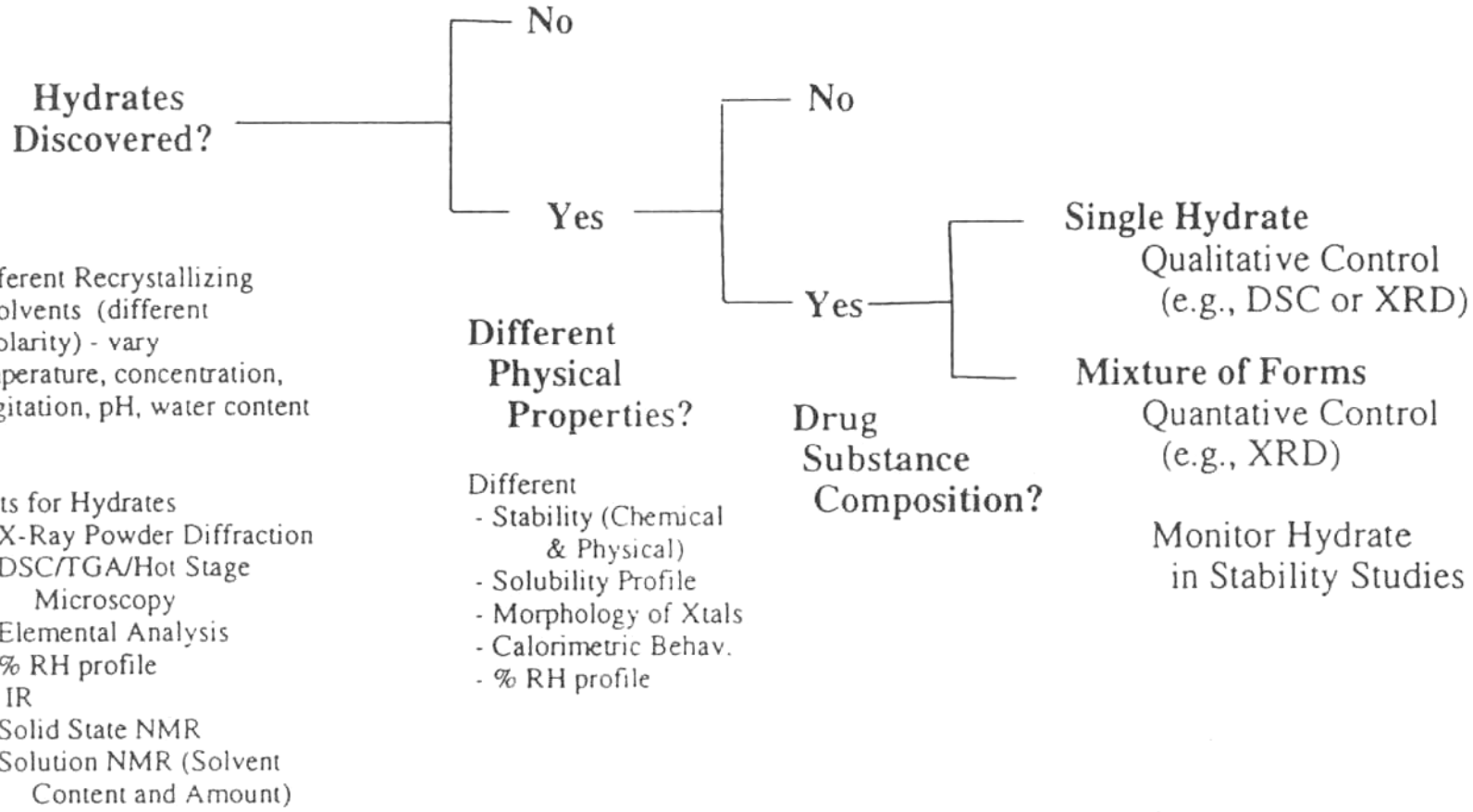
Tests for Polymorphs
- X-Ray Powder Diffraction
- DSC (Thermoanalytical Methods)
- Microscopy
- IR
- Solid State NMR

Different
- Stability (Chemical & Physical)
- Solubility Profile
- Morphology of Xtals
- Calorimetric Behav.
- % RH profile

Flow chart/decision tree for polymorphs.

HYDRATES (SOLVATES)

Drug Substance and Solvent



Flow chart for solvates or hydrates.

Figure 1: The dissolution – time curves for anhydrous and hydrated theophylline in water at 25°C. The two types of open circles represent successive experiments (18).

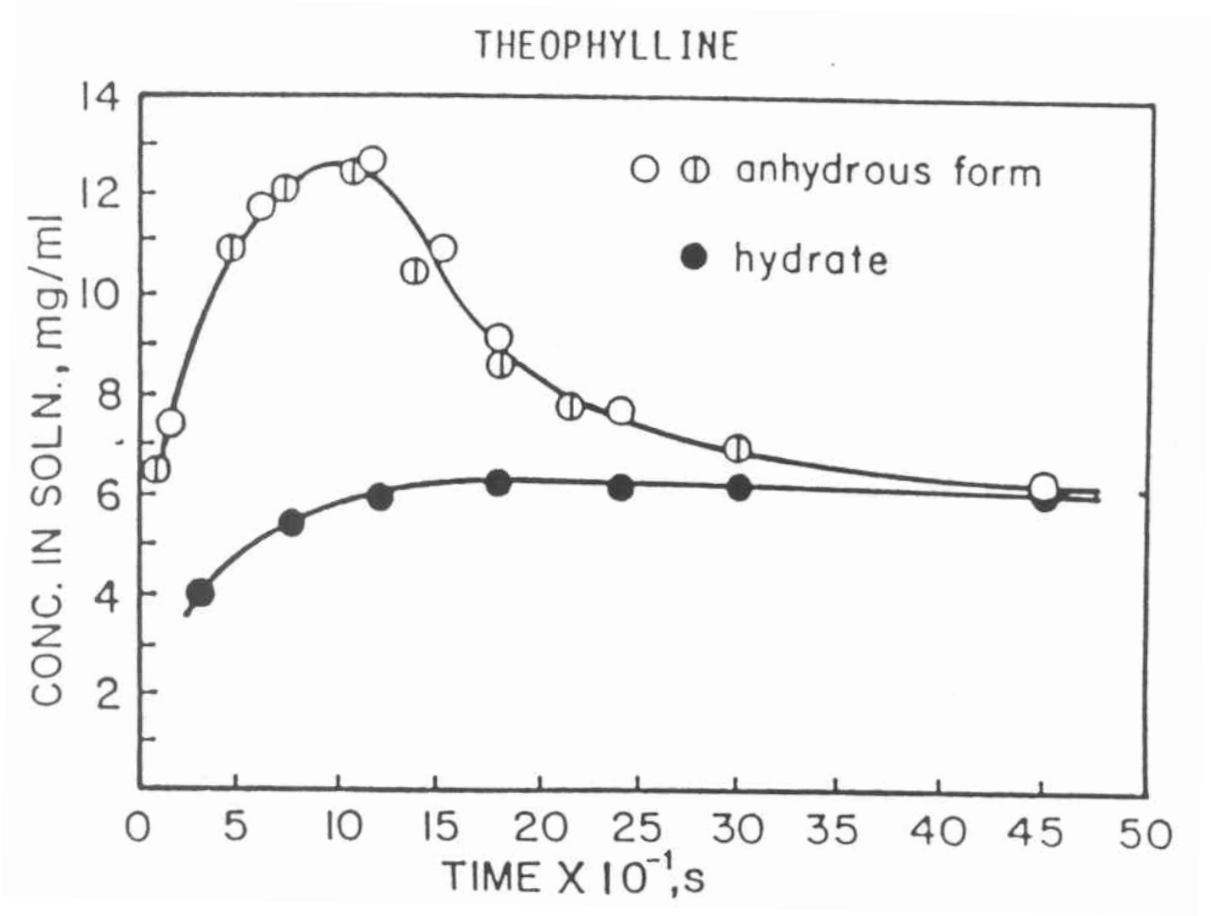
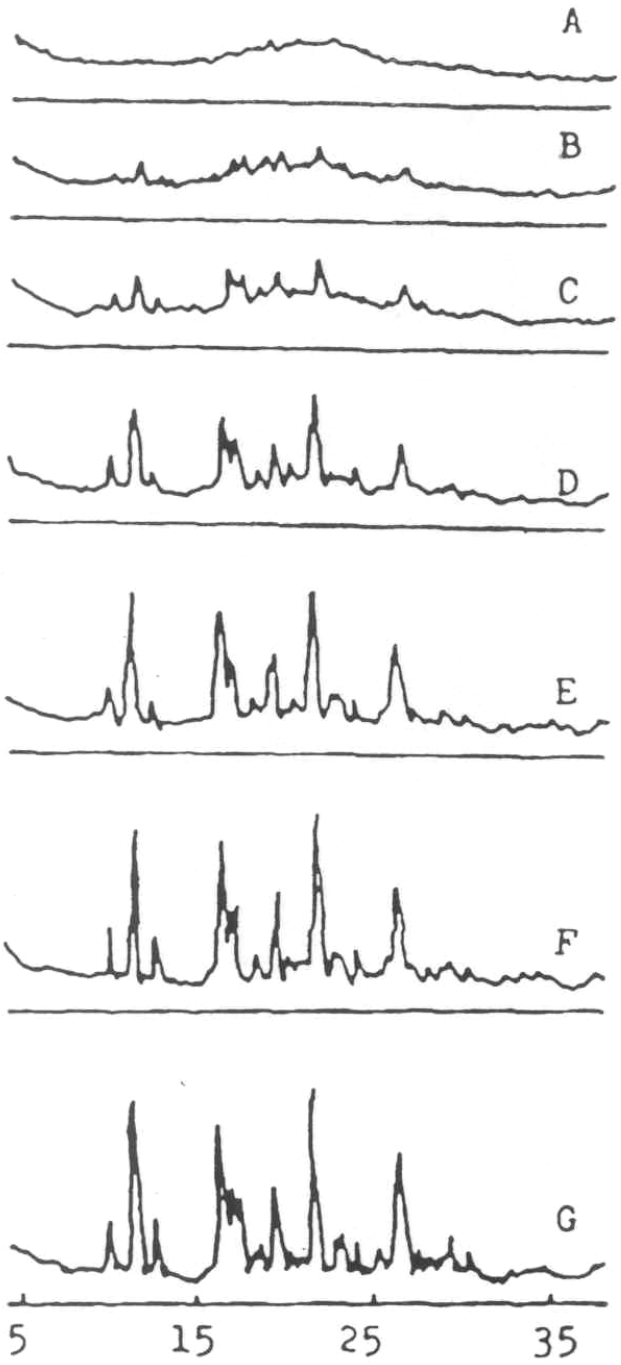
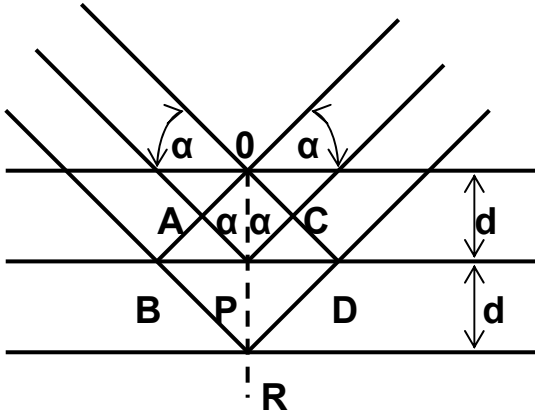


Figure 2: Behavior of amorphous indomethacin upon standing: A, at start; B, 24 h; C, 48 h; D, 7 d; E, 14 d; F, 30 d; G, 67 d.



Rentgenska praškovna difrakcija



$AP + PC = n\lambda$

$AP = PC = d \cdot \sin\alpha$

$n\lambda = 2d \cdot \sin\alpha$ Braggova enačba

1. Razmaki med plastmi atomov (d) ≈ λ
2. Urejenost razporeditve atomov (centrov odboja)

Rentgenska kristalografija (rentgenska difrakcija)

Difrakcija ~ lom

Vir rentgenskih (X) žarkov:

- obsevanje kovinske "tarče" z žarkom visoko energetskih e^-
- snov izpostavimo primarnemu X – žarku, da dobimo sekund. X - žarek (fluorescenca)
- radioaktivni vir → razpad → X – žarki

▪) konstruktivna (indestruktivna) interferenca

Figure 3: Powder X-ray diffraction patterns of the polymorphs of 8 – (2 – methoxycarbonylamino – 6 – methylbenzyloxy) – 2 – methyl – 3 – (2 – propynyl) – imidazo {1,2 - a}pyridine (1).

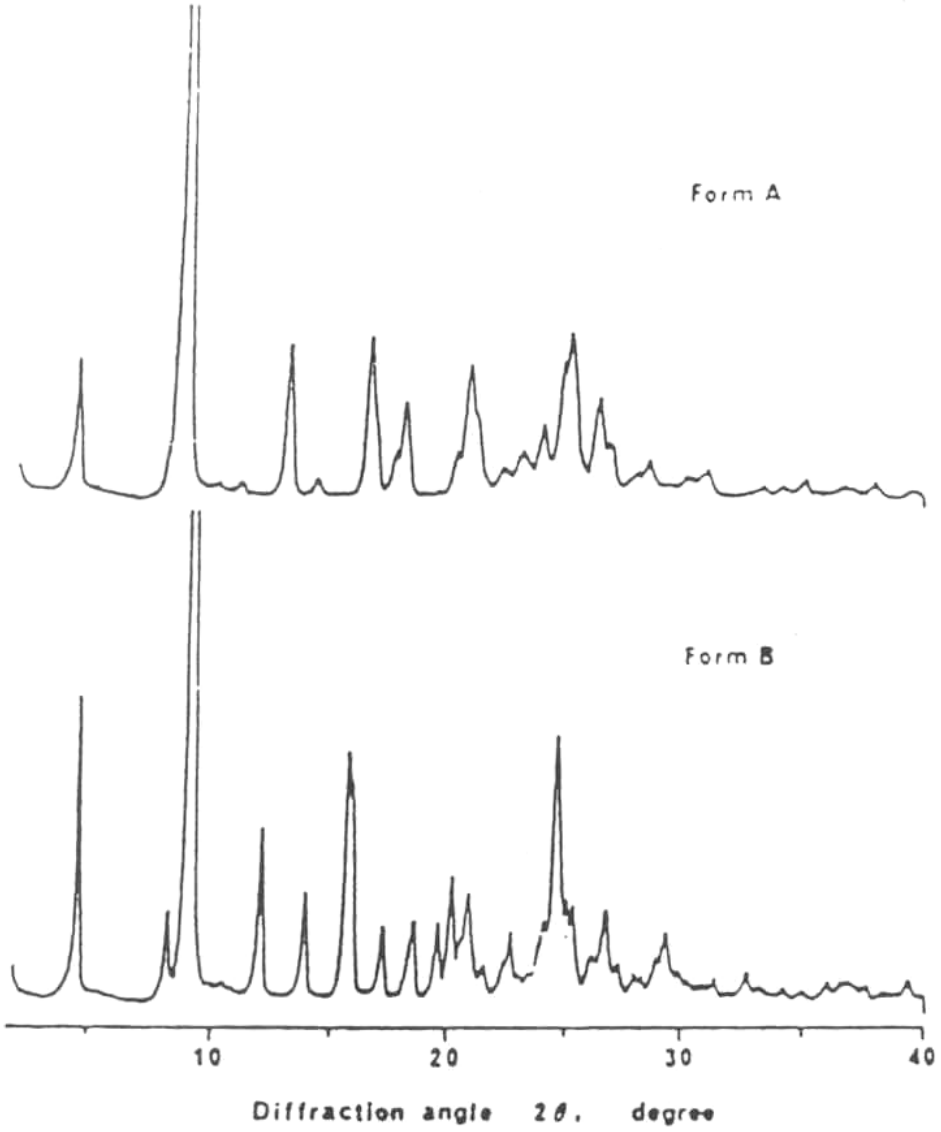
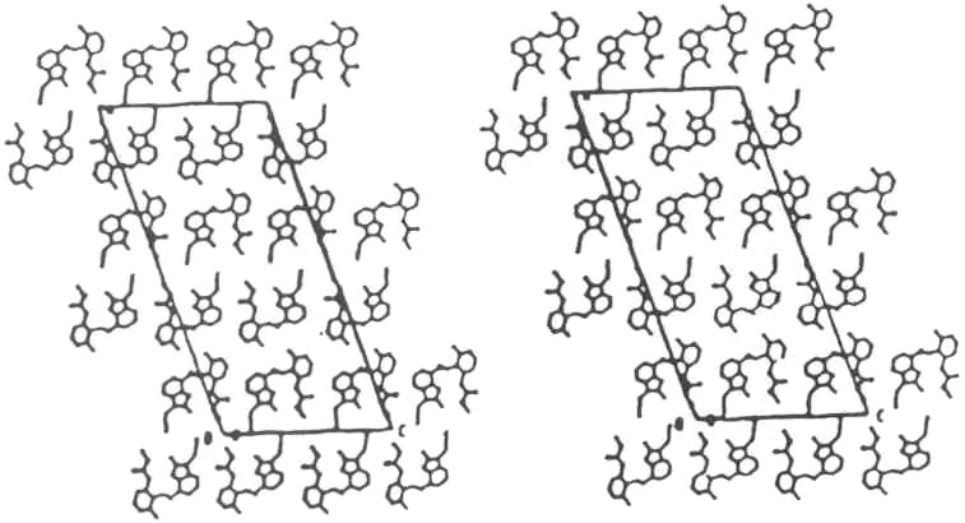


Figure 4 : Spectroscopic drawings of the crystal packing of both polymorphs of 8 – (2 – methoxycarbonylamino – 6 – methylbenzyloxy) – 2 – methyl – 3 – (2 – propynyl) – imidazo {1,2 - a}pyridine viewed along the shortest axis (Form A, b – axis; Form B, a – axis).



Form A

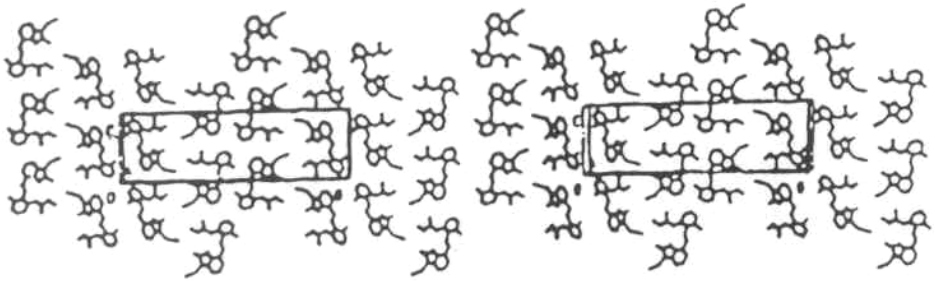


Figure 5: Solid state NMR of the two Chrystal Forms of Prednisolone.

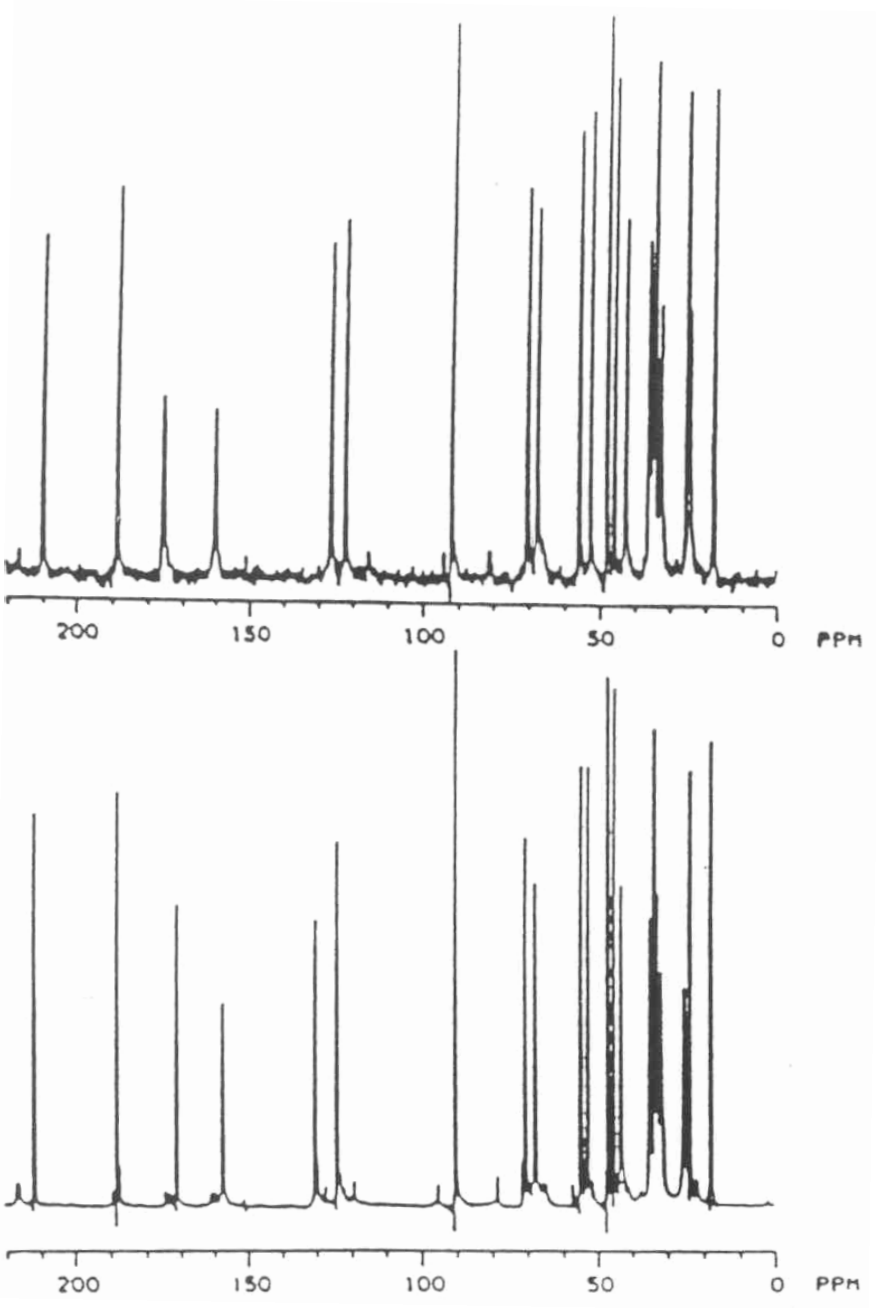
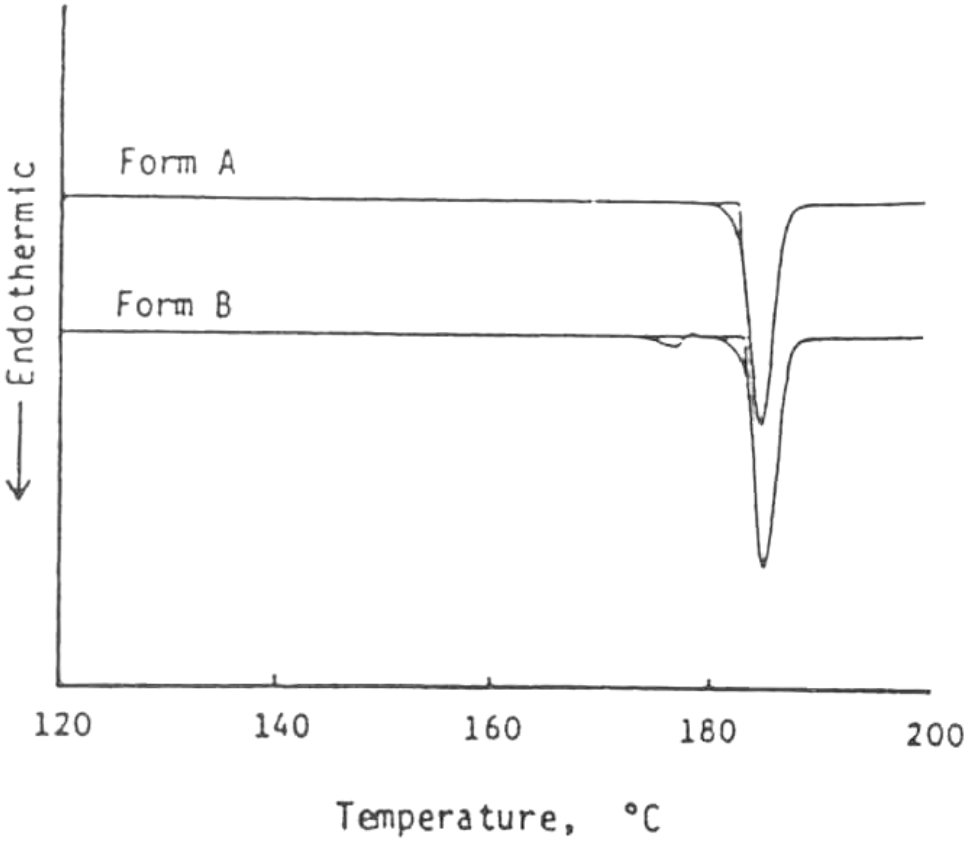


Figure 6: DSC thermal curves of the polymorphs of 8 – (2 – methoxycarbonylamino – 6 – methylbenzyloxy) – 2 – methyl – 3 – (2 – propynyl) – imidazo {1,2 - a} pyridine (1). These curves show that Form A melts whereas Form B undergoes a small endothermic transition and then melts at the same temperature as Form A.



Polymorphism

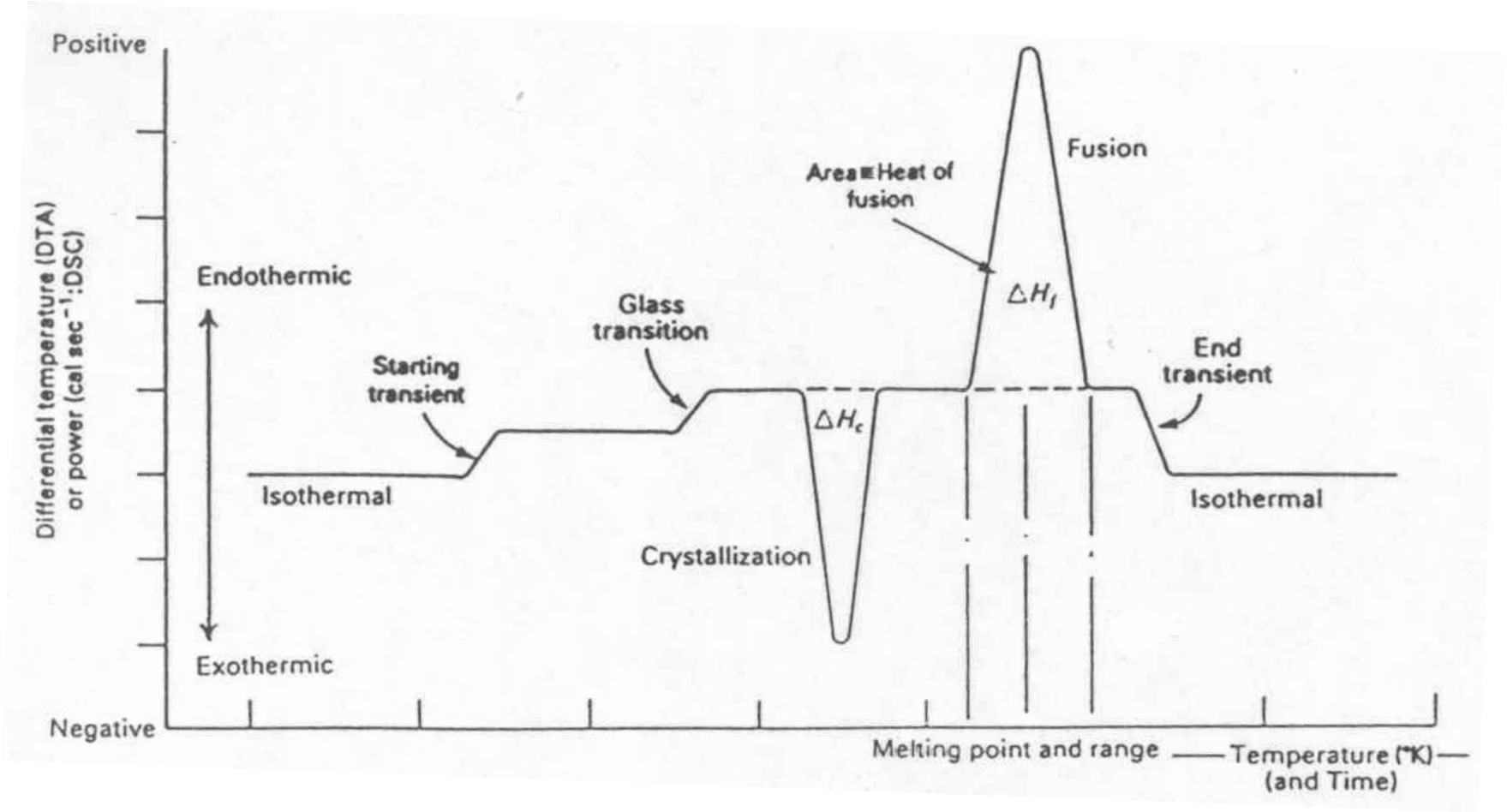
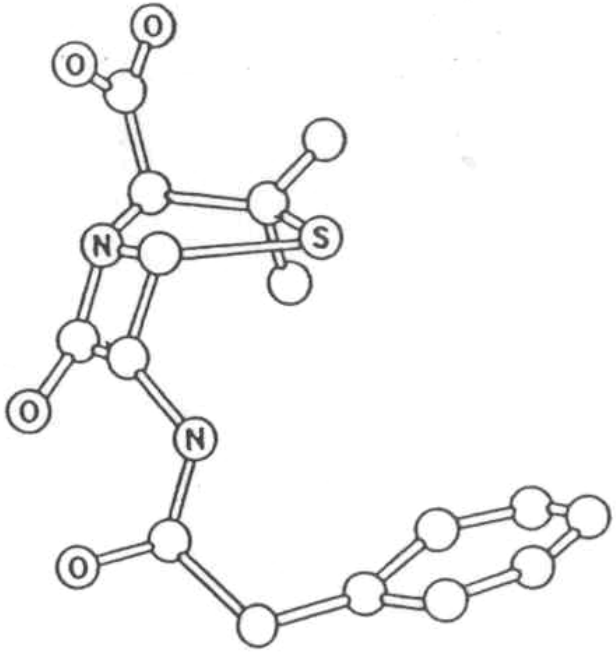


Figure 7: Schematic thermogram

Figure 8: *(a)* Electron density map of potassium benzylpenicillin (adapted from G. L. Pitt, *Acta Cryst.* 5, 770, 1952). *(b)* A model of the structure that can be built from analysis of the electron density projection.

(a)



(b)

Polymorphism and pseudopolymorphism: influencing the dissolution properties of the guanine derivative acyclovir

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[b]*Krka, p.o., Novo mesto, R and D Division, Novo mesto, Slovenia*
[c]*Department of Pharmaceutical Science, University of Trieste, Trieste, Italy*

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Abstract

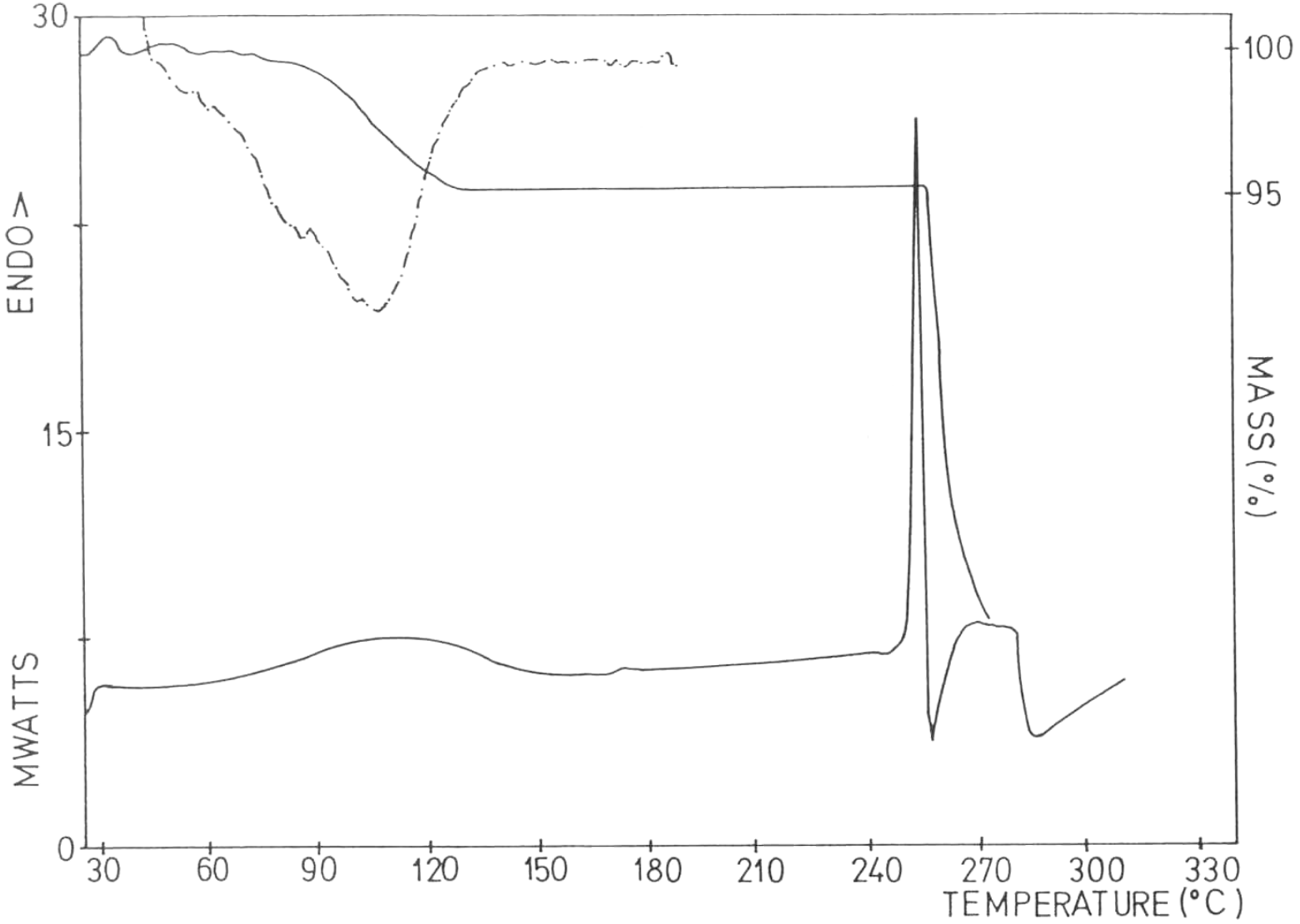
In this work we established that acyclovir exists in hydrated form and that the ratio between acyclovir and water molecules in the crystal structure is 3:2. The anhydrous crystalline form of acyclovir was also prepared. Both crystalline forms were examined by means of thermal analyses, X-ray powder diffraction, infrared spectroscopy, solubility and dissolution rate studies. The differences in almost all tested parameters between the acyclovir hydrated and anhydrous forms were observed. They were explained by different crystal forms of the substances examined. It was found, that besides hydrate, two anhydrous forms of acyclovir are present: the unstable one, obtained at a drying temperature below 150°C (which converts to the hydrate almost immediately in the atmosphere), and the stable one, obtained at drying temperatures above 150°C (which shows, on heating to 172°C, the solid–solid transition). It was thus postulated that acyclovir can exist as a pseudopolymorphic and polymorphic solvate.

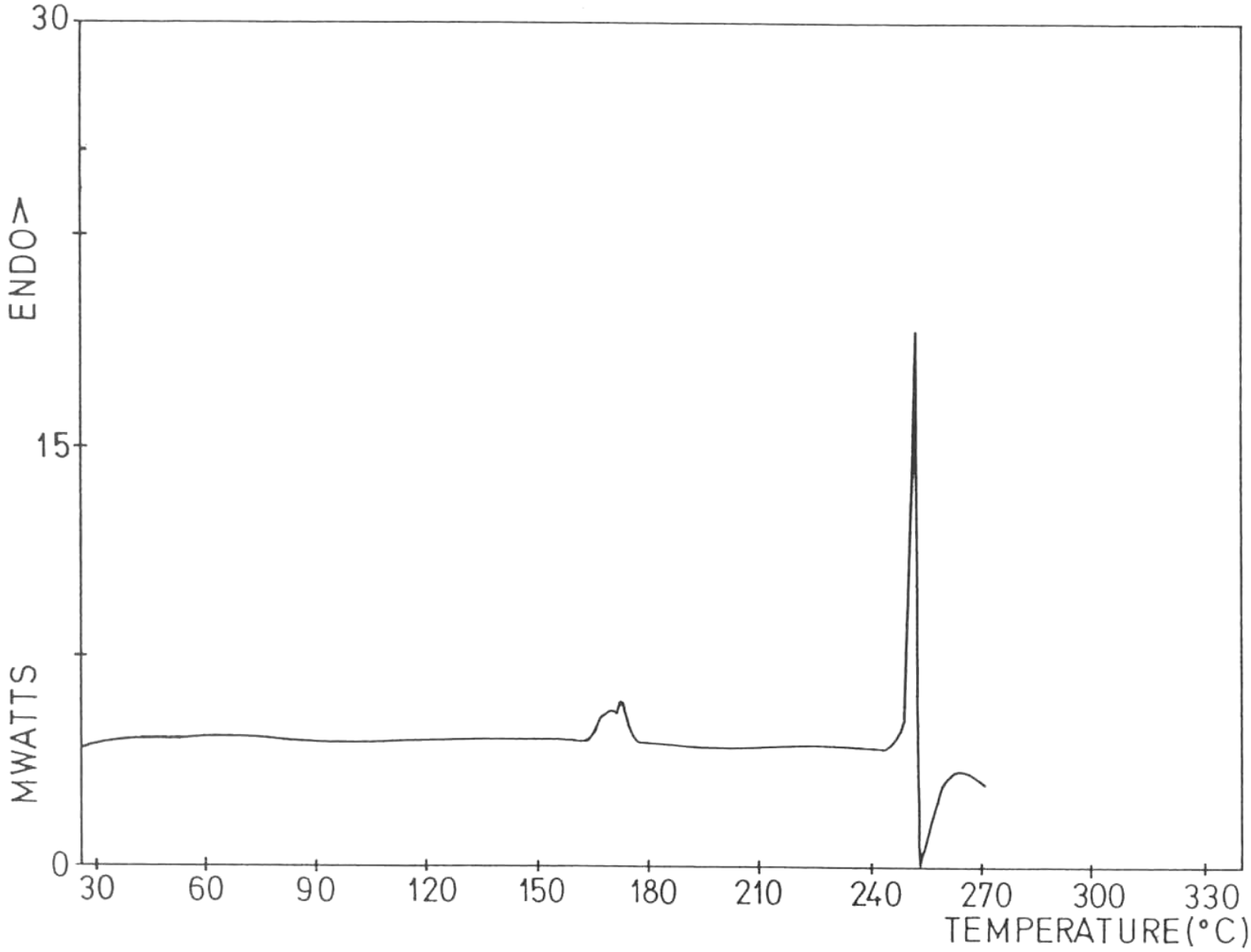
Keywords: Polymorphic solvate; Pseudopolymorphic solvate: Acyclovir; Anhydrous acyclovir; Dissolution behavior; Solid–solid transformation

Karl FISCHER

$$C_5H_5N{\cdot}J_2 + C_5H_5N{\cdot}SO_2 + C_5H_5N + H_2O \rightarrow 2\ C_5H_5N{\cdot}HJ + C_5H_5SO_3$$

$$C_5H_5SO_3 + CH_3OH \rightarrow C_5H_5N(H)SO_4CH_3$$


30
15
0
ENDO >
MWATTS
100
95
MASS (%)
30
60
90
120
150
180
210
240
270
300
330
TEMPERATURE (°C)


30
15
0
ENDO>
MWATTS
30
60
90
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240
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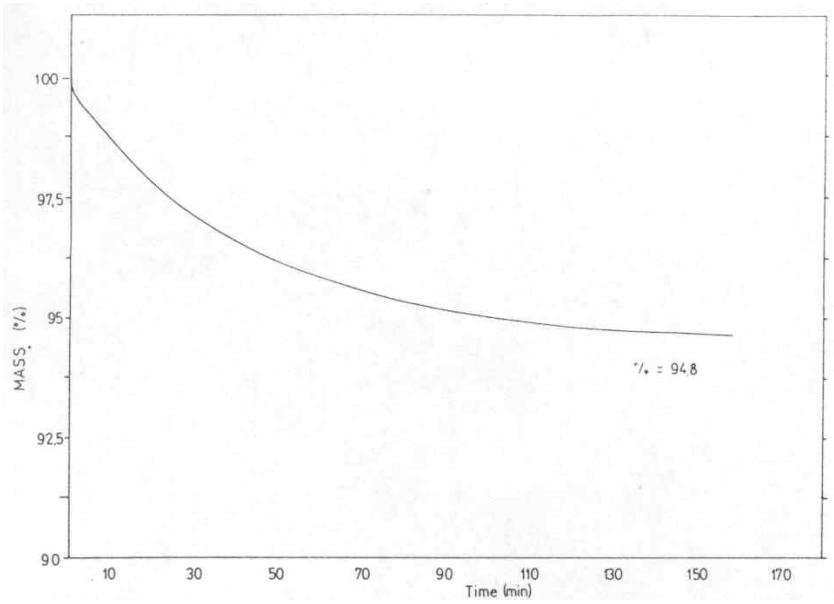
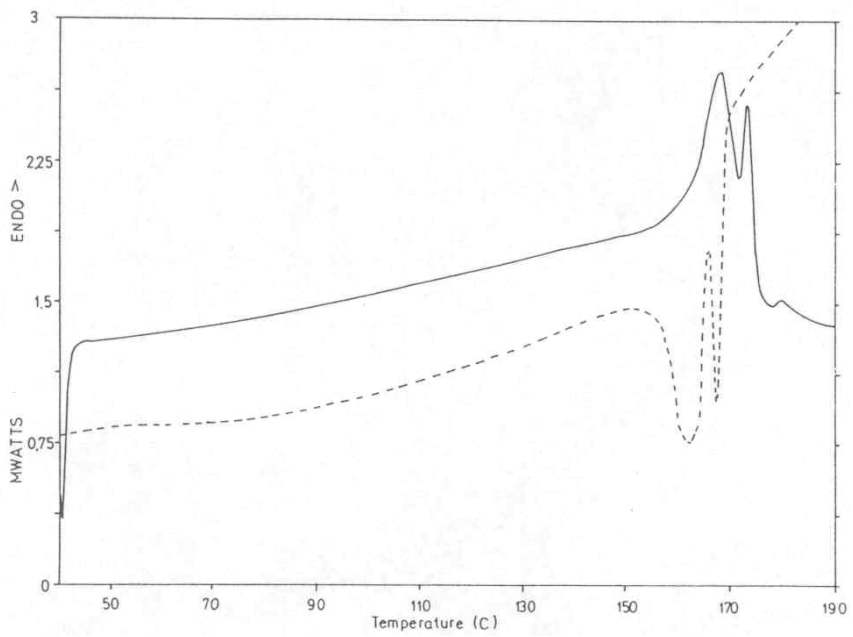
300
330
TEMPERATURE(°C)


100
97,5
95
92,5
90
MASS (%)
%= 94,8
10
30
50
70
90
110
130
150
170
Time (min)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2,25
1,5
0,75
0
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MWATTS
50
70
90
110
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150
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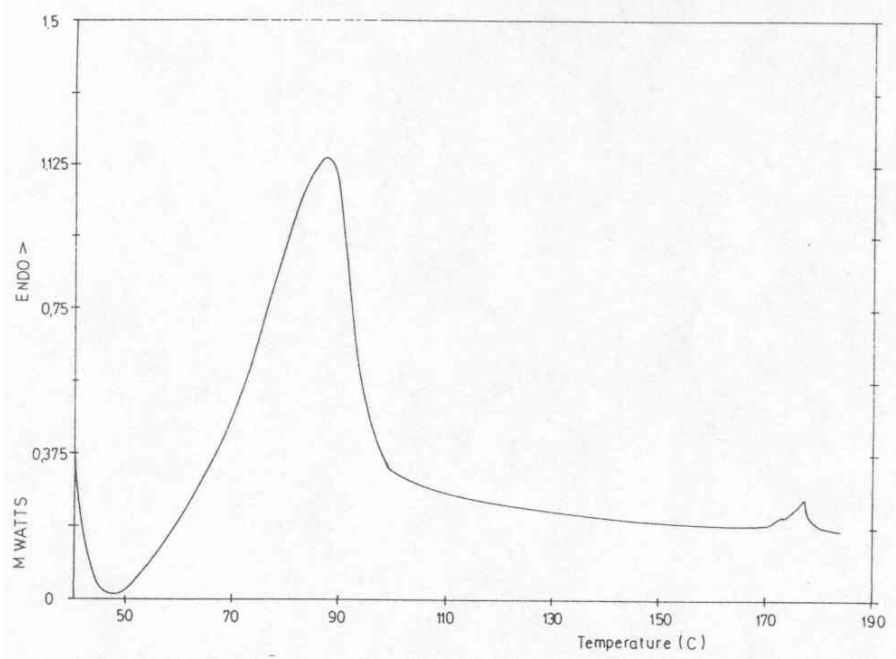
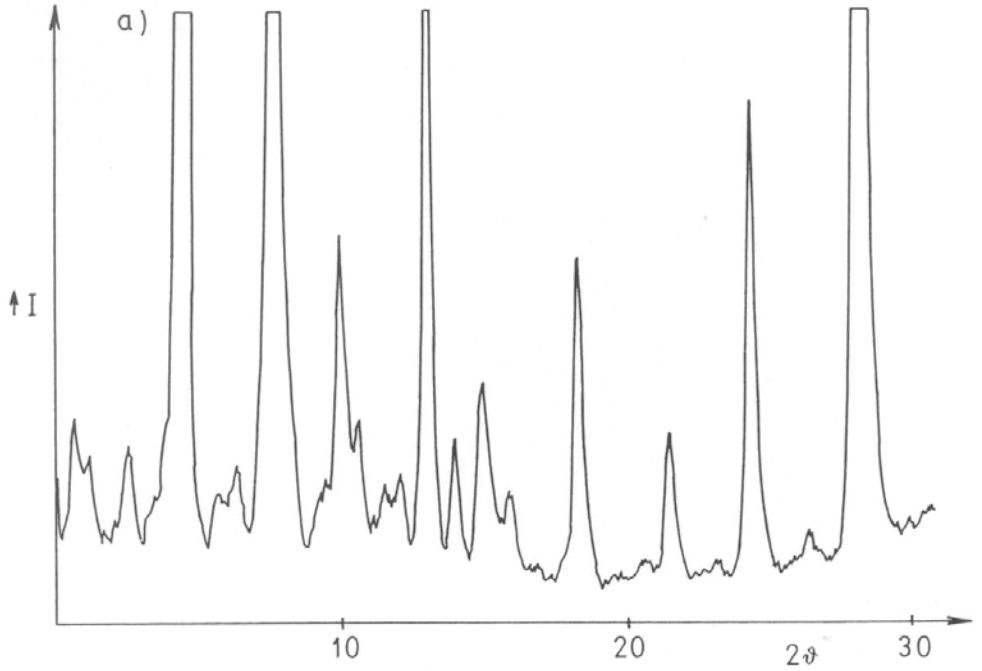
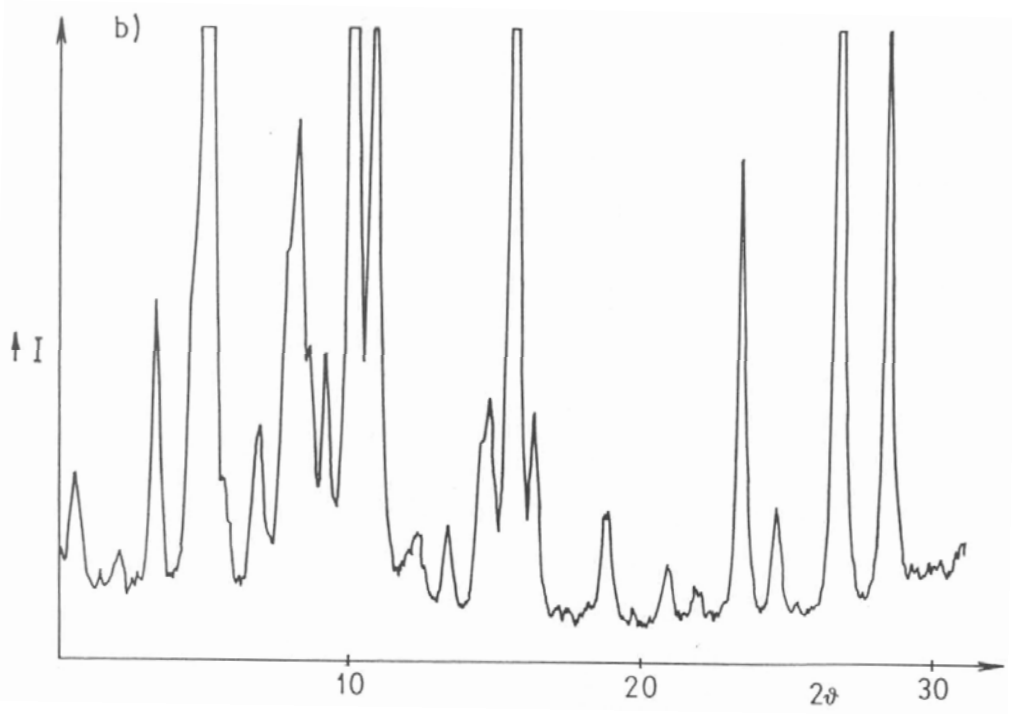
190
Temperature (C)


1,5
1,125
0,75
0,375
0
ENDO >
M WATTS
50
70
90
110
130
150
170
190
Temperature (C)

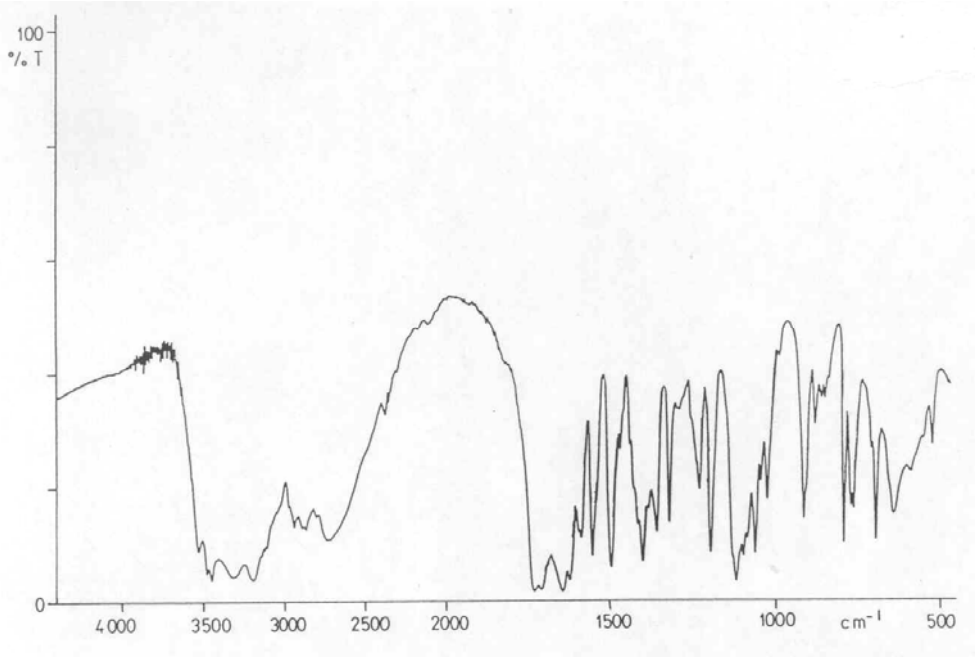
a) hidrat



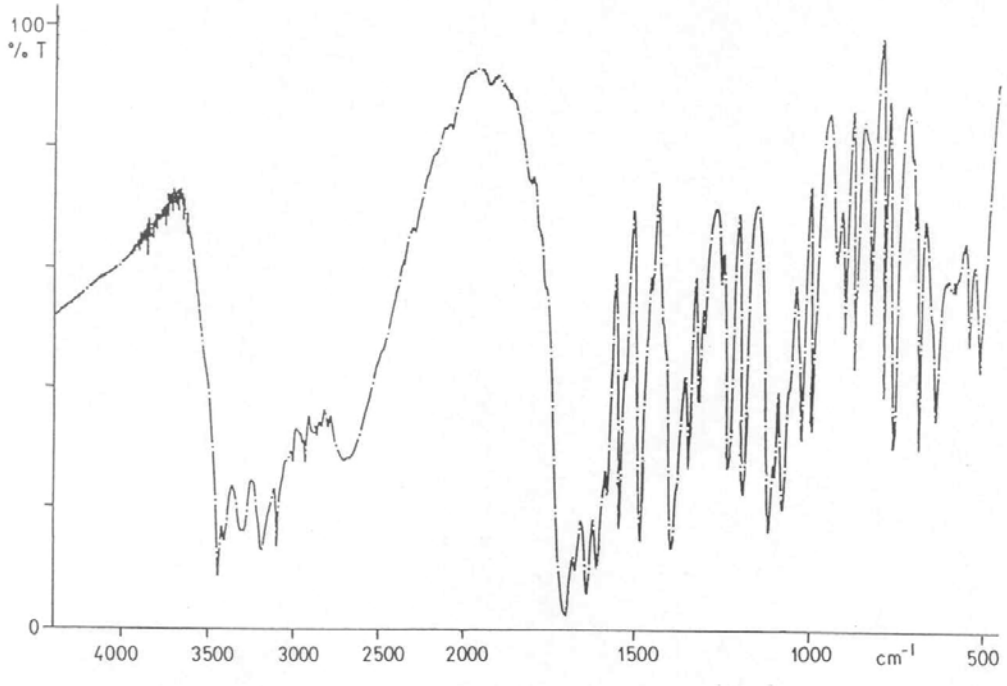
b) brezvodni

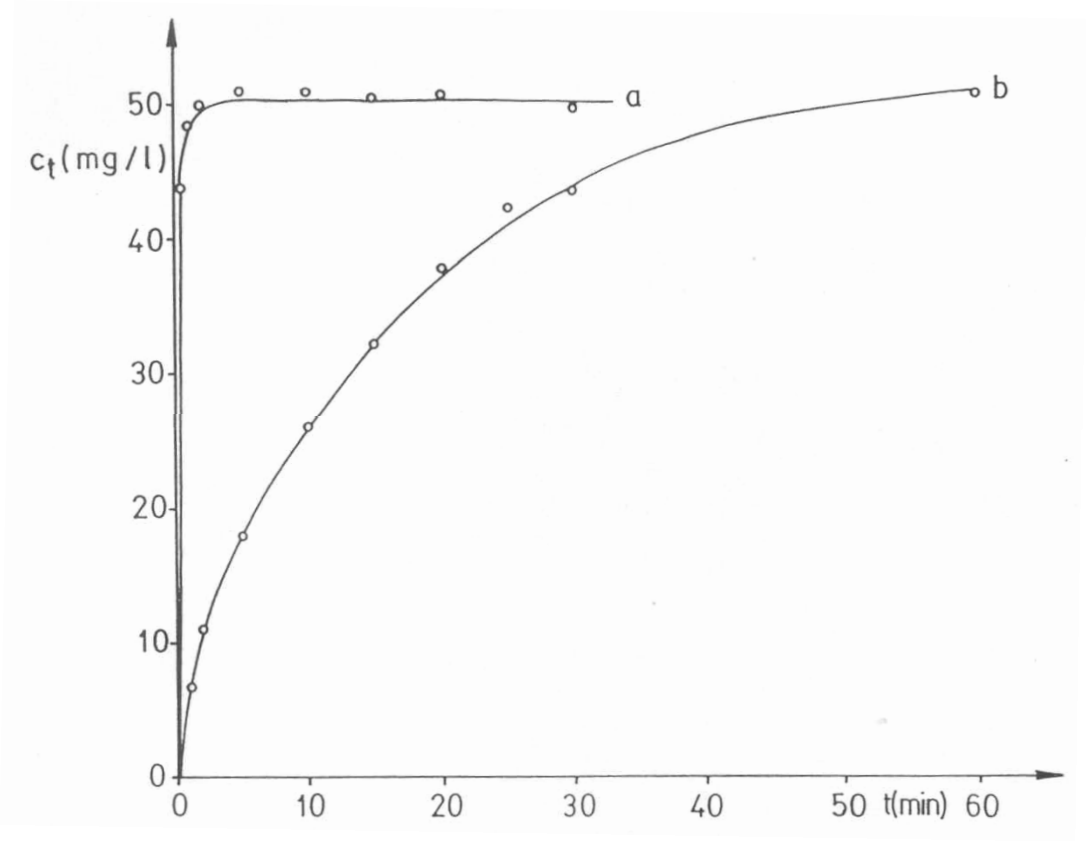


hidrat



brezvodni





conc. (mg/l.cm^2)

min	5	10	20	30	60	120	180
anhydrous K – A11	0,4	0,5	1,1	1,6	2,4	3,2	4,0
K – A11 hydrate	0,6	0,9	1,6	2,3	4,2	6,7	9,4