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POLYMORPHISM AND SOLVATES OF FLECAINIDE BASE

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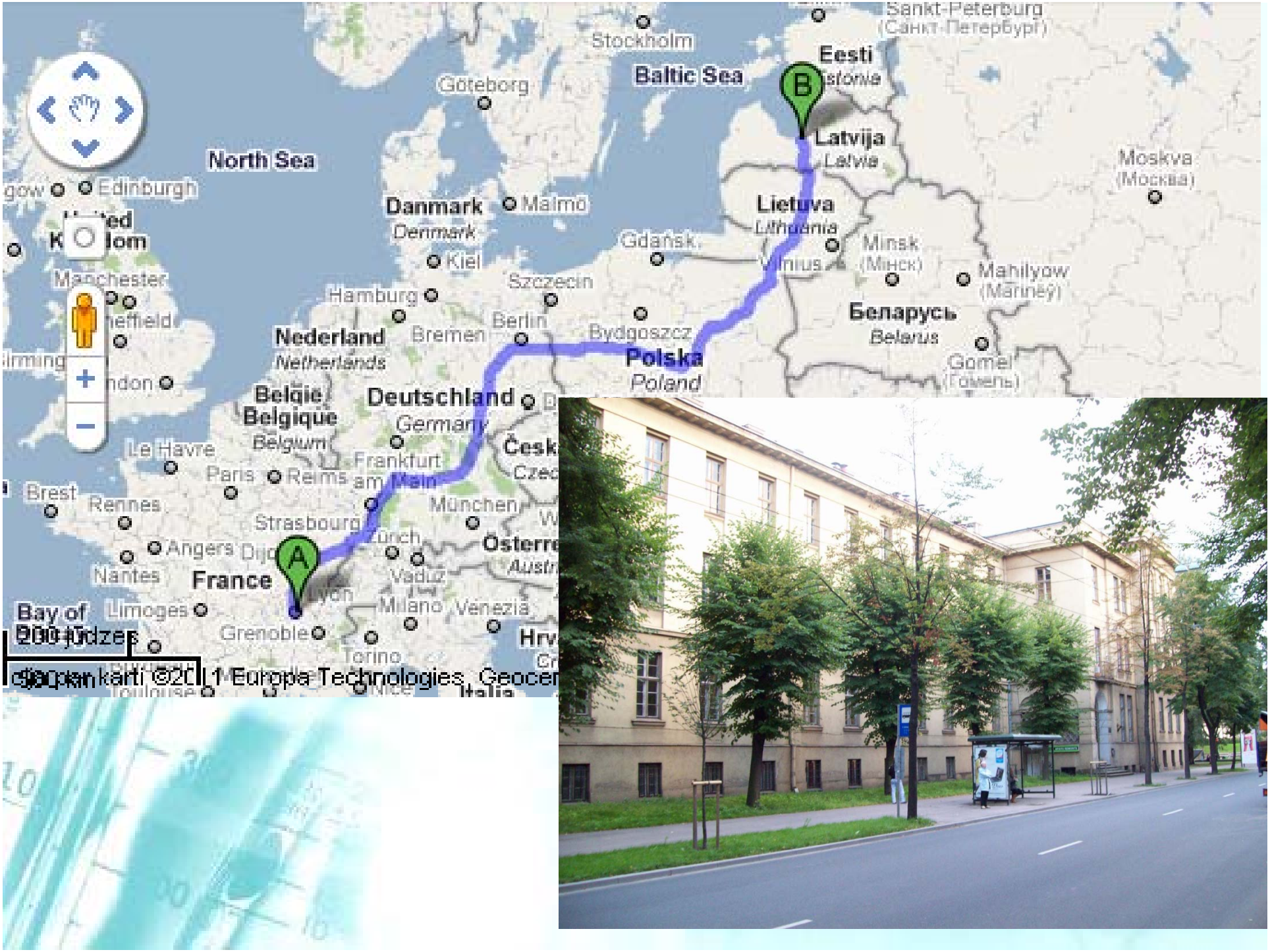
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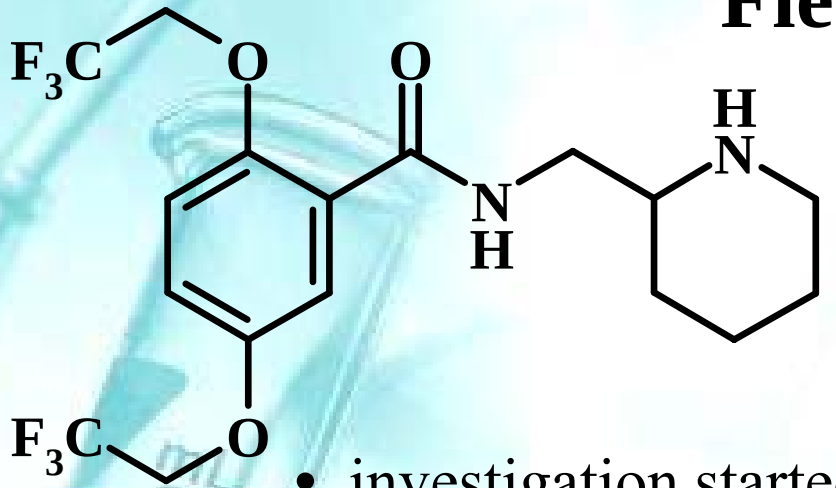
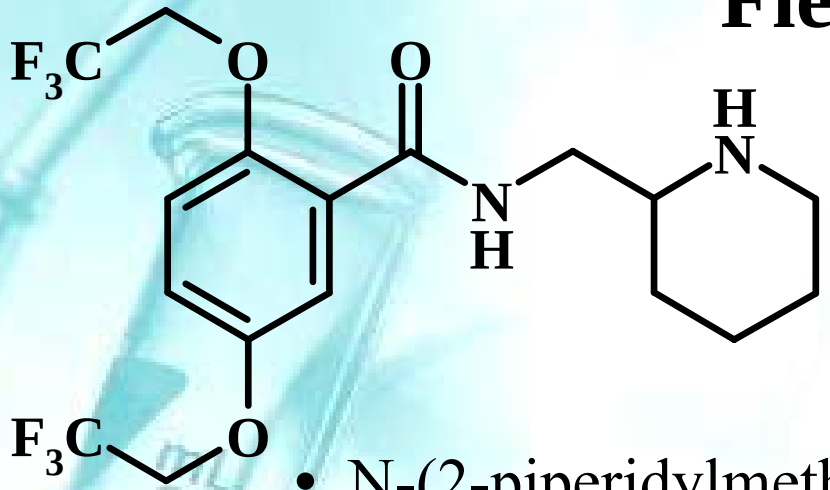
Flecainide and flecainide base



- investigation started with practical problem, crystallization of flecainide base led to formation different crystalline phases (JSC GRINDEKS, Rīga, Latvia)

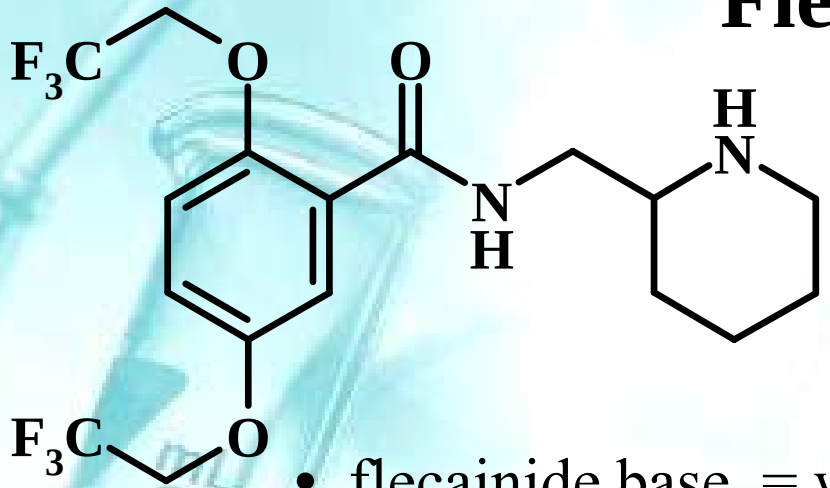
- now mainly scientific interests, no so practical

Flecainide and flecainide base



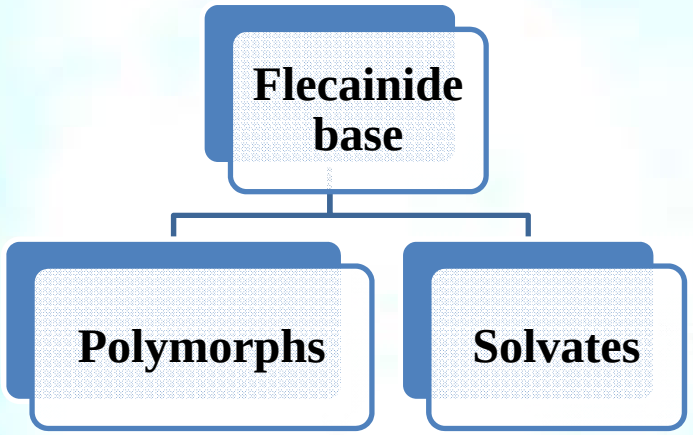
- N-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide
- antiarrhythmic agent used to prevent and treat tachyarrhythmias (abnormal fast rhythms of the heart)
- Flecainide was originally sold under the trade name **Tambocor®, also Almarytm®, Apocard®, Ecrinal®,** and **Flécaine®** (patent free since 10th Feb 2004)

Flecainide and flecainide base



- flecainide base = white solid substance, practically insoluble in water, soluble in alcohols
- as it is insoluble in water flecainide acetate is used as active pharmaceutical ingredient
- flecainide acetate is produced from base, adding stoichiometric amount of acetic acid

Investigations



Four polymorphic forms:

Ib
IIb
IIIb and
IVb

Solvates with alcanols starting from methanol and finishing with decanol.

Solvate with DMSO

How flecainide base investigation was done (general scheme)

Solid substance with not known polymorphh and solvate properties

Treatment of obtained substance with water, possible hydratation and dehydratation studies

DTA, PXRD, KF, IR analysis of forms obtained (if any)

Heating of substance (DTA, PXRD) (without solvent treatment)

Analysis of substances obtained, explanation of DTA curves

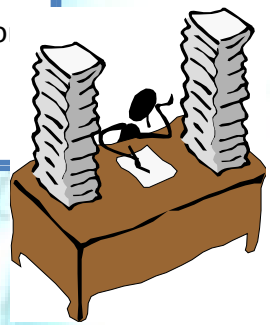
Preparation of pure polymorphic forms for lattice parameter determination

Recrystalization from solvents, spray drying

Determination of exact composition of crystalline phases obtained

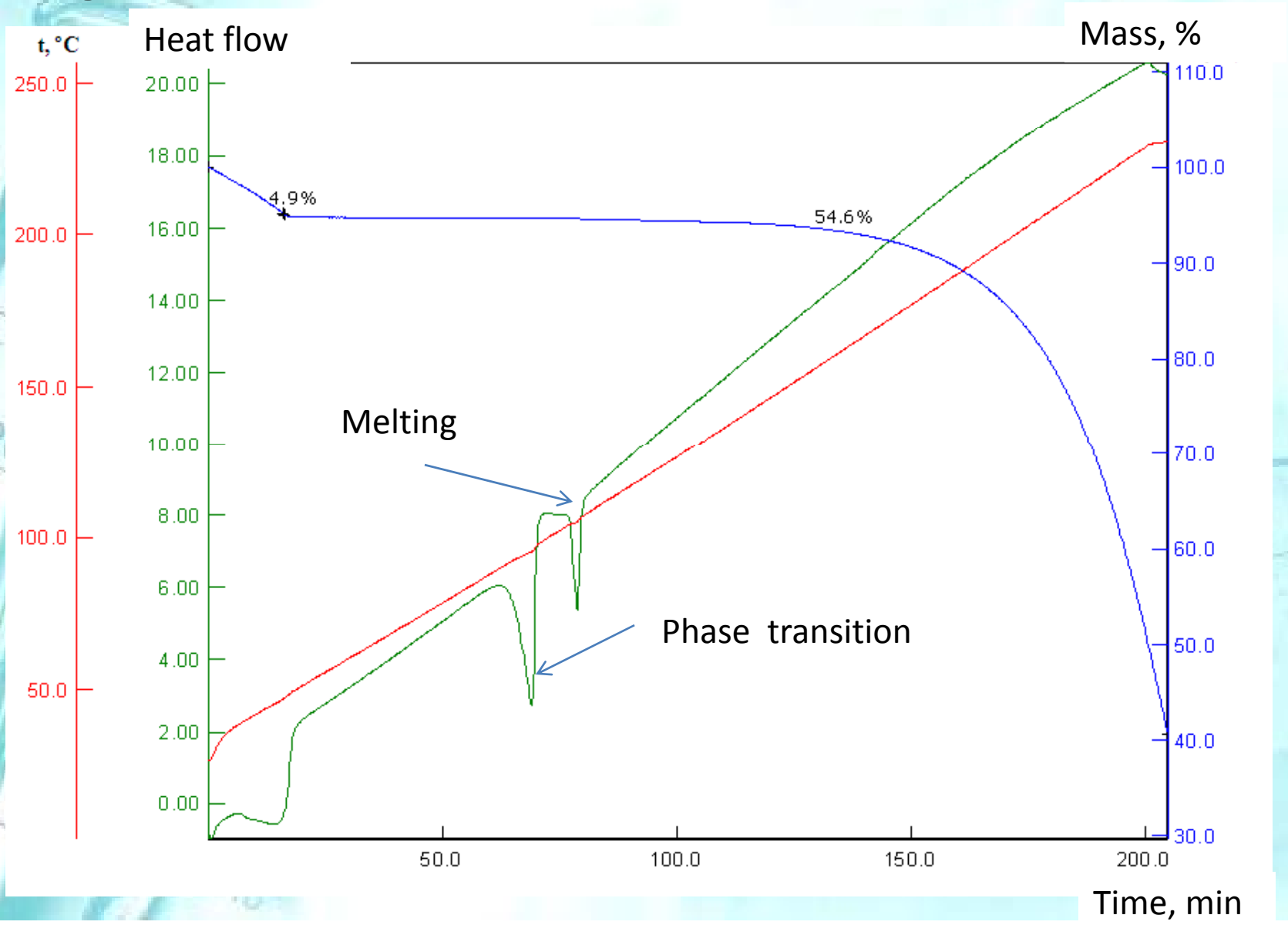
Preparation of pure solvate forms for indexinf and possible structure determination

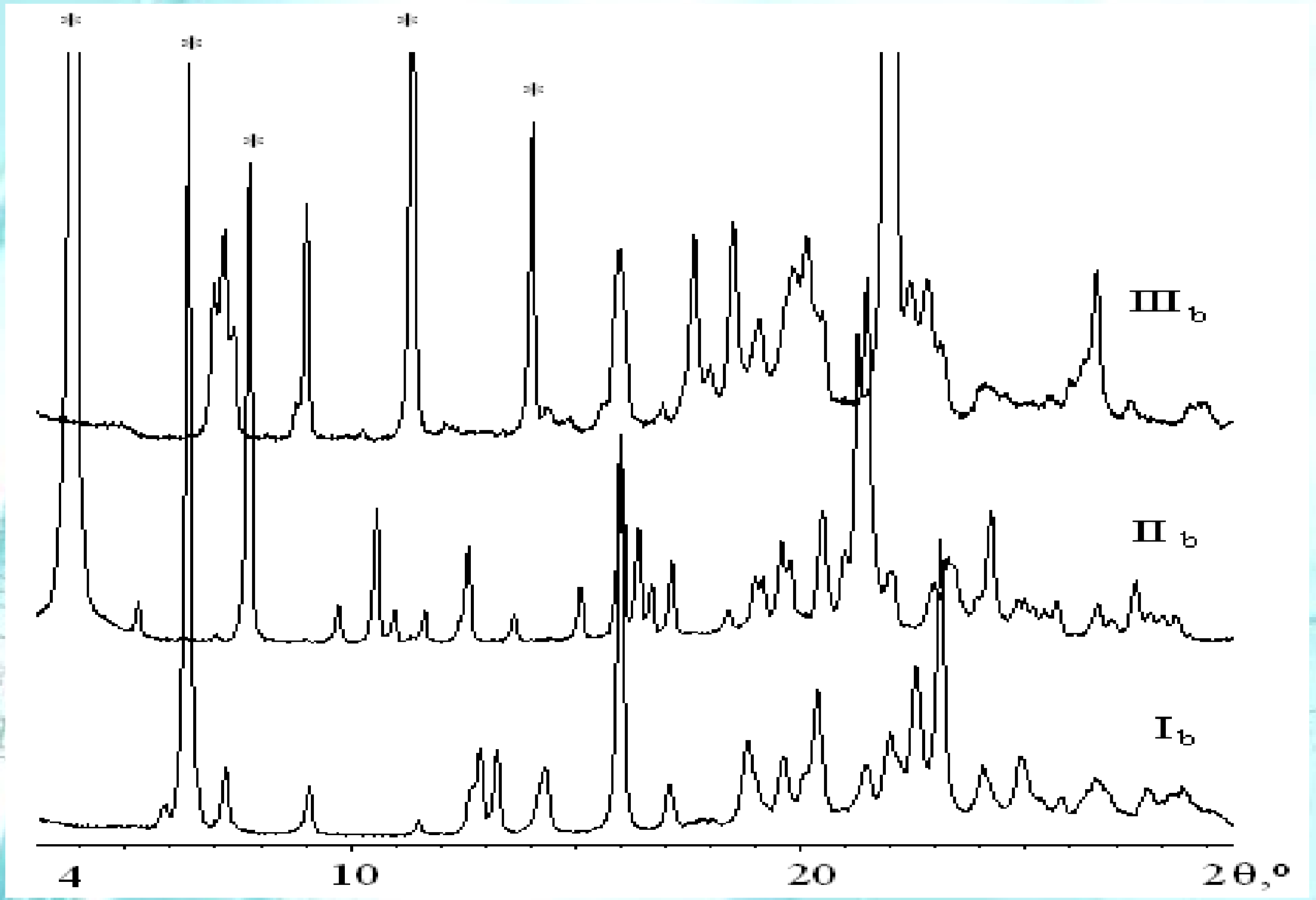
Study of databases fo same od similar compounds



Start of investigations

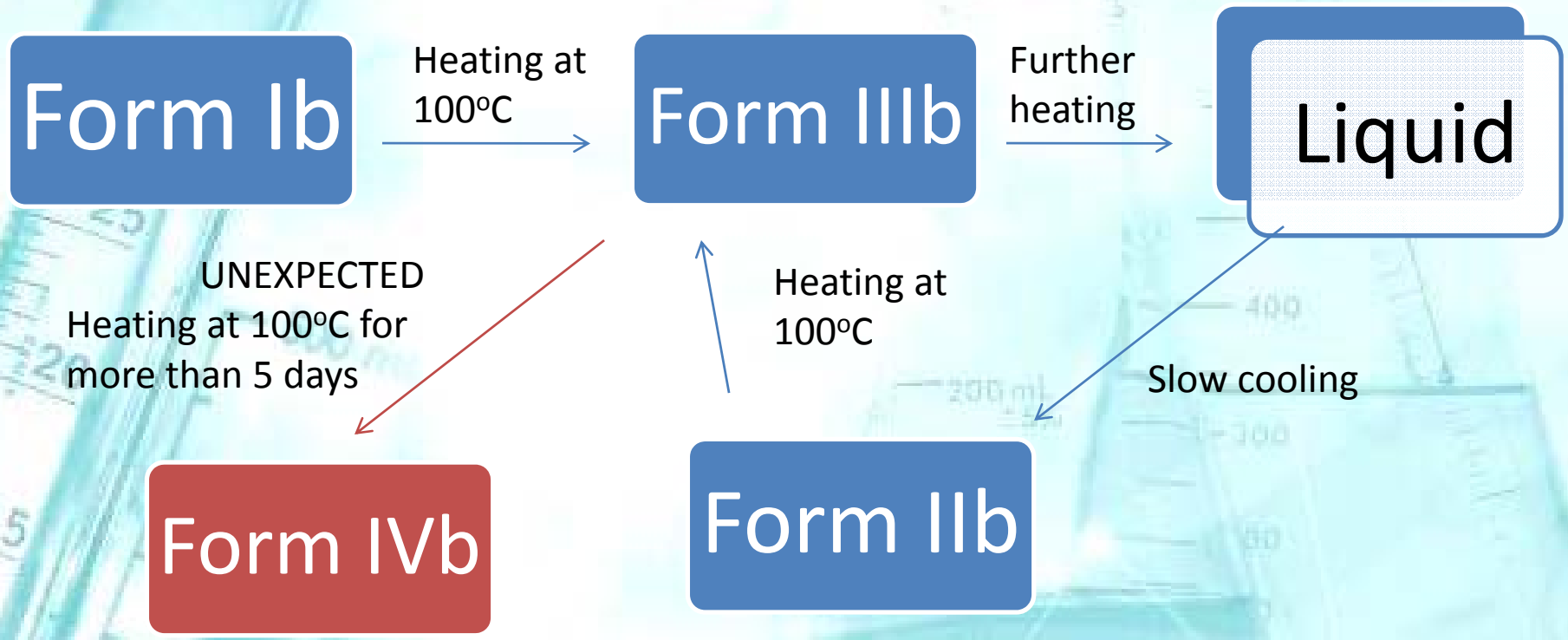
Heating flecainde base (DTA curve)





PXRD patterns of flecainide base polymorphs

Scheme for phase transitions of flecainide base



Relative stabilities of flecainide base polymorphs

I_b								
II_b								
III_b								
IV_b								X
t, °C	Room tem.	40	50	60	70	80	90	100

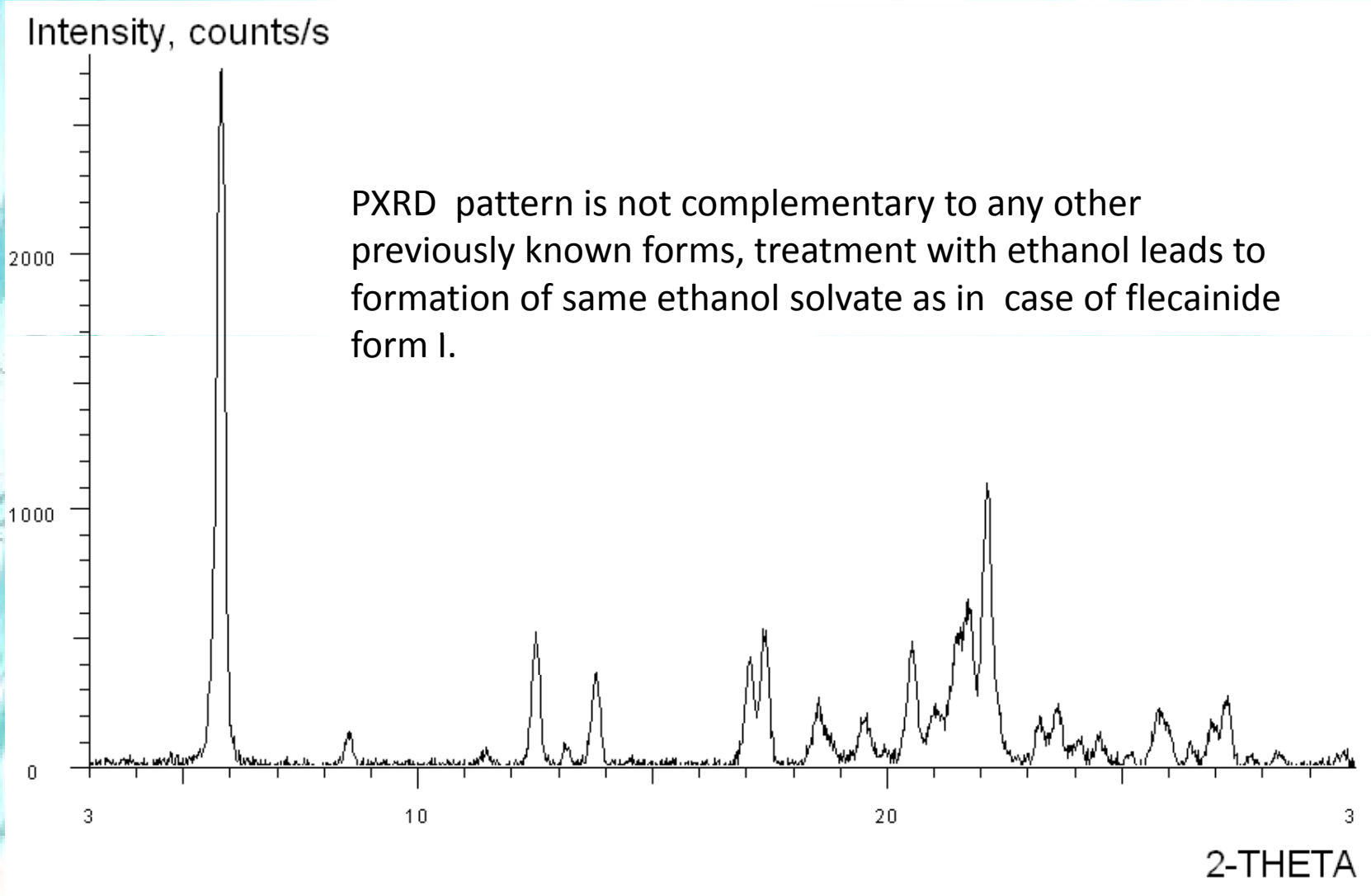
I_b form is thermodinamically stable

I_b form is kinetically stable but observed phase transition during storage for 2 months

II_b form is obtained but it is metastable and transforms to IIIb

Forma III_b termodinamiski stabila.

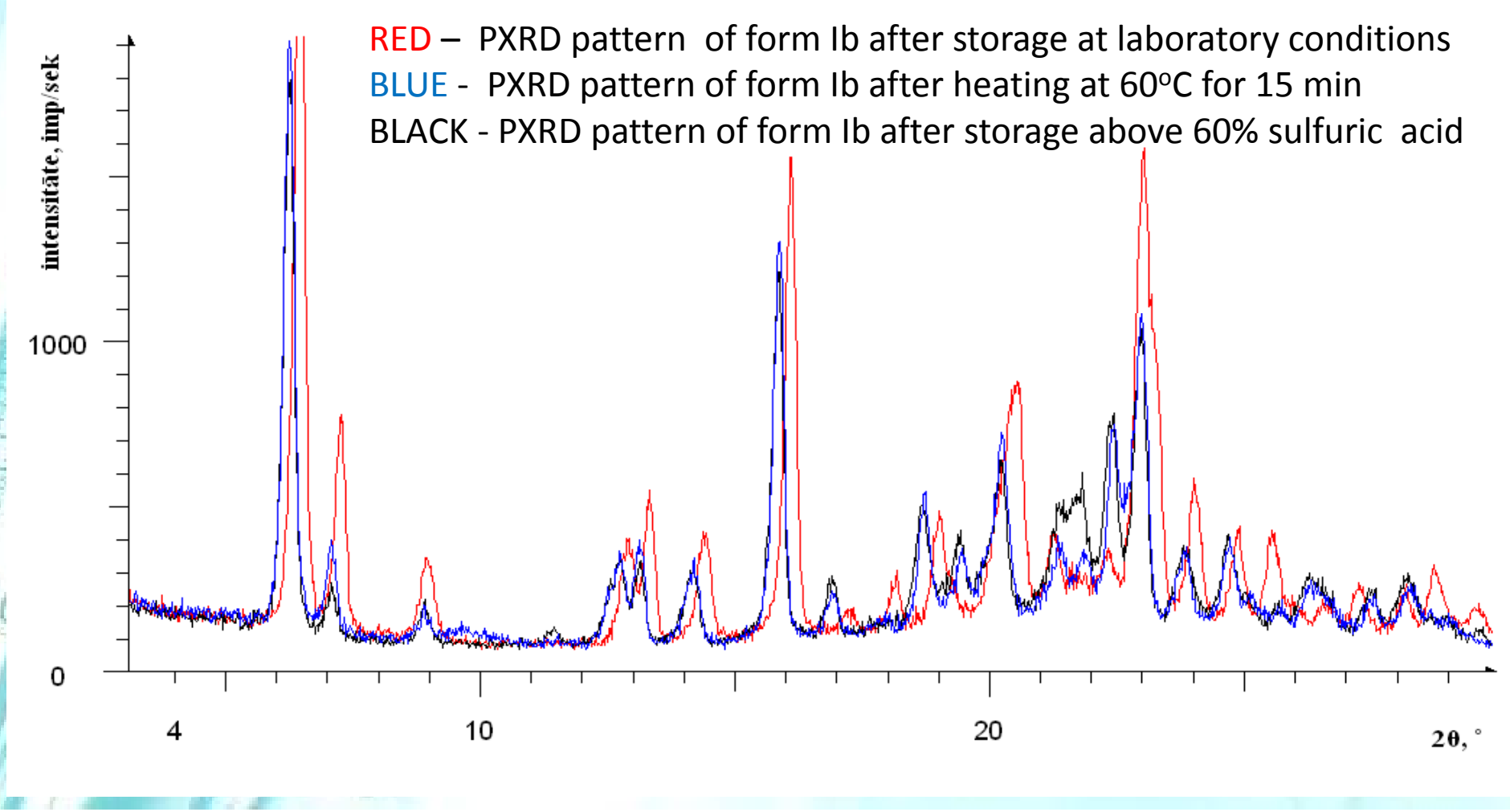
PXRD pattern of new flecainide form IVb



PXRD pattern is not complementary to any other previously known forms, treatment with ethanol leads to formation of same ethanol solvate as in case of flecainide form I.

Hydrate formation

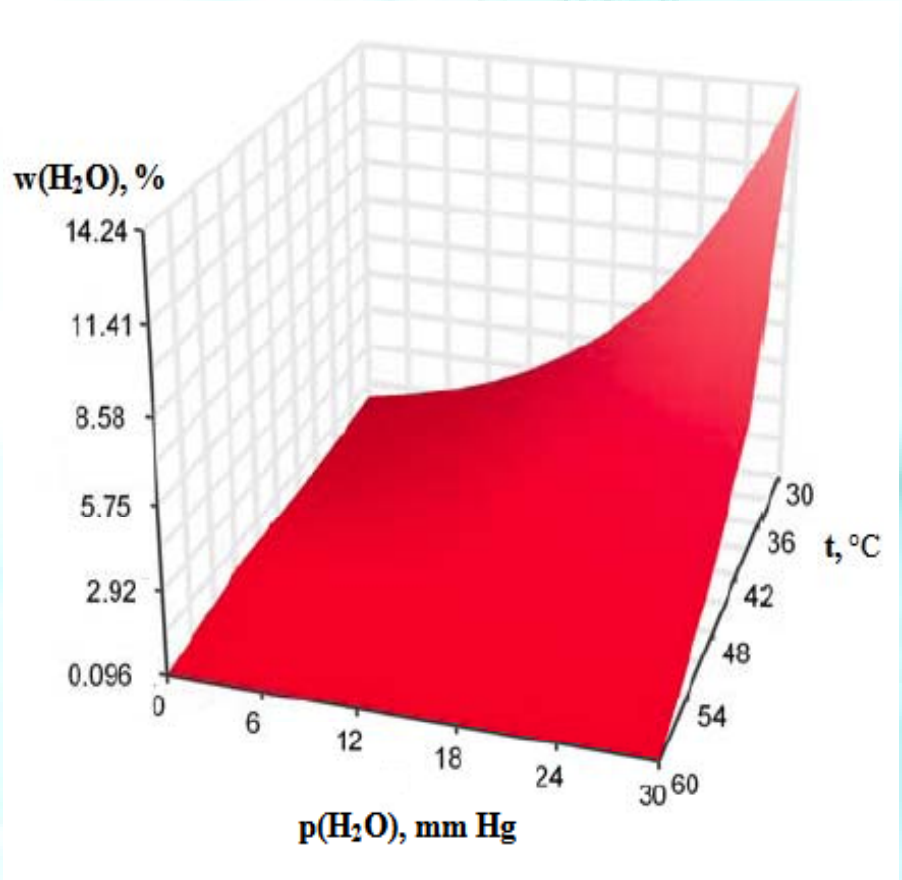
During storage at high relative humidities flecainde base form Ib it changed PXRD pattern little bit ...



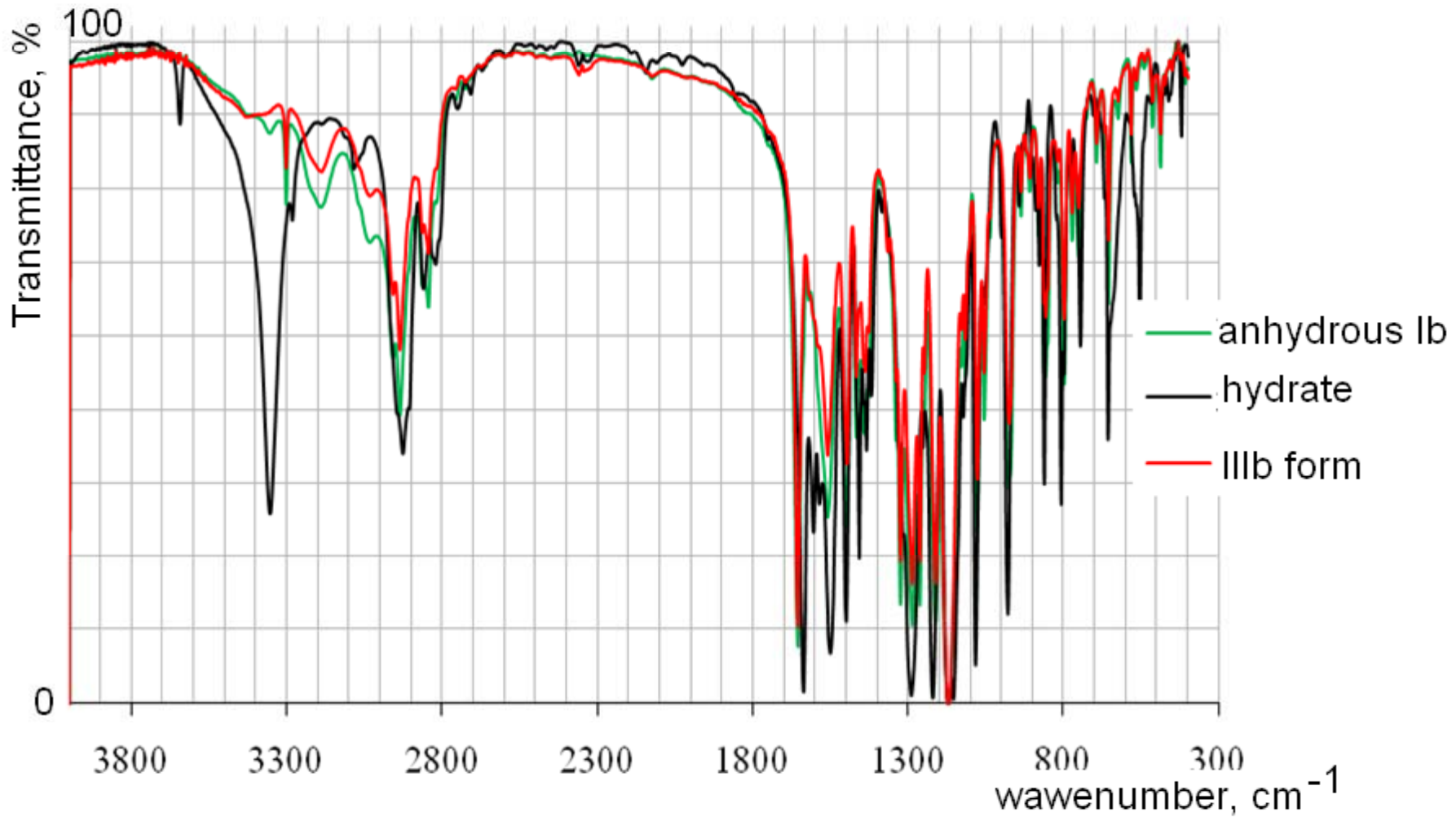
Further hydrate studies

Flecainide base held at specially designed conditions (changed temperature and relative humidity), non stoichiometric nature

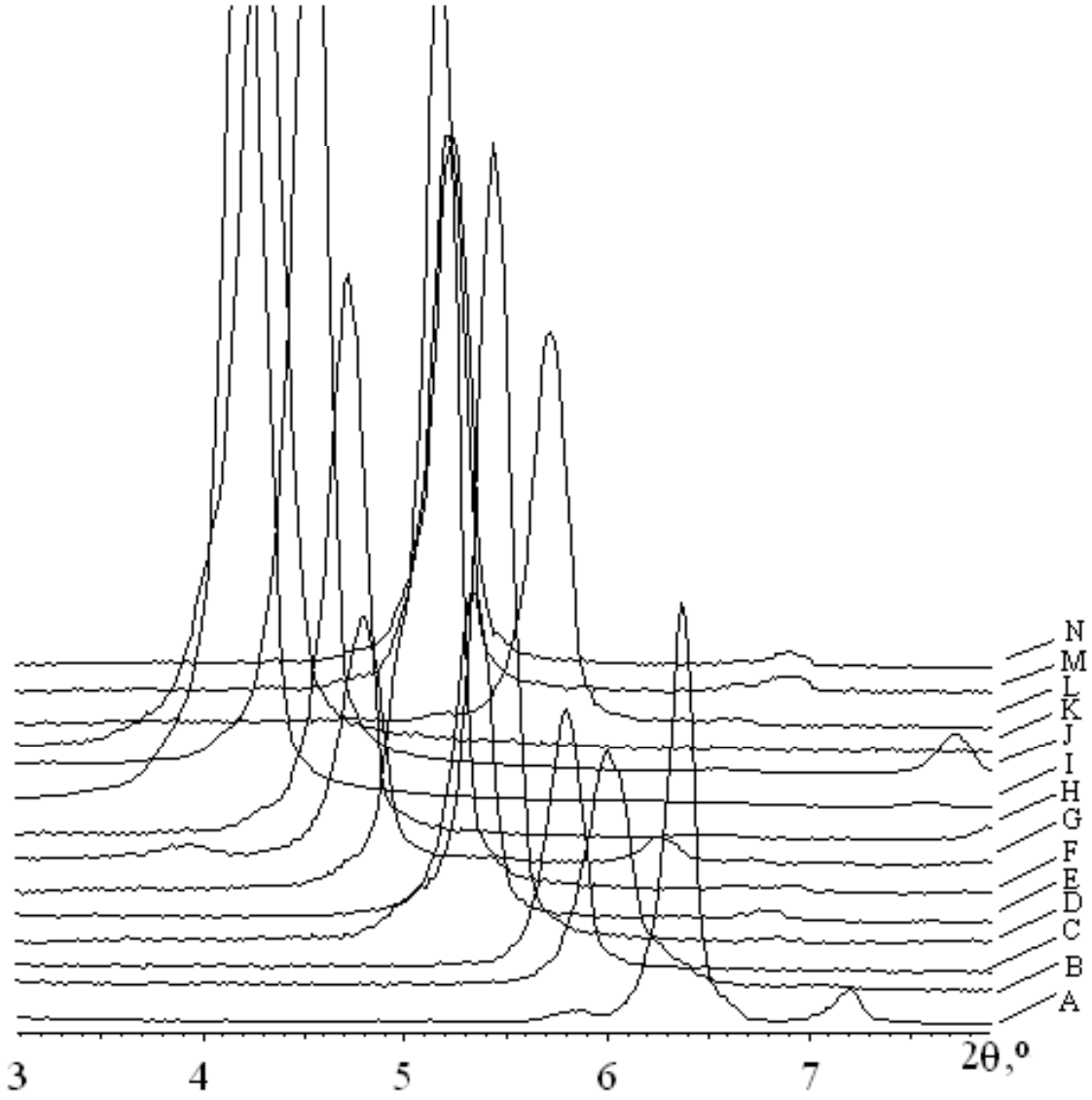
22°C		30°C		40°C	
$p(H_2O)$, mm Hg	N	$p(H_2O)$, mm Hg	N	$p(H_2O)$, mm Hg	N
14,09	2,28	25,80	2,33	44,8	2,11
9,51	1,26	17,26	1,21	30,80	1,26
4,37	1,08	8,23	1,03	14,74	0,81
0,83	0,18	1,65	0,21	3,13	0,30
50°C		60°C		70°C	
$p(H_2O)$, mm Hg	N	$p(H_2O)$, mm Hg	N	$p(H_2O)$, mm Hg	N
75,00	2,28	121,70	2,08	191,90	1,37
52,50	1,50	86,10	1,50	139,30	1,42
25,70	0,37	43,50	0,09	70,30	0,14
7,39	0,19	9,65	0,03	16,08	0,05



IR spectra for hydrate, anhydrous Ib and IIIb forms

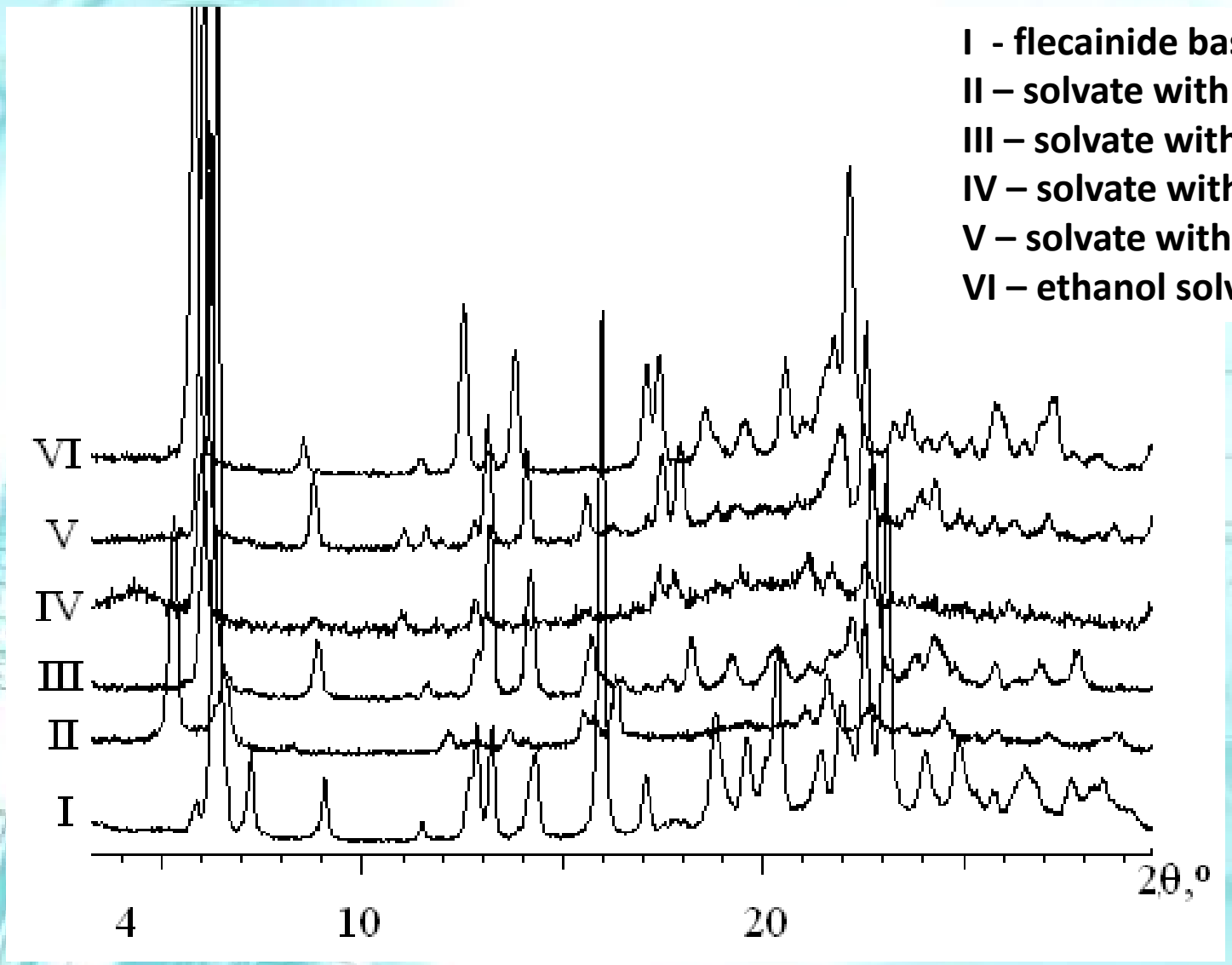


Solvate formation with organic solvents



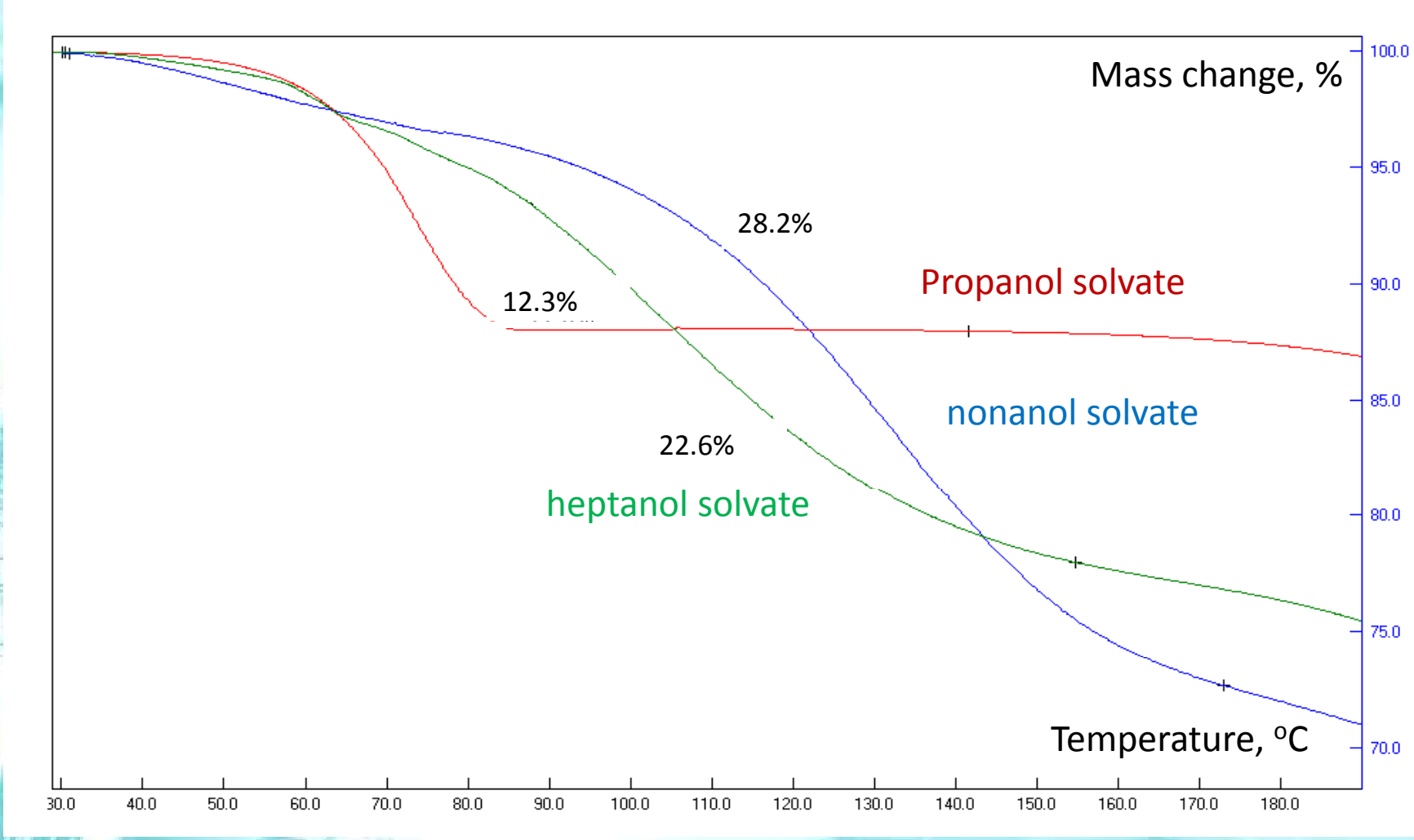
A – Ib form
B – methonol solvate
C – ethanol solvate
D – n-propanol solvate
E – n-buthanol solvate
F – n-penthanol solvate,
G – n-hexanol solvate
H – n-hepthanol solvate
I – n-octanol solvate
J – n-nonanol solvate
K – n-decanol solvate
L – isopropanol solvate
M – isopenthanol solvate
N – isobuthanol solvate

Solvate formation with organic solvents



I - flecainide base Ib form
II – solvate with benzyl alcohol
III – solvate with acetonitrile
IV – solvate with DMSO
V – solvate with DMF (formamide)
VI – ethanol solvate

Determination of solvate composition



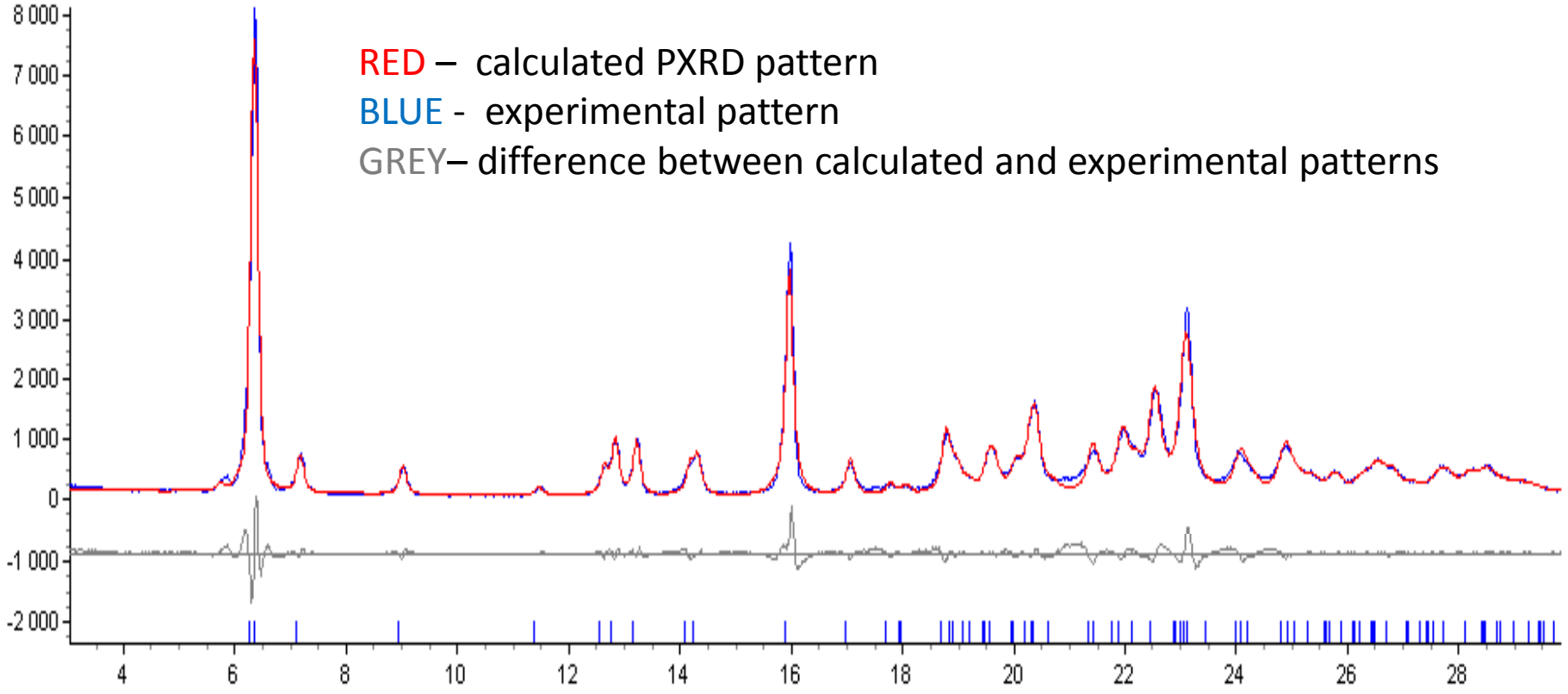
Determination of solvate composition

Solvate composition determined by DTA/TG analysis, for every second confirmed by gas chromatography.

No.	Solvent	Molar mass of solvent, g/mol	Mass change, %	Solvent amount in moles divided by amount of flecainide (N)
1.	Methanol	32,05	6,7	0,93
2.	n-propanol	60,11	12,3	0,966
3.	n-penthanol	88,17	14,9	0,822
4.	n-heptanol	116,23	22,6	1,04
5.	n-nonanol	144,29	28,2	1,13
6.	Isobutanol	88,17	16,6	0,935
7.	benzylalcohol	108,14	21,0	1,02
8.	DMSO	78,13	15,5	0,971
9.	DMFA	73,09	13,8	0,903
10.	acetonitrile	41,05	8,3	0,91

Indexing, calculation of lattice parameters

Lattice parameters were calculated using computer programs: ITO , Dicvol, Ntreor09



Lattice parameter refinement in computer programm TOPAS for flecainide Ib form

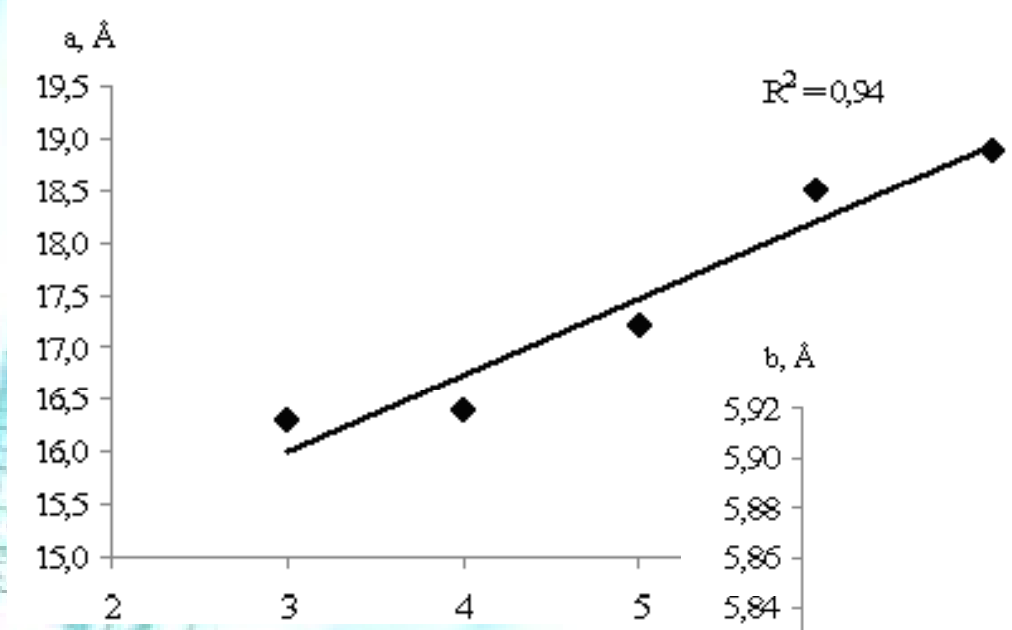
Indexing, calculation of lattice parameters

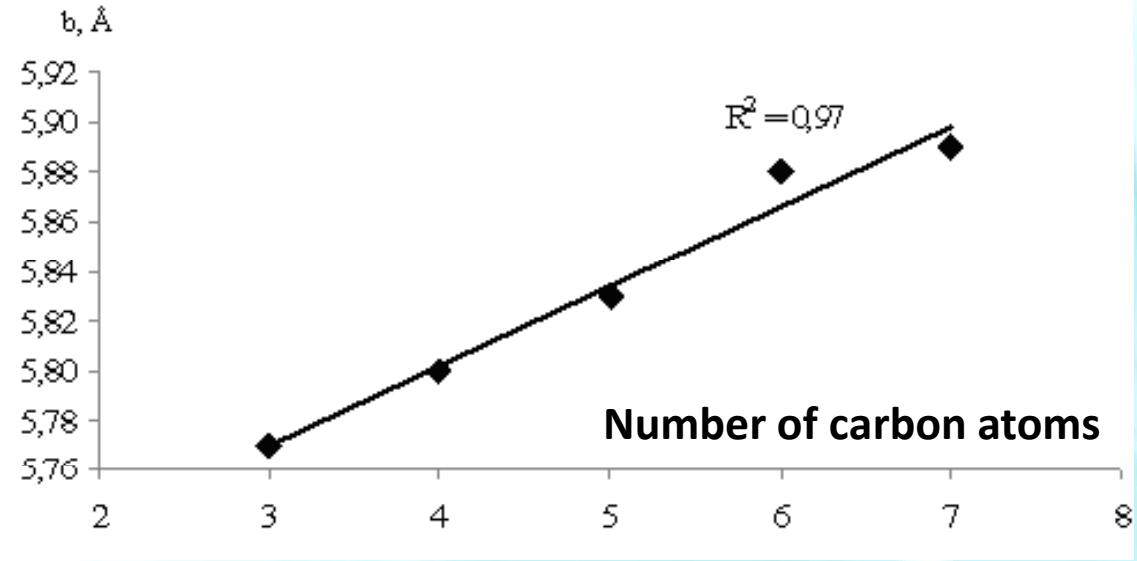
Lattice parameters of flecainide solvates with lowest alcohols

Alcohol	*a*, Å	*b*, Å	*c*, Å	*β*, º	V, Å^3	ρ, g/cm^3	R_{wp}
Methanol	15,333	5,752	14,376	92,54	1266,6	1,17	16,6
Ethanol	15,261	5,642	14,129	90,33	1216,4	1,26	15,5
n-Propanol	16,302	5,774	13,782	93,84	1294,4	1,22	15,6
n-Buthanol	16,416	5,802	13,815	94,61	1311,6	1,24	21,8
…							

Indexing, calculation of lattice parameters

Lattice parameter trends –parameters a and b increases while c has small changes (±0.2 Å).





Main conclusions

1. Flecainide base forms four crystalline modifications which are abbreviated as Ib, IIb, IIIb and IVb.

2. Flecainide base can bind with 4.8% water (at laboratory temperatures), which is lost at further heating 50-60^{o}C. Anhydrous Ib form is obtained.

3. Heating of Ib form sharp phase transition is obtserved, formation of fom IIIb.

4. Polymorph IIb can be obtained by crystallization from melt.

5. Flecainide base forms solvates with polar and non-polar protic solvents (alcohols), but solvates are not obtained with aprotic solvents (except DMSO). All solvates with organic solvents appeared to be monosolvates.

6. Flecainide base Ib crystalizes as orthorobmbic crystalls. For structure data obtained further refinement is necessarry.