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DSC STUDIES ON THE POLYMORPHISM AND PSEUDOPOLYMORPHISM OF PHARMACEUTICAL SUBSTANCES

A complex system for studying physico-chemical behaviour of binary mixtures

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A complex system including thermoanalytical methods, infrared spectroscopy and X-ray powder diffraction for studying physico-chemical behaviour of binary mixtures is described. This system has been tested by investigating binary mixtures of amphetamine hydrochloride salts.

These studies have proved that among the selected compounds the primary and secondary amine hydrochloride salts exhibit conglomerate forming tendency, while the tertiary amine hydrochloride salts form molecular compounds (racemates). For the *p*-fluoro amphetamine hydrochloride the existence of two polymorphic modifications has been detected.

Keywords: pharmaceutical substances, polymorphism, pseudopolymorphism

Introduction

In the pharmaceutical industry the most interesting mixtures are the binary mixtures of stereoisomers (both diastereoisomeric and enantiomeric mixtures) and those of the polymorphic modifications.

For the differences in the useful biological activity of the mirror image isomers [1], their separation is a crucial question on laboratory as well as on industrial scale. In the case of chiral compounds the quality of the interaction in the solid state has a great influence on the selection of the enantiomer separation method [2], and the use of the complex system for studying physico-chemical behaviour of binary mixtures can facilitate and accelerate the elaboration of new optical resolution methods (which is the field of activity of our research team).

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This system is specified to detect and identify the quality and the components of enantiomer-mixtures and mixtures of polymorphic modifications. Its use may reveal and prove other important features of the given compound connected with the structure of the solid state. Thus conglomerate crystallization ability, polymorphism and the effect of solid-vapour equilibrium are also detectable.

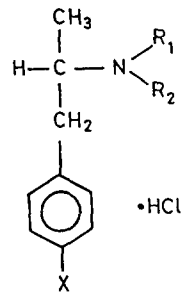
What makes the use of this system necessary might the question arise.

It is well known that the components of binary mixtures can be distinguished by 'almost traditional' instrumental methods like infrared spectroscopy, density measurement, and thermoanalytical methods, like thermogravimetry, hot stage microscopy, DSC and other more expensive analytical methods like solid state NMR and single crystal X-ray diffraction [3].

However, the output of any of the individual methods can be misinterpreted therefore their appropriate combination would only provide unambiguous information about the nature of the investigated binary system.

In the following an interview is given on the scope and limitations of the individual methods in distinguishing and characterizing the components of binary mixtures and in identifying the interactions between the components in solid state. The applicability of the system is illustrated by the complex study of the differently substituted HCl salts of β-phenyl-isopropyl amines (Table 1).

Table 1 Model compounds

Compounds number	X	R_1	R_2	
II	F	H	H	
III	H	H	CH_3	
V	F	H	CH_3	
V	H	CH_2–C≡CH	CH_3	
VI	F	CH_2–C≡CH	CH_3	

A complex system for studying physico-chemical behaviour of binary mixtures

Having chemically identified samples, first the DSC and the thermogravimetric measurements are to be performed. If weight loss takes place at a temperature, where a DSC peak was recorded, it can be considered either as chemical decomposition, or decomposition of solvates. Knowledge of the circumstances

and the use of EGA (Evolved Gas Analysis) can help us to distinguish them. With the combined use of DSC and thermogravimetry the sublimation can also be detected.

If there is no weight loss correlated with a DSC peak, the latent heat can represent an isomerization reaction, a polymorphic transition, or the melting of the substance. An easy distinction between the chemical isomerization or polymorphic transformation can be made by infrared spectroscopy. With the aid of the hot stage microscope it is easy to distinguish a polymorphic transformation from the melting process.

The combination of the above methods is shown in Fig. 1.

The system provides the following information on the individual and the two-component mixtures: melting points, heats of fusion, heats of transition, existence and relative stability of polymorphic modifications, the sublimation ability at atmospheric pressure. This set of data enables us to construct the binary phase diagram with the aid of the Schröder van Laar and the Prigogine-Defay equations [2] (provided the system is nearly ideal), thus decide about the nature of the interaction between the components e.g. the solid state is composed of the mechanical mixture (conglomerate – one eutectic), molecular compound (two eutectics) or solid solution (no eutectic) formed from the crystalline substances [2].

All these thermal effects as well as the vibration frequence and intensity differences between the infrared spectrum of the racemate and those of the enantiomers, and similarly between the spectra of the polymorphic modifications are to be attributed to the different molecular conformation and/or arrangement in the crystal lattice [4].

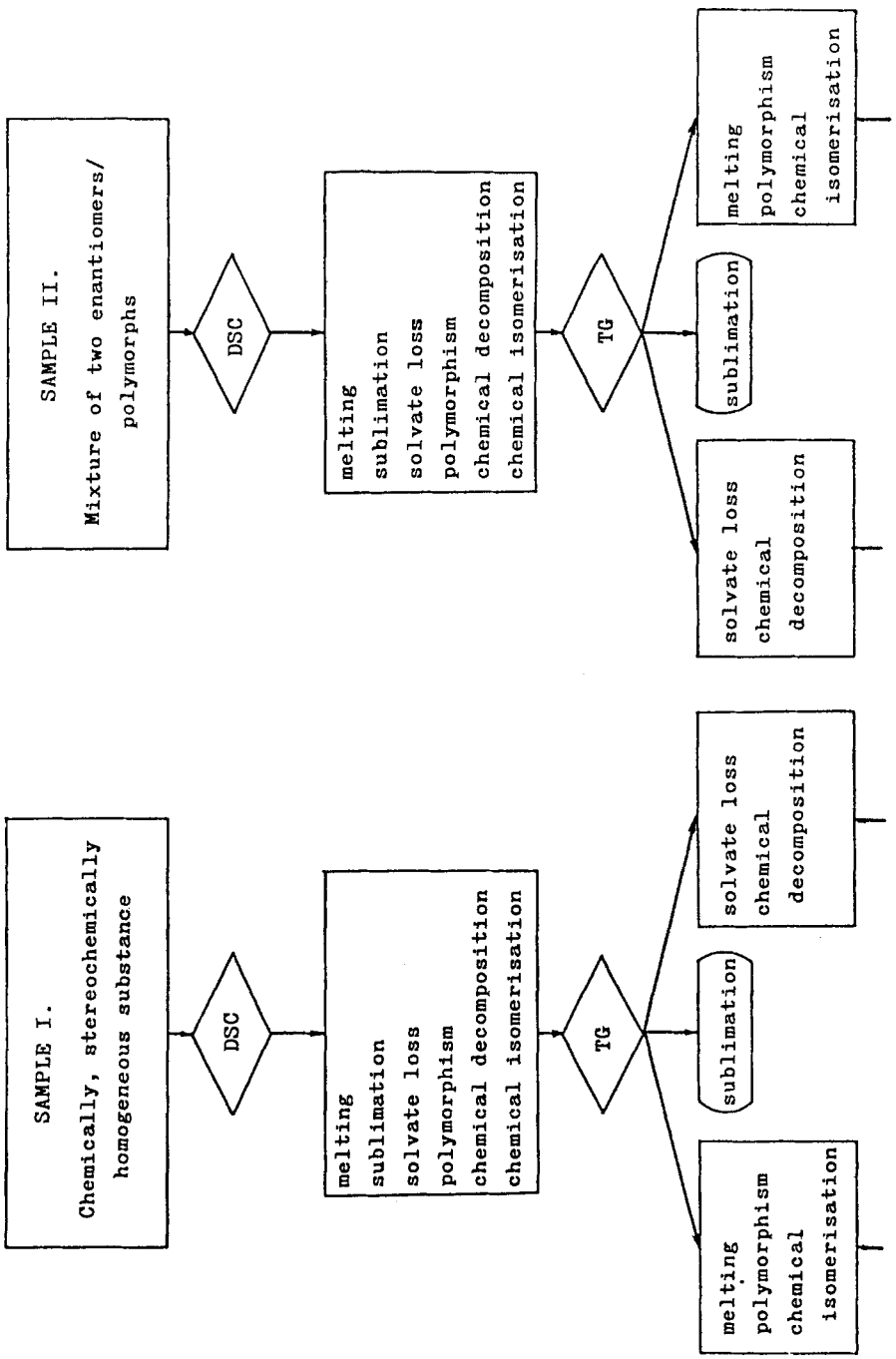
More information on the structural properties of the investigated substances can be obtained by X-ray crystallography (powder and single crystal measurements).

Binary mixtures of amphetamine derivatives

The reported system was tested by a number of amphitamine derivatives (Table 1) in order to check its applicability and reliability in identifying conglomerate/molecular compound formation of the individual enatiomers and in discovering polymorphic modifications (if any).

The thermoanalytical characteristics are compiled in Table 2.

The studied compounds exhibited practically negligible decomposition (less than 2%) before melting. (To avoid the unwanted decomposition we used her-


SAMPLE I.
Chemically, stereochemically homogeneous substance
DSC
melting
sublimation
solvate loss
polymorphism
chemical decomposition
chemical isomerisation
TG
sublimation
solvate loss
chemical
decomposition
melting
polymorphism
chemical
isomerisation
SAMPLE II.
Mixture of two enantiomers/ polymorphs
DSC
melting
sublimation
solvate loss
polymorphism
chemical decomposition
chemical isomerisation
TG
sublimation
solvate loss
chemical
decomposition
melting
polymorphism
chemical
isomerisation

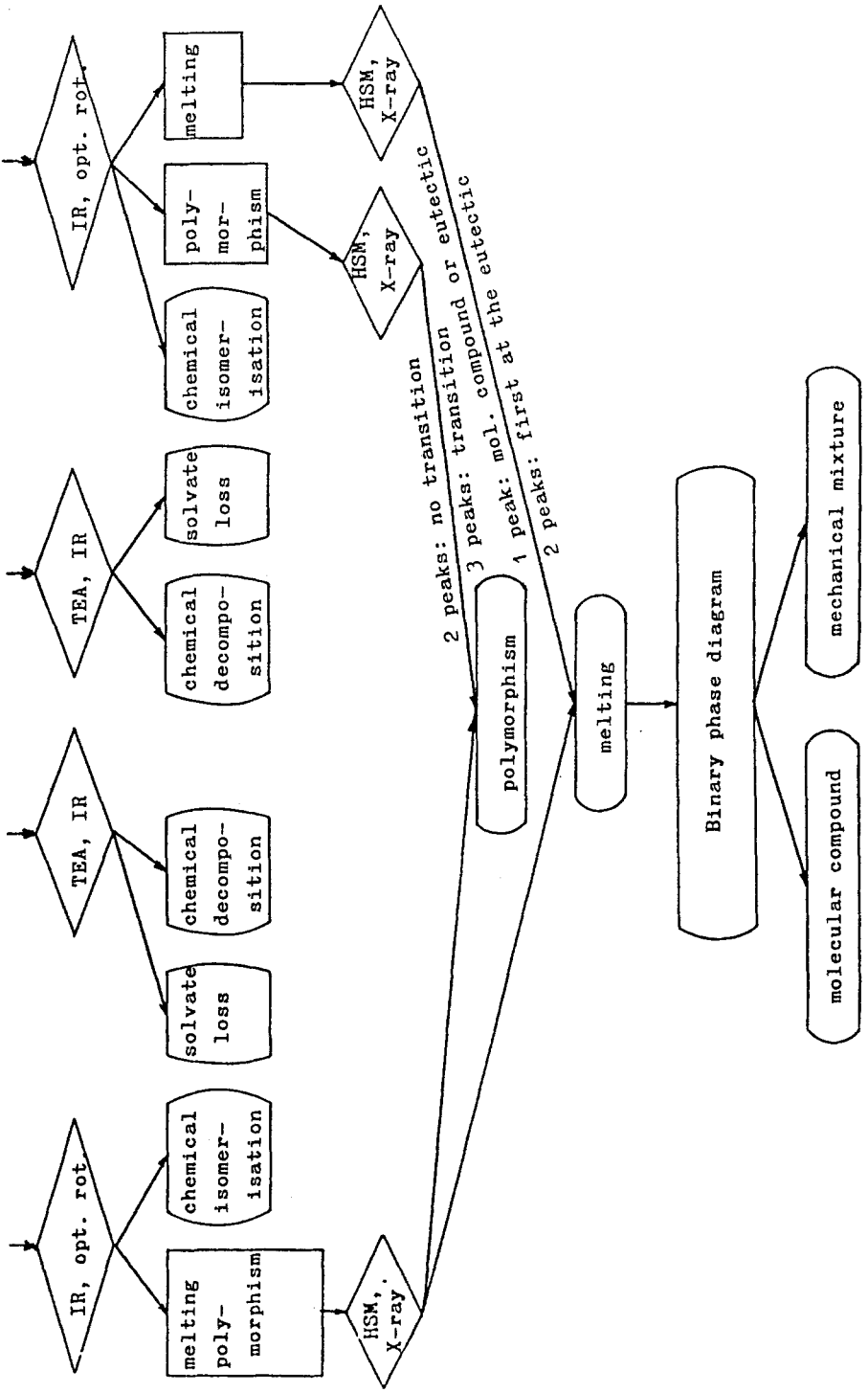


Fig. 1 The system used for studying two-component mixtures

metically closed sample holders.) Binary mixtures of mirror image isomers were detected for compounds (–)–II, (+)–II, (+)–IV/A, (–)–V/A and (+)–VI/A.

Besides, the thermogravimetric measurements indicated that all of our compounds sublime even at room temperature.

Table 2 Data obtained using thermoanalytical (thermogravimetry and DSC) methods

Compound number	T_1 / K	ΔH_1 / J·g^{-1}	T_2 / K	ΔH_2 / J·g^{-1}	Comments
(±) – II	429.3	116			
(+) – II/A	470.7	132			
(+) – II/B	465.9	*	467.4	*	1) 2)
(–) – II	430.9	10.5	462.4	113	1) 2)
(+) – II	428.0	18.4	458.7	14.5	1) 2) ^
(±) – III	405	119			
(–) – III	446	138			
(±) – IV	386.9	106			
(–) – IV/A	425.9	127			
(–) – IV	390.7	107	402.7	10.7	1) 2) ^
(±) – V	402.9	100			
(–) – V	415.8	102			
(–) – V/A	400.8	111			1) 2) ^ #
(±) – VI	414.5	88.1			
(+) – VI	439.1	101			
(–) – VI	437.0	102			
(+) – VI/A	417.0	106	426.1	12.8	1) 2) ^

1) polymorphism?
2) mixture of mirror-image isomers?
* can not be integrated separate
^ peak temperatures of the melting
\# expanded melting

T_1 temperature of the first peak
ΔH_1 enthalpy of the first peak
T_2 temperature of the second peak
ΔH_2 enthalpy of the second peak

Our observations were confirmed by the comparison of the infrared spectra of the optically pure and racemic substances and by their visually traced behaviour on hot stage microscope.

Heating the sample on a hot stage microscope a clear distinction can be made between a monotonous melting process and a polymorphic transition. For the compound (+)-II/B the transformation of the polymorphs was followed visually as it is shown by the images in Fig. 2.

The evaluation of the data led us to the conclusion that:

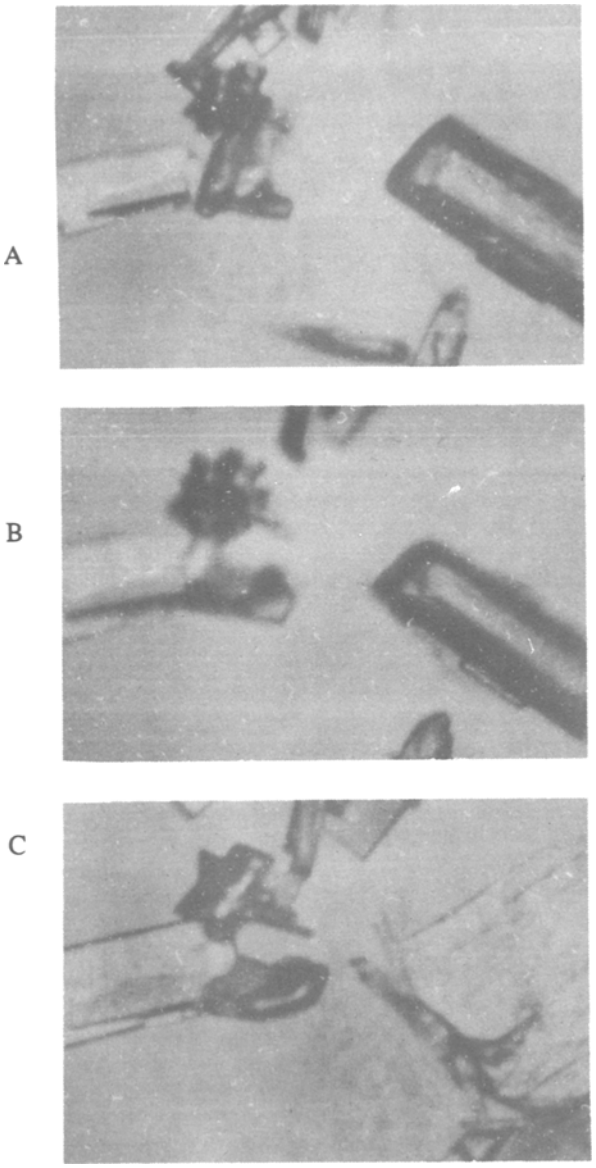


Fig. 2 The polymorphic transition of the *p*-fluorine-amphetamine-hydrochloride [(+)-II/B].Image A: Crystals at 460 K Image B: Upon heating by 1 deg/min, a part of the crystals starts to melt (indicated by the arrow) at 466 K Image C: By 469 K, the molten crystal got recrystallized. (At 271 K the crystals melt again)

a) The *p*-fluoro-amphetamine hydrochloride salt can exist in two polymorphic modifications.

b) The enantiomers of primary and secondary amine hydrochlorides in the studied family of compounds form conglomerates, while the tertiary amine hydrochlorides exhibit molecular compound forming tendency (Table 3).

Table 3 Data and information obtained from the binary phase diagrams

Data used for the binary phase diagram calculations					Conclusions obtained from the binary phase diagram				
Comp. no.	T_E / K	T_R / K	ΔH_E / J·g^{-1}	ΔH_R / J·g^{-1}	T_{eut} / K	x_{eut}	A	B	Verification
II	470.7	429.3	132	116	424.6	0.5	+		IR
III	446	405	138	119	405.3	0.5	+		IR
IV	425.9	386.9	127	106	389.0	0.5	+		IR
V	415.8	402.9	102	100	396	0.72		+	IR
VI	439.1	414.5	101	88.1	412	0.64		+	IR

A) Conglomerate
B) Molecular compound
IR Infrared spectroscopy
T_E Melting point of the enantiomers
T_R Melting point of the racemate
ΔH_E Heat of fusion of the enntiomers
ΔH_R Heat of fusion of the racemate
T_{eut} Melting point of the eutectic
x_{eut} Composition of the eutectic

Our studies revealed that this complex system is suitable not only to identify conglomerate/molecular compound formation, but it can help in indicating and identifying existing polymorphs and polymorphic transformations induced by heating.

* * *

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Zusammenfassung — Zur Untersuchung des physikalisch-chemischen Verhaltens binärer Gemische wird ein komplexes System, bestehend aus thermoanalytischen Methoden, IR und Röntgendiffraktion nach dem Debye-Scherrer-Verfahren, beschrieben. Dieses System wurde an binären Gemischen von Amphetaminhydrochloridsalzen getestet.

Die Untersuchungen zeigten, daß von den gewählten Verbindungen die Hydrochloride der primären und sekundären Amine eine Tendenz zur Konglomeratbildung zeigen, während die Hydrochloride der tertiären Amine Molekülverbindungen (Racemate) bilden. Für *p*-Fluoramphetamin-Hydrochlorid wurde die Existenz von zwei polymorphen Modifikationen nachgewiesen.