

THERMAL ANALYSIS AND POWDER X-RAY DIFFRACTION STUDY OF TERPIN Evidence of a eutectic 'hydrate/anhydrous form'

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Abstract

When the DSC analysis of different samples of terpin hydrate is carried out, a non identified small endotherm is observed at about 100°C, just before the melting endotherm. This phenomenon is detected whatever the experimental conditions are.

After some trials, this endotherm was identified as an eutectic formed with terpin hydrate and desolvated terpin (17/83).

The importance of the experimental conditions is preponderant. In an open pan, the desolvation occurs and the melting endotherm of the anhydrous form can be observed at 105°C. In a closed pan, no desolvation is detected and the melting endotherm at 120°C is that of the terpin hydrate.

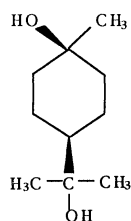
The eutectic exhibits a good compression ability and a fast dissolution. Its stability is correct. Its use in therapeutic tablets can be envisaged.

The eutectic structure could be, more generally, favourable to compression owing to the isotropic texture of this particular solid state.

Keywords: differential scanning calorimetry, eutectic, terpin

Introduction

Terpin hydrate is a drug widely used as an expectorant, in tablets and alcoholic solutions. Terpin which was prepared by hydration of α -pinene, crystallizes with one molecule of water to give 'terpin hydrate'. Two isomers could be found: the *cis*-terpin is the usual pharmaceutical form.



anhydrous *cis*-terpin; molecular weight: 172.27

When heating the terpin hydrate, dehydration occurs giving the very hygroscopic anhydrous form. During heating, at nearly 100°C, sublimation is observed.

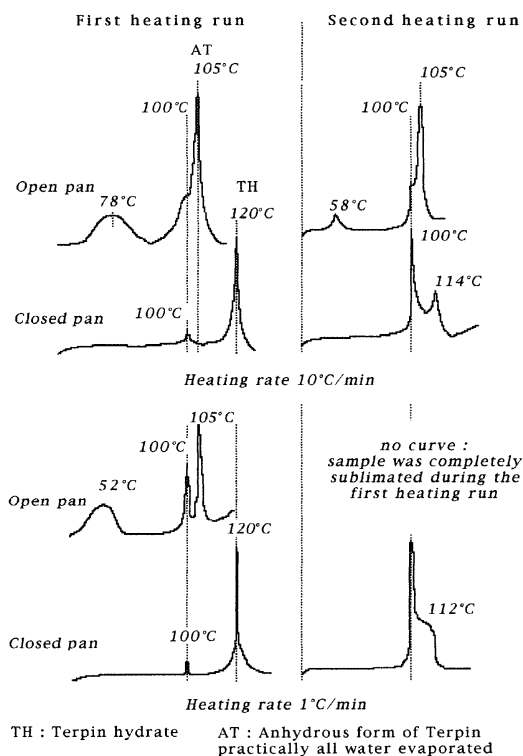


Fig. 1 DSC curves of marketed terpin

During a study in order to carry out a new oral solid dosage form, the DSC analysis of different samples of terpin hydrate led us to observe several thermodynamic events (Fig. 1):

- in open pan, a desolvation endotherm can be observed at 60/80°C and the melting endotherm of the desolvated form occurs at 105°C in accordance with the literature [1, 2].

- in a closed pan, no desolvation is detected and the melting endotherm of the terpin hydrate is observed at 120°C as it is commonly described [2, 3].

Surprisingly, at about 100°C, just before the melting endotherms, we could detect a more or less clear endothermic event which we tried to identify in our study.

Materials

Terpin hydrate from several origins: Merck (Darmstadt, Germany); Cooper (Melun, France); four terpin hydrate samples from different origins which were kindly supplied to us by Lipha Laboratories.

Methods and galenic characterizations

Different thermoanalytical methods have been applied for the characterization of the samples. Furthermore, pharmaceutical tests have been applied for the selected materials.

For a thermomicroscopy study, the terpin hydrate sample was deposited between slide and cover slip in a silicon oil droplet. The slide was introduced in a hot stage Mettler FP 82 and the examination was made under a Wild Leitz M 20 microscope. The heating rate was $5^{\circ}\text{C min}^{-1}$.

A differential scanning calorimetry study was carried out using a DSC 20/TA 3000 Mettler device. Trials were made either in an open pan, without a lid, or in a closed pan. The heating rates were either 1 or $10^{\circ}\text{C min}^{-1}$, from 25 to 130°C , under anhydrous nitrogen flow.

A phase diagram 'terpin hydrate/anhydrous form' was then constructed, using the same device. The DSC method we used, proceeded in two steps.

In the first step, the dehydration of terpin hydrate was carried out in an open pan: a certain mass of terpin hydrate was heated in an open pan from 45 to 110°C at $4^{\circ}\text{C min}^{-1}$, and then submitted to 110°C for 5 min.

In the second step, the eutectic formation was realized in a closed pan: after the addition of a calculated amount of terpin hydrate upon the anhydrous terpin formed in the first step, the pan was immediately closed. A second heating run, from 45 to 140°C , at $5^{\circ}\text{C min}^{-1}$ was then carried out.

A third heating run, in the same conditions, was compulsory for a complete obtention of the eutectic, in the case of a low concentration of hydrate form.

A TG 50/ TA 3000 Mettler device was used for thermogravimetry studies. Samples have been heated from 25 to 140°C , at $5^{\circ}\text{C min}^{-1}$.

Two types of study were carried out in powder X-ray diffraction, using three different devices. Powder X-ray diffraction was carried out either at room temperature, or by using a linear temperature program.

At room temperature, X-ray diffraction was obtained with a Guinier de Wolff camera (CuK_{α} radiation: $\lambda=1.54178$) fitted with a Siemens X-ray generator.

For powder X-ray diffraction measurements vs. temperature, two devices were used: a Guinier Lenne camera (Nonius), fitted with a Siemens X-ray generator, in which the sample was submitted to a heating rate of $1.5^{\circ}\text{C h}^{-1}$, from 20 to 110°C , and a Siemens D 5000 Diffractometer, in which the temperature/time cycle was consecutively 30 , 40 , 50 , 60°C during one hour for each temperature, and then 70 , 75 , 80 , 85°C during two hours for each temperature. The diffractograms were recorded at the end of each temperature step, from $2\theta=10^{\circ}$ to $2\theta=39^{\circ}$.

Among the pharmaceutical tests, compression ability of the materials we have selected was first studied. In the aim of the use of a drug powder in therapeutic tablets, it is very interesting to know if this substance can be compressed either directly or only after a previous granulation treatment. Unfortunately, terpin hydrate exhibits a poor compression ability.

In order to test compression properties, we used the '1 cp method' of Guyot [4] which was developed for pure raw material and can be easily applied in the case of small sample masses. A weighed sample of the pure raw material was compressed

under standardized conditions using an instrumented single punch tablet machine Frogerais OA which has been fitted with force and displacement sensors connected by electronic bridges to a microcomputer where data are stored and processed by a specific software.

The characteristics of the tablets obtained are measured, especially the crushing strength (CS) using a Schleuniger hardness tester 6D.

The compression capacity of the material is deduced from the behaviour of same weight samples compressed with different adjustments. Different compression forces were used. For each compression level, recorded compression parameters are measured on a unique tablet.

The upper punch displacement was adjusted to reach maximal compression forces between 0 and 2500 daN. During compression, the forces developed at the level of upper and lower punches, Y_1 and Y_2 respectively, are registered. The ratio Y_2/Y_1 is indicative of the force transmission through the powder bed during compression.

Data for tablet crushing force is represented as a function of compression pressure. CS/Y_1 is indicative of the compression ability: the higher this ratio, the better the compression ability is. For convenience, this value is multiplied by 10^5 and named 'cohesion index' (CI).

The dissolution rate of terpin was determined in 800 ml of water at 37°C , respectively in continuous flow cells [5] for the drug powders, and according to the stirring paddle method of the European Pharmacopoeia, for the tablet obtained by compression of the selected materials. The dissolution medium was assayed for terpin concentration using a colorimetric method based on the reduction of phosphomolybdic acid by the dehydrated terpin [6]. As a matter of fact, terpin does not absorb in UV.

Results and discussion

An investigation was performed by DSC with all the batches we collected for terpin hydrate. As a first conclusion, for all the batches we tested, whatever their origin may be, an endotherm at about 100°C could be seen, however, with a broad range of energetic changes.

Identification of the endotherm at 100°C

Several hypothesis may be put forward to explain the endotherm which occurs at about 100°C during the heating runs.

Intervention of a second desolvation process

As a matter of fact, when thermogravimetric analysis is carried out on terpin hydrate, two steps can be observed (Fig. 2). The first one was approximately between 26 and 74°C (mass loss: 6.3%), and the second step, between 74 and 102°C (mass loss: 5.8%). The comparison of the sum of the values for the two steps (12.1%) with the theoretical value of the water content for the terpin hydrate (10.5%) and the value we found by the Karl Fischer method (10.2%, CV% 2.1%) indicates a good agreement. The little difference observed between the total mass loss at 102°C and the

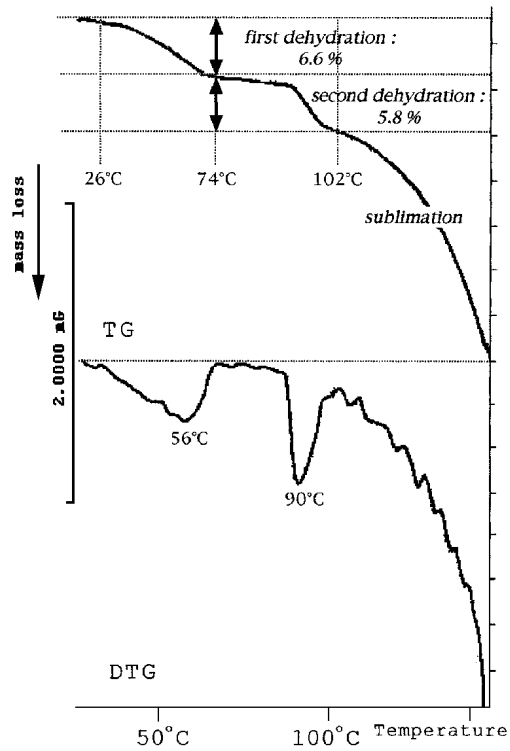


Fig. 2 TG curve of terpin hydrate



Fig. 3 Powder X-ray diffraction pattern of terpin hydrate vs. temperature

theoretical water content must be ascribed to the beginning of a sublimation phenomenon of terpin.

These results are also confirmed by powder X-ray diffraction vs. temperature (Fig. 3). At 20°C, it is possible to observe the structure of terpin hydrate in accord-

ance with JCPDS data [7]. A very clear structural change corresponding to the first dehydration which produces hemisolvate could be observed at 56°C. At 75°C, it is possible to observe a very slight change in the diffraction pattern, which corresponds to the second dehydration and the advent of the anhydrous form.

The reflections of anhydrous form are weak and very broad, which could be explained by a partial transformation into the amorphous form. Unfortunately, due to the sample lying for a long time at hot temperatures, total sublimation occurs at nearly 83°C.

As we could see in Fig. 2, thermogravimetric analysis showed a more progressive phenomenon, which could be due to kinetics problems: as a matter of fact, the heating rate was 5°C min⁻¹ as far as thermogravimetric analysis was concerned and 1.5°C h⁻¹ when powder X-ray diffraction was carried out, using a Guinier Lenne camera. This low heating rate is needed for a sufficient film exposure.

However, the gradual water loss of the terpin hydrate demonstrated by thermogravimetry compared with the abrupt change of the crystal structure at 56°C observed by the X-ray diffraction pattern could be explained. As a matter of fact, it is generally accepted that many solvates keep their crystal structure even to a total loss of the solvent molecules. However, a partially defective crystal structure is unstable and may, at any given point of dehydration or desolvation, spontaneously change into the crystal form of the desolvated molecule or into a crystal form with a lower stoichiometric ratio solvent to organic or inorganic molecule. In case of the terpin hydrate changing gradually to the water content of the hemi-hydrate between 26 and 74°C, a sudden structural change with the X-ray diffraction is observed for 56°C, the temperature for which, according to DTG, the rate of water loss is at maximum. At 56°C the water molecules not integrated into the hemi-hydrate form are forced to move out of the hemi-hydrate lattice by diffusion through the lattice layers.

The similar observation for the transformation from the hemi-hydrate to the anhydrous form of terpin is difficult to elucidate by the X-ray diagram, because the sample mass disappeared by sublimation at 83%.

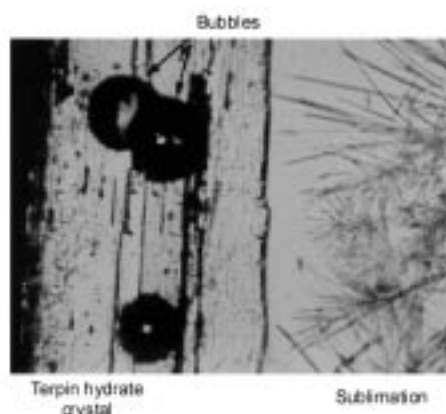


Fig. 4 Evidence of desolvation from a terpin hydrate crystal at 115/118°C in a thermomicroscopy experiment

In spite of these observations, the endotherm which appears at about 100°C can not be ascribed to the second desolvation since, as can be seen from Fig. 1, it clearly increases when a second heating run is carried out.

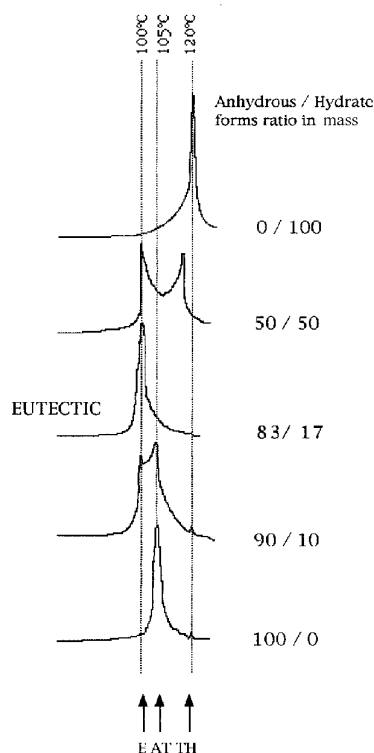
Furthermore, the second desolvation is clearly pointed out using thermomicroscopy. When the sample is heated under silicon oil, an important bubble escape occurs after 115°C, just before and during the melting (Fig. 4). So, it seems that the endotherm at 100°C is not due to the second desolvation.

Is the endotherm at 100°C due to the sublimation of terpin sample ?

Sublimation could be a possible explanation: as a matter of fact, sublimation is an endothermic phenomenon and terpin hydrate is sublimable.

However, under the microscope, using a hot stage (heating run: 5°C min⁻¹), we can see that sublimation begins slowly at nearly 90°C and increases dramatically after 110°C. This can not correspond to a sharp endotherm at 100°C. On the other hand, the total mass loss (12.1%) is not much higher than the water content found by the Karl Fischer Method (10.1%).

Another explanation must be found which could be the best one.



E : eutectic point at 100°C
 AT : melting point of the anhydrous form of Terpin at 105°C
 TH : melting point of the Terpin hydrate at 120°C

Fig. 5 DSC curves of mixtures 'anhydrous/hydrate' forms of terpin

The formation of a eutectic melting

The existence of a eutectic 'terpin anhydrous form/terpin hydrate' was quoted by Schoorl many years ago [8]. So, we tried to construct the phase diagram. The classical method by interpretation of the temperature kinetics during the cooling down of various melted physical mixtures, was not possible due to the glassy state of the melt which crystallizes after a long delay. In addition, the water could escape from the measurement device during heating, leading to a change in the 'anhydrous/hydrate' forms ratio. It is the reason why we used the DSC method described in the experimental section. Samples containing increasing amounts of anhydrous form in terpin hydrate are heated in a sealed pan.

On Fig. 5, some characteristic DSC curves are reported, showing the evolution of the different endotherms as a function of the proportion of anhydrous form in terpin hydrate. The peak temperature and the enthalpies of the thermodynamic events are plotted vs. the anhydrous form percentage (in mass) in the tested mixture.

On the phase diagram presented in Fig. 6, it can be observed that an eutectic mixture is obtained for the proportions of 'anhydrous form/terpin hydrate', approximately for 83/17: in this case, only one endotherm is detected, that is to say that of the eutectic 'anhydrous/hydrate form' of terpin.

It must be noted that the experiments leading to the eutectic detection are made in closed atmosphere in a sealed pan: we are not in quasi-equilibrium conditions. As

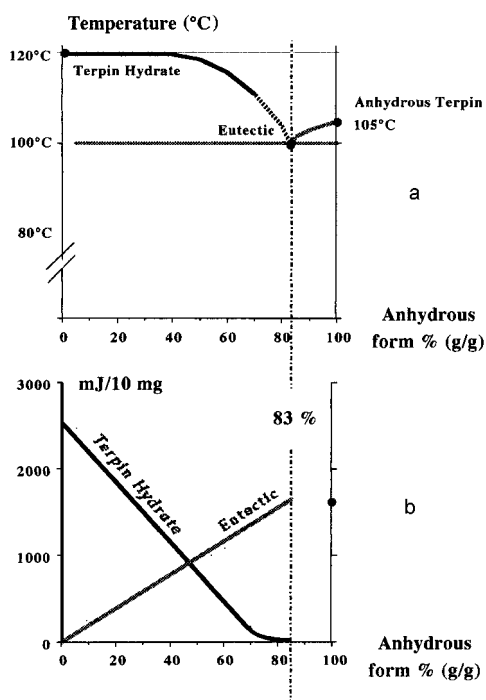


Fig. 6 The phase diagram anhydrous form/terpin hydrate (a); endotherm enthalpies of the terpin hydrate and eutectic endotherm in regard of the anhydrous form content (b)

a matter of fact, a certain water vapor tension, corresponding to the water of the terpin hydrate fraction in the pan, is lying upon the mixture during heating. This vapor pressure is certainly causing the observed stability of the hydrate.

The melting point of the terpin hydrate is constant until more than 42% g/g of the anhydrous form is added. However the peak enthalpy is practically linear decreasing from the pure hydrate to the eutectic mixture of 83% g/g. For higher values of this ratio, the melting endotherm of the anhydrous form appears from 103 to 105°C. This shift is a consequence of the two endotherms of the eutectic system and the terpin anhydrate.

Therefore, the endotherm observed on DSC curves of terpin hydrate at about 100°C is caused by a certain amount of the eutectic mixture between the anhydrous form and the terpin hydrate.

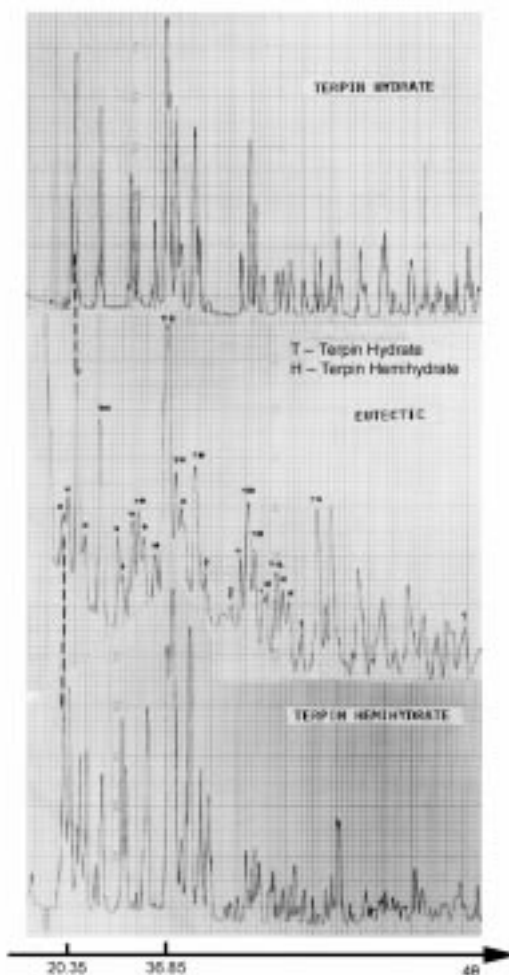


Fig. 7 X-ray diffraction patterns of terpin hydrate, terpin hemi-hydrate and eutectic. Superposition of hydrate and hemihydrate diffraction lines (TH)

Physical and technological study of the eutectic mixture

The question had been brought forward to use the eutectic mixture of the terpin anhydrate and the terpin hydrate for formulation purpose, instead of terpin hydrate. As a matter of fact, the formation of eutectic mixtures is known to give generally an improvement in the dissolution rate of drugs. Furthermore, terpin hydrate exhibits a poor compression ability which could be improved by the eutectic formation. These were the two reasons why we studied some physical and technological properties of the 'anhydrous form/terpin hydrate' eutectic.

The eutectic mixture was prepared on a larger scale by mixing 83 parts of anhydrous form obtained by desolvation of terpin hydrate at 110°C, with 17 parts of terpin hydrate. This physical mixture is melted in a stoppered dish, in an oven, at 135°C for 20 min.

Powder X-ray diffraction

The powder X-ray diffraction patterns of terpin hydrate, eutectic, and terpin hemihydrate are reported on Fig. 7. The great unstability of the anhydrous form did not allow to carry out a trial using the Guinier de Wolff camera. We tried to record the X-ray diffraction pattern of the anhydrous form from the film obtained by a Guinier Lenne camera but there were only some very broad reflections. So, we tried then to obtain the diffractogram of anhydrous form using the Siemens D 5000 diffractometer. The very low heating run described under methods, allows to identify clearly the variations of the crystalline structure. Rather clear differences are detected between the hydrate, the hemihydrate and the anhydrous form (Fig. 8). The powder X-ray diffraction pattern of the eutectic mixture is made up of numerous reflections, and among these, essentially those of the hemihydrate and terpin hydrate. The other reflections could be those more particularly due to the anhydrous form.

In conclusion of this study using X-ray diffraction, we can say that the X-ray diffraction pattern of the eutectic is an addition of the reflections of terpin hydrate and,

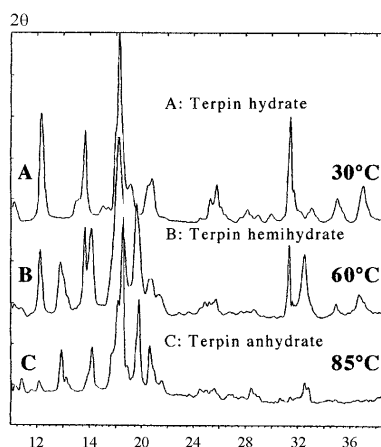


Fig. 8 Diffractograms obtained during heating cycle of terpin hydrate, at 30°C (start), 60°C (after 3 h), 85°C (after 11 h) using D 5000 Diffractometer

principally, those of a desolvated form which can be hemihydrate or anhydrous form. This addition of reflections and the observation of only one endotherm in DSC, the temperature of which is less than the melting of the two components, are indicative of an eutectic formation.

Dissolution rate

As can be seen in Table 1, no improvement of the dissolution rate was detected for the eutectic mixture compared with the terpin hydrate.

Table 1 Dissolution rates of terpin hydrate (1a) and eutectic (1b)

Time/ min	(1a)			(1b)		
	$\bar{m}/\%$	$\sigma_{(n-1)}$	CV/%	$\bar{m}/\%$	$\sigma_{(n-1)}$	CV/%
7.5	72.2	12.0	16.6	61.5	6.7	11.0
15	88.0	8.1	9.2	79.8	2.4	3.0
30	95.5	4.5	4.7	90.9	3.8	4.2
45	99.1	1.4	1.4	93.8	4.0	4.3
60	99.1	1.1	1.1	100	0	0

Table 2 Compression characteristics of terpin hydrate (2a) and eutectic (2b)

	Y_1 (daN)	Y_2 (daN)	Y_2/Y_1	Crushing strength (CS)	Cohesion index (CI)
(2a)	371	330	0.889	0.01	
	1036	958	0.925	0.8	77
	1350	1249	0.925	1.1	81
	1665	1546	0.928	1.1	66
	2001	1907	0.916	0.8	38
	2163	2001	0.925	0.8	37
(2b)	63	49	0.781	0.2	320
	563	502	0.892	1.6	284
	905	811	0.896	2.3	254
	1102	991	0.899	2.5	227
	1444	1298	0.899	3.1	215
	1968	1767	0.898	3	152

Two explanations are possible ones: either the solubility of terpin hydrate is sufficient to smooth away the differences in dissolution rates, or, when in contact with water, the solid desolvated form turns into terpin hydrate before dissolution.

Compression ability

The pure eutectic and the pure terpin hydrate powders are compressed on a single punch tablet machine in standardized conditions, using increasing compression forces. Crushing strength of compacts obtained are plotted vs. the compression force. The higher the slope of the straight line obtained is, the better the compression properties are. This study was made on the same sieved fraction (200 to 500 μm).

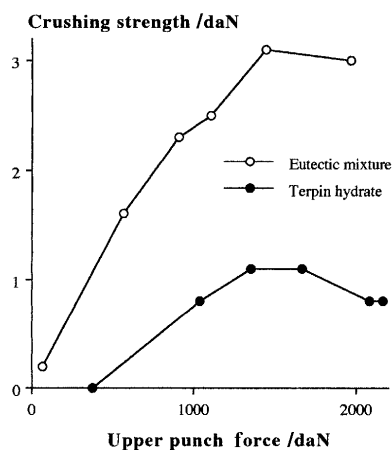


Fig. 9 Crushing strength of compacts vs. the compression force applied

It can be observed in Table 2 and in Fig. 9, that the compression ability of the eutectic mixture is clearly better than that of terpin hydrate.

Stability study

For a possible use of this new form in therapeutic tablets, a stability study was compulsory. DSC was used for this stability study. As a matter of fact, the eutectic mixture exhibits a single symmetrical peak which is the melting endotherm. The advent of either a shouldering or a second peak is an indication of instability. The 200–500 μm particle size fraction was stored in stoppered glass flask, at room temperature, for several months. Results are reported in Table 3.

At the present time of experiments, stability is good in case the flask was not opened too often. After four openings of the container, a shouldering may appear which becomes a second peak after ten months. However, after ten months, the eutectic form is conserved in case the flask has been rarely opened.

A humidity tight packaging seems to be appropriate.

Pharmaceutical application

From this study, it seemed that the eutectic mixture of the terpin anhydrate and hydrate could be an interesting material for pharmaceutical use. So, the eutectic mixture was introduced in a classical formulation for tablets, prepared by direct com-

pression. By comparison, tablets were prepared with the same formula either with terpin hydrate or with eutectic instead of the terpin hydrate.

Table 3 Stability of the eutectic mixture of the terpin anhydrate and hydrate by DSC curves

Storage time	Batches/°C			
	1	2	3	4
0	100.2	100.4	100.7	100.4
5 days	101	100.6		
10 days	101			
1 month	100.5	100.6	100.9	
2 months	100.5	100.1	100.1	
4 months				100.6
8 months	101.0 1 peak + shouldering	101.4	100.6	100.3
9 months				100.5
10 months	100.6 115.9	100.4		
12 months		100.7 1 peak + shouldering	100.9	

Each individualized peak is represented by the temperature of its summit.
Shouldering is mentioned

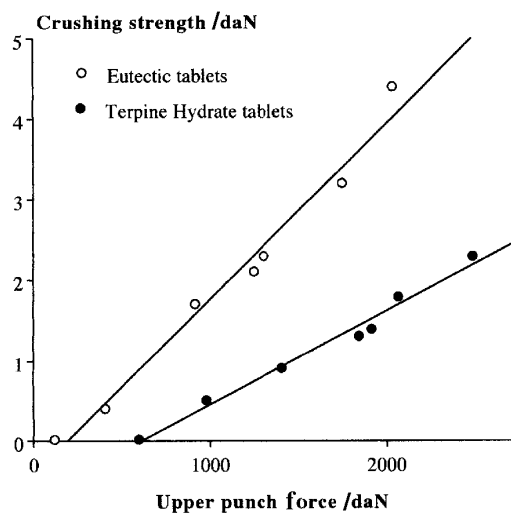


Fig. 10 Crushing strength of eutectic and terpin hydrate tablets vs. the compression force applied

The formula was as follows:

Terpin (from hydrate or eutectic)	150 mg
Tabletose®	100 mg
Maize starch	40 mg
Magnesium stearate	1.5 mg

The compression properties of these two powder mixtures and dissolution rate of terpin issued from the tablets were compared.

The compression ability improvement by using the eutectic mixture is clear as can be seen on the Fig. 10. It is possible to obtain therapeutic tablets exhibiting a good hardness with a relatively low compression force, by direct compression.

The dissolution rate of terpin from the eutectic mixture in tablets is rather similar to that from the terpin hydrate, which was satisfying (Fig. 11).

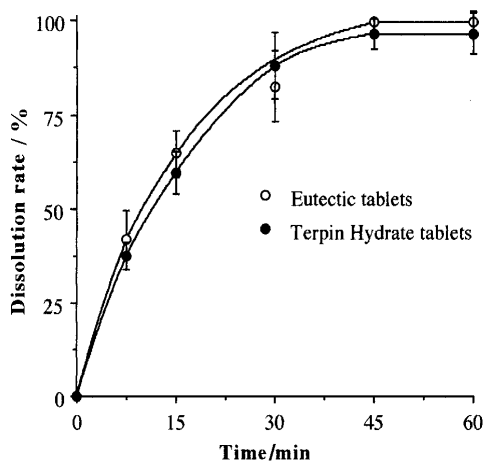


Fig. 11 Dissolution rates of terpin from either terpin hydrate or eutectic tablets

The eutectic mixture seems to be a good raw material for preparing tablets.

Stability is not a problem to study in tablets, because the important improvement achieved by the eutectic mixture is restricted to the compression step.

Conclusions

The endotherm which appears at about 100°C just before the melting endotherm of either terpin hydrate (in a closed pan) or anhydrous form (in an open pan) is that of an eutectic mixture of terpin hydrate and dehydrated form.

From X-ray diffraction pattern, it is difficult to say if this dehydrated form is either the anhydrous terpin or its hemihydrate which could be the equilibrium form.

The presence of this eutectic endotherm is constant whatever batches we tested. Only at a high relative humidity, the stability of this eutectic is not satisfactory.

On the other hand, it is obvious that the behaviour in DSC is different according to the conditions: in an open pan, the desolvation is clearly pointed out, when, in a

closed pan, desolvation can not be observed, because of the buildup of a high water partial pressure. More generally, the DSC is to be carried out in both conditions, i.e. close or open pan, in the case of solvated forms such as hydrates.

From a technological point of view, it would perhaps be interesting to study in more detail the compression ability improvement caused by the eutectic formation.

This form can be considered as a polycrystalline material which gives to this material an isotropic texture very favourable to compression.

This idea could be a good working hypothesis in the processing of directly compressible substances.

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