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Thermal behaviour of a multicomponent solvent pharmaceutical hydrate during vacuum contact drying

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Abstract — A pharmaceutical drug is industrially dried with a vacuum drying process for which the energy is supplied by contact. This product is wetted with a multicomponent solvent i.e. a solvent for which components are miscible. Moreover, two hydration states exist for this drug (tetrahydrate and monohydrate). These singularities induce a different thermal behaviour from the one of porous media described in literature. The local analysis of temperature kinetics allows us to define accurately the operation progress. The free solvent vaporisation stage of the process does not result in a classical temperature plateau on account of a selective removing of one component. On the contrary, the change of hydration state (tetrahydrate to monohydrate) results in a new temperature plateau. © Elsevier, Paris.

vacuum drying / hydrates / pharmaceutical drug / water-acetone selectivity

Résumé — Comportement thermique d'un hydrate pharmaceutique imprégné d'un solvant multiconstituant lors du séchage sous vide par contact. Une substance pharmaceutique est industriellement séchée par un procédé sous vide, avec un apport énergétique effectué par contact. Ce produit est imprégné d'un solvant multiconstituant, i.e. un solvant dont les composants sont miscibles. En outre, il présente deux états d'hydratation (tétrahydrate et monohydrate). Ces singularités se traduisent par un comportement thermique sensiblement différent du comportement des milieux poreux décrits dans la littérature. L'analyse locale des cinétiques de température permet de définir précisément le déroulement de l'opération. La phase de vaporisation du solvant libre ne correspond pas au plateau classique de température, en raison de l'élimination sélective de l'un des constituants. En revanche, le changement d'état d'hydratation impose un nouveau palier en température. © Elsevier, Paris.

séchage sous vide / hydrates / produit pharmaceutique / binaire eau-acétone / sélectivité

Nomenclature

e	sample width	m
F_m	mass flux density	$kg \cdot m^{-2} \cdot s^{-1}$
P	pressure	Pa
Q	heat flux density	$W \cdot m^{-2}$
RH	relative humidity	%
T	temperature	°C
X	solvent content	
z	distance	m

Subscripts

a	acetone
atm	atmosphere
b	boundary
mono	monohydrate
res	heat resistor
tetra	tetrahydrate
vessel	vacuum vessel

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1. INTRODUCTION AND PROBLEM

Vacuum contact drying process is applied to a pharmaceutical drug for which two hydration states exist [1, 2, 3]:

– tetrahydrate whose moisture content (dry basis) X_{tetra} is equal to 0.2;

– monohydrate whose moisture content X_{mono} is equal to 0.05.

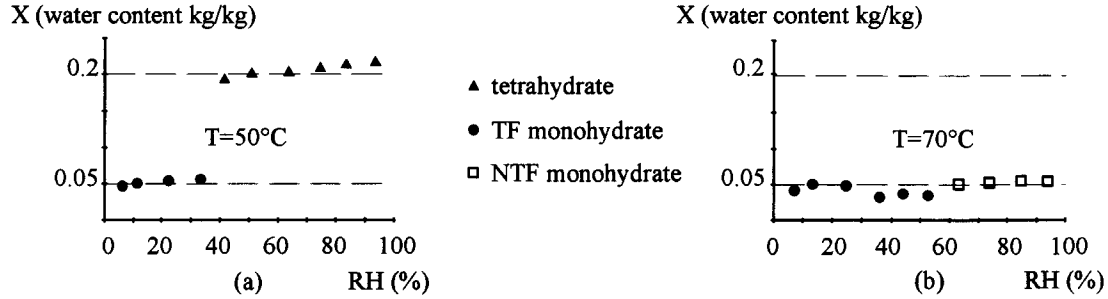

Figure 1. Examples of desorption isotherms: (a) $T = 50$ °C, (b) $T = 70$ °C.

The nature of the bound water (water molecules of hydration) implies that, in the hygroscopic field, molecules of our product can only have two distinct water content values: X_{tetra} or X_{mono}. Concerning the monohydrate, two polymorphs exist: the metastable therapeutic form TF and the non therapeutic form NTF which is the stable one.

From desorption isotherms coupled with infrared spectroscopy, an equilibrium diagram (*figures 1* and *2*) showing the distribution of the different forms is determined [4].

The desorption isotherms present two plateaux, each one corresponding to an hydration state. This behaviour is classical for hydrates [5, 6]. For low temperatures, tetrahydrate and TF monohydrate are the two stable forms. With increasing temperature, the stability area of tetrahydrate decreases (frontier AB). This remains true until the frontier BC is reached. The boundary temperature T_b, representing BC, depends on the relative humidity of the atmosphere. Above T_b, the tetrahydrate vanishes and is replaced by the NTF monohydrate for high relative humidities. The frontier BD is practically $RH = 50$ %. This diagram is only relevant for desorption from tetrahydrate.

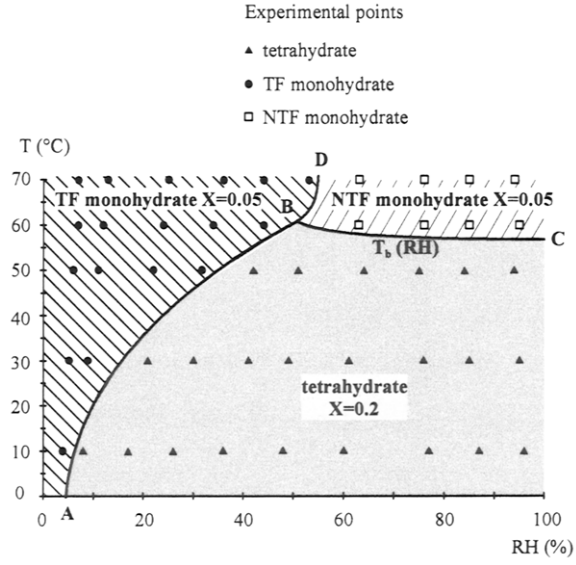

Figure 2. Equilibrium diagram of the different pseudo-polymorphic forms deduced from desorption isotherms; experimental points from desorption isotherms (*figure 1* and [4]): ▲ ● □.

In this article dedicated to the analyse of the particular thermal behaviour of the drug under vacuum drying, the problem of the monohydrate polymorphism [7] is not considered. For this study, the two forms of the monohydrate and consequently the two hatched areas on the diagram are not distinguished.

In order to elucidate the singular thermal behaviour during drying, it is essential to know exactly the constitution of the material. The manufacturing process of the drug is divided into three steps: crystallisation, filtration and drying. An aqueous solution of the product is poured into acetone where crystallisation occurs. A tetrahydrate suspension in a solution of water and acetone is then formed. After filtration, the product consists of three phases (*figure 3*).

Solid phase: tetrahydrate

Bound water corresponds to water molecules of hydration. Acetone presence does not have any influence on the hygroscopic equilibrium. The hygroscopic threshold is equal to the tetrahydrate moisture content $X_{\text{tetra}} = 0.2$.

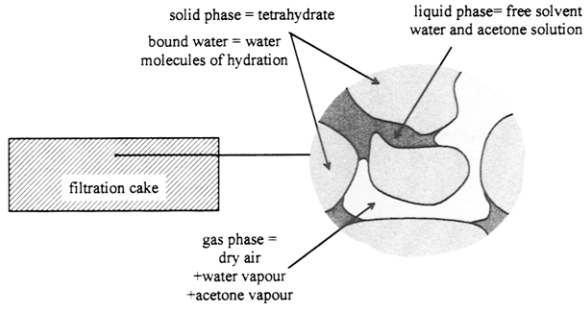

Figure 3. Zoom on the filtration cake.

Liquid phase

It is a mixture of water and acetone containing a very small amount of dissolved solid phase.

Gas phase

It is an ideal mixture of dry air, water vapour and acetone vapour. Each component is considered as a perfect gas. The gas phase fills vacant spaces of the liquid phase.

At the beginning of drying, the material is a filtration cake of the pharmaceutical product. The wetting solvent is a solution of water and acetone for which the mass fraction of acetone is 0.65. The diameter of the samples is 50 mm and their thickness is 15 mm. During drying, the multicomponent solvent of water and acetone is removed and tetrahydrate is dehydrated into monohydrate.

The physics involved during vacuum contact drying of a classical porous medium have been discussed by numerous authors [8, 9, 10]. Two main differences are encountered here:

- the wetting solvent is a multicomponent one,
- the wetted medium is an hydrate.

From experimental measurements of internal temperatures, it is shown that these particularities induce a singular thermal behaviour. The analysis of this behaviour provides an accurate representation of the involved physical phenomena.

2. EXPERIMENTAL SET-UP

The experimental set-up is a vacuum contact drying system. The material is put in a polycarbonate vessel where pressure is reduced to a constant value by a vacuum pump (*figure 4*).

Energy is supplied by a heat resistor constituting the sample holder bottom. The heat resistor temperature remains constant during the whole drying operation. The lateral sides of the material are insulated from heat and mass transfer, hence drying is monodimensional following the z axis (*figure 5*).

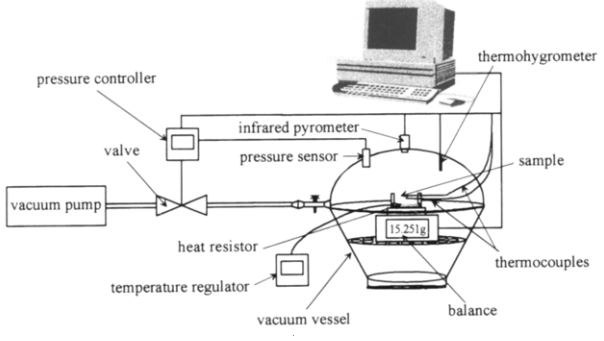

Figure 4. Vacuum contact drying experimental set-up.

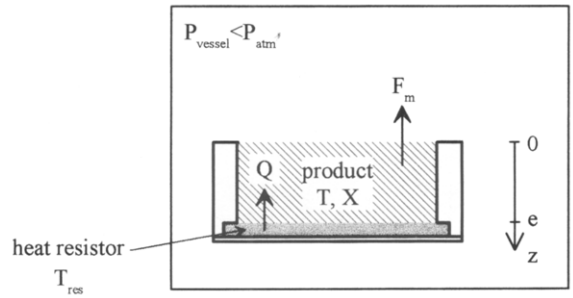

Figure 5. Sample holder used for vacuum contact drying.

The experimental set-up has the following instrumentation: a balance which enables the determination of the moisture content evolution, three thermocouples to measure the internal temperatures, an infrared pyrometer to indicate the surface temperature, a thermohygrometer to measure the temperature and the relative humidity evolution in the vessel and two pressure sensors to respectively regulate and control the pressure.

3. DRYING KINETICS

We can differentiate two regimes in vacuum drying [11].

- Evaporation drying: the temperature is lower than the solvent boiling point at the working pressure.

- Vaporisation drying: the temperature is equal to the solvent boiling point for the working pressure; moisture vaporises massively within the product, accelerating mass transport on account of pressure gradients between the product and the external atmosphere; vacuum allows vaporisation at low temperatures.

For this study, a working pressure P_{vessel} equal to 15 mbar is selected corresponding to the pressure of the industrial process. To illustrate our analysis, two representative examples of heat resistor temperatures T_{res} are considered: 50 °C (industrial contact temperature) and 70 °C (*figure 6*). It will be shown below that in each case, the situation corresponds to vaporisation drying.

As the equilibrium relative humidity of the atmosphere of the vessel is equal to 0 % (the vacuum pump removes vapours coming from the material), the anhydrous form is formed if drying is not interrupted. Consequently, the drying process is terminated when the monohydrate form is obtained. From the kinetics given on *figure 6*, it is deduced that future drying experiments have to be stopped after about 5,5 h for $T_{\text{res}} = 70$ °C and after about 8 h for $T_{\text{res}} = 50$ °C. Indeed, after this drying time, the average moisture content is equal to the monohydrate moisture content X_{mono} (0.05).

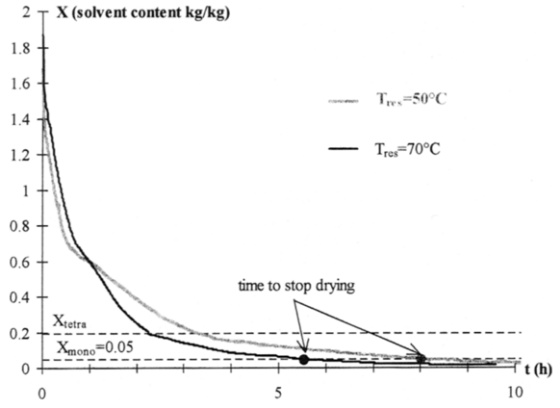

Figure 6. Average solvent content kinetics of the pharmaceutical drug in vacuum contact drying for a 15 mbar pressure and two heat resistor temperatures, 50 °C and 70 °C. At $t = 0$, T is about 20 °C and X is about 1.8.

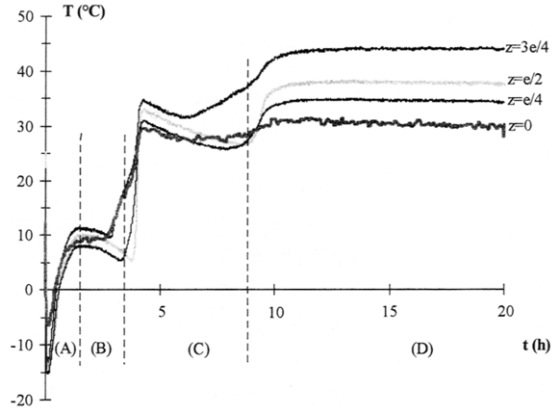

Figure 7. Evolutions of the internal and surface temperatures of the pharmaceutical drug during vacuum contact drying for $P_{\text{vessel}} = 15$ mbar (vessel pressure) and $T_{\text{res}} = 50$ °C (heat resistor temperature); e is the sample width (*figure 5*).

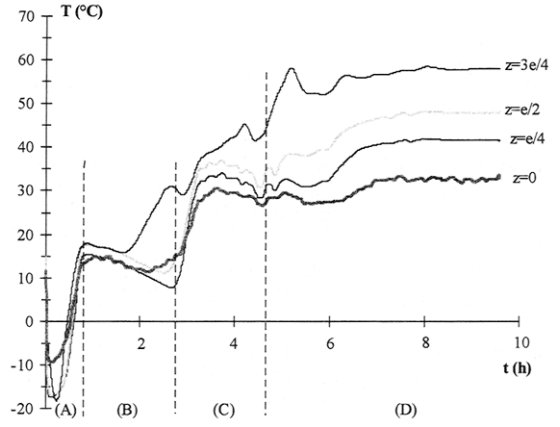

Figure 8. Evolutions of the internal and surface temperatures of the pharmaceutical drug during vacuum contact drying for $P_{\text{vessel}} = 15$ mbar and $T_{\text{res}} = 70$ °C; e is the sample width (*figure 5*).

4. THERMAL BEHAVIOUR ANALYSIS

The study is carried out with 3 thermocouples for the internal temperatures and with the infrared pyrometer for the surface temperature.

For the two heat resistor temperature conditions, all temperature kinetics have the same shape (*figures 7* and *8*).

The difference lies in the final temperature value which depends on the situation of the thermocouple. It corresponds to the establishment of a conductive profile between the heat resistor temperature and the vessel atmosphere temperature [9, 12]. These curves can be divided in four parts (*figures 7* and *8*).

Stage (A)

The temperature sharply decreases until negative values (maximum about −15 °C) then rapidly goes up again to about 10–15 °C.

Stage (B)

A plateau appears. The temperature stabilises to 10–15 °C. It corresponds to the water boiling point at the working pressure.

Stage (C)

After a sharp increase, a new plateau appears for a value of 30 °C. The temperature of the different slices do not increase simultaneously. The closer the slice is to the heat resistor, the earlier the temperature rises.

Stage (D)

The temperature increases again to reach its final value. A conductive profile establishes itself between the sample bottom in contact with the heat resistor ($T = T_{\text{res}}$) and the free surface ($T = T_{\text{vessel}}$).

In order to emphasise the singular thermal kinetics of the product, the same experiment is carried out on a classical hygroscopic porous medium. This medium is constituted of a solid lattice, bound water (adsorbed water on the solid surface), free water (liquid phase) and water vapour (gas phase). As it is illustrated in *figure 9*, the three classical stages usually described are observed [11].

Stage (A')

Vacuum is created in the vessel. The temperature decreases to the boiling point of water corresponding to the working pressure.

Stage (B')

Free water vaporises within the material. Two phases (liquid and vapour) are present in the product.

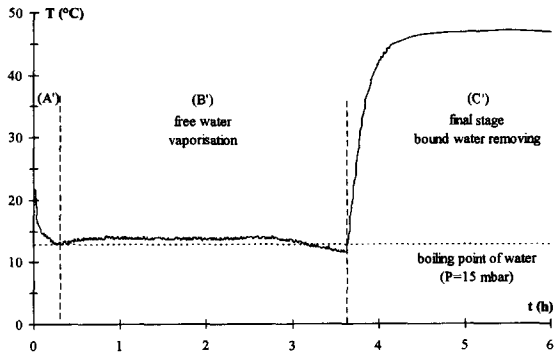

Figure 9. Temperature evolution of a classical porous medium impregnated of water during vacuum contact drying for $P_{vessel} = 15$ mbar and $T_{res} = 50$ °C.

The whole supplied energy is consumed by moisture vaporisation. Temperature is equal to the boiling point of water and remains constant as long as free water is present in the product.

Stage (C')

Final stage. Simultaneously, the bound water is removed and the product temperature is increasing. A conductive profile of temperature settles within the material.

By comparing our pharmaceutical drug and a classical porous medium behaviours, only stages (B) and (D) (*figures 7* and *8*) can be explained. They correspond respectively to stages (B') and (C') (*figure 9*). So as to interpret stages (A) and (C), the two particularities of the pharmaceutical product under investigation are invoked: the wetting solvent is a multicomponent (water and acetone solution) and two hydration states exist. To illustrate our analysis, only the results for the 50 °C heat resistor temperature are presented in this paper. For T_{res} equal to 70 °C, results are similar and confirm our conclusions.

4.1. Multicomponent solvent influence

With respect to drying of products impregnated with multicomponent solvent, selectivity is the main problem studied up to now [13, 14]. Selectivity means preferential removing of one component of the solvent. The total selectivity in the most general case of drying is controlled by the thermodynamic equilibrium as well as by mass transfer.

If drying is non selective, the three classical phases of vaporisation drying (stages (A'), (B') and (C') on *figure 9*) are described. Only the value of the boiling point is different. It is imposed by the solution composition.

If drying is selective, the solution composition continuously varies. Consequently, the free solvent vaporisation phase (phase (B') on *figure 9*) does not impose a constant temperature.

So as to evaluate selectivity, the evolution of the solution boiling point following composition has to be known for the working pressure.

4.1.1. Vapour-liquid equilibrium of the water-acetone binary solution under reduced pressure

The vapour–liquid equilibrium diagram of the water-acetone binary solution for the working pressure of 15 mbar is calculated from the NRTL model [15] by using Prophy Plus code. This diagram is given in *figure 10*.

Acetone is the more volatile of the two components: for nearly all liquid phase compositions, the equilibrium vapour phase is richer in acetone. For instance, for a liquid phase mass fraction of acetone equal to 0.05, the equilibrium vapour phase mass fraction of acetone is about equal to 0.9 (points × in *figure 10*). For a large range of liquid phase composition, solution boiling points are well below 0 °C. The boiling point becomes positive (in °C) when acetone proportion is very low. Temperature values of the pharmaceutical product during the vacuum drying phase (A) (*figures 7* and *8*) can be explained by acetone presence in the solvent. In order to confirm this assertion, drying of a classical porous medium impregnated by a water-acetone solution is performed.

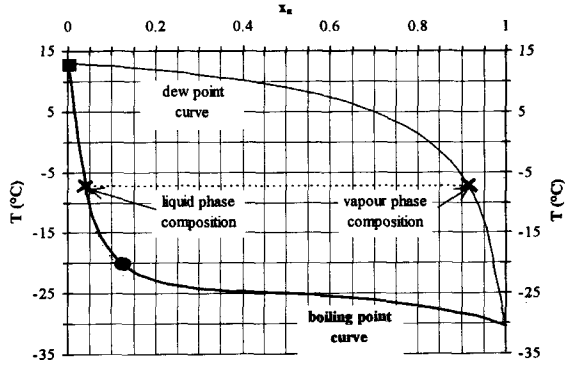

Figure 10. Liquid–vapour thermodynamic equilibrium diagram of water–acetone binary for a 15 mbar pressure; x_a is the mass fraction of acetone in the binary liquid solution.

4.1.2. Drying of a classical porous medium impregnated by a water-acetone solution

Figure 11 compares drying of a classical porous medium wetted with pure water and wetted with a water-acetone solution corresponding to the impregnating solvent of the pharmaceutical product (mass fraction of acetone $x_a = 0.65$).

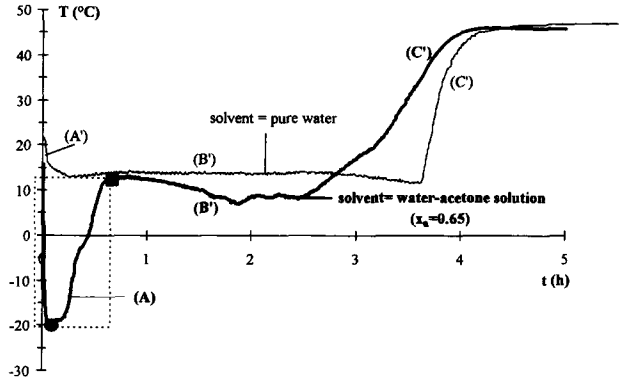

Figure 11. Comparison of vacuum contact drying of a classical porous medium impregnated of water and of a water–acetone solution for $P_{vessel} = 15$ mbar and $T_{res} = 50$ °C.

For the classical porous medium impregnated of the water-acetone solution (*figure 11*, bold line), the phase (A) (*figures 7* and *8*) appears. Firstly, the temperature decreases to the boiling point imposed by the solution composition (point • in *figures 10* and *11*). Then acetone is removed selectively. Consequently, the solvent becomes depleted in acetone. As is indicated on *figure 10*, the boiling point increases with the solvent water proportion until it reaches pure water boiling point (point ■ in *figures 10* and *11*). From this time, the temperature evolution becomes classical as only pure water remains (phases (B′) and (C′)).

4.1.3. Conclusion

Multicomponent solvent presence allows to explain the phase (A) (*figures 7* and *8*) of the pharmaceutical product vacuum drying. However the appearance of a new plateau (phase (C)) remains unanswered. To complete the thermal behaviour analysis, another characteristic of the problem is studied: the existence of two hydration states.

4.2. Hydration states influence

During this second temperature plateau (phase (C)), the average moisture content of the product evolves between the values of 0.2 (tetrahydrate) and 0.05 (monohydrate). Moreover, as the vaporisation phase (phases (A) and (B) on *figures 7* and *8*) finishes, the whole free water vanishes. Consequently, the second plateau seems to correspond to the presence of tetrahydrate and monohydrate mixtures.

To confirm this assumption, the water content (acetone vanished) of a slice ($z = e/2$) within the material (*figure 12*), for which the temperature evolution is followed, is determined for different drying times around the plateau (points a, b and c in *figure 13*). To complete

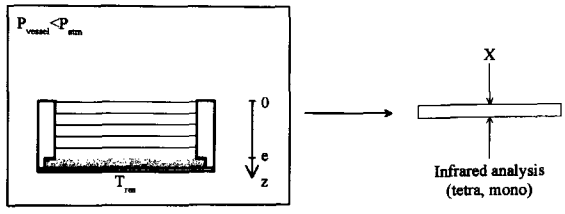

Figure 12. Water content measurement and infrared analysis of the slices.

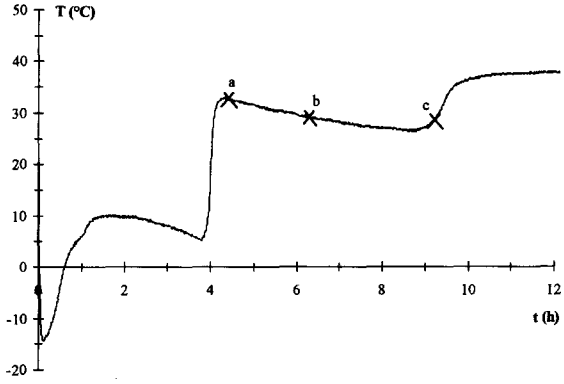

Figure 13. Temperature evolution of the slice located at $z = e/2$ during vacuum contact drying for $P_{vessel} = 15$ mbar and $T_{res} = 50$ °C; study of the second plateau.

the results, an infrared analysis allowing us to distinguish tetrahydrate and monohydrate is also performed on the slices.

Results allow us to conclude that the second temperature plateau (phase (C) on *figures 7* and *8*) corresponds to the dehydration of tetrahydrate into monohydrate. At the beginning of the plateau (point a in *figure 13*), the average water content of the slice which is equal to that of the tetrahydrate (0.2) ensures that only tetrahydrate exists. During the plateau (point b on *figure 13*), the average water content of the slice is intermediate between tetrahydrate and monohydrate. Infrared analysis confirms logically that the slice consists in mixtures of tetrahydrate and monohydrate. At the end of the plateau (point c in *figure 13*), the average water content of the slice (0.05) indicates that only monohydrate remains.

Tetrahydrate and monohydrate constitute two distinct solid phases of our pharmaceutical drug. The whole energy supplied by the heat resistor is consumed by the change of hydration state. As long as the two hydrates (tetrahydrate and monohydrate) coexist, the temperature is constant. Then, when the tetrahydrate has completely vanished, the hydration state change is terminated and the temperature increases. This plateau is similar to the plateau imposed by the vaporisation of free water (liquid to gas phase change).

To support this result, the *figure 14* taken from Badens et al. [16] shows that the appearance of a plateau caused by the change of hydration state has also been observed for gypsum (calcium sulphate dihydrate). The first plateau corresponds to the dehydration of the gypsum into the hemihydrate and the second one to the dehydration of the hemihydrate into the anhydrous form.

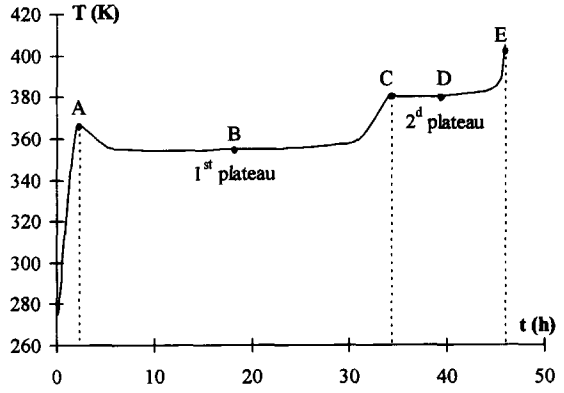

Figure 14. Thermal behaviour of gypsum (calcium sulphate dihydrate) during dehydration for a water vapour pressure of 9 mbar (*figure 7* from Badens et al. [16]).

4.3. Summary

To sum-up, the product temperature evolution analysis allows us to distinguish the different vacuum drying stages (*figure 15*).

Stage (A)

Free solvent is vaporised with a selective removing of acetone. The temperature increase is caused by the variation of the solvent composition.

Stage (B)

Temperature is constant. Acetone has vanished; the whole energy supplied by the heat resistor is consumed by the free water vaporisation.

Stage (C)

Free water has been entirely removed. The temperature of the product increases until a new plateau appears caused by the dehydration of tetrahydrate into monohydrate. Indeed, the whole energy provided by the heat resistor is consumed by the change of hydration state (tetrahydrate to monohydrate).

Stage (D)

Final stage. When the change of hydration state is finished, the temperature of the product increases again.

5. CONCLUSION

This thermal analysis of vacuum contact drying for a complex pharmaceutical product gives a correct physical description of the drying progress in two cases frequently met in pharmaceutical and fine chemistry industries: drying of a product wetted with a multicomponent solvent and drying of hydrates.

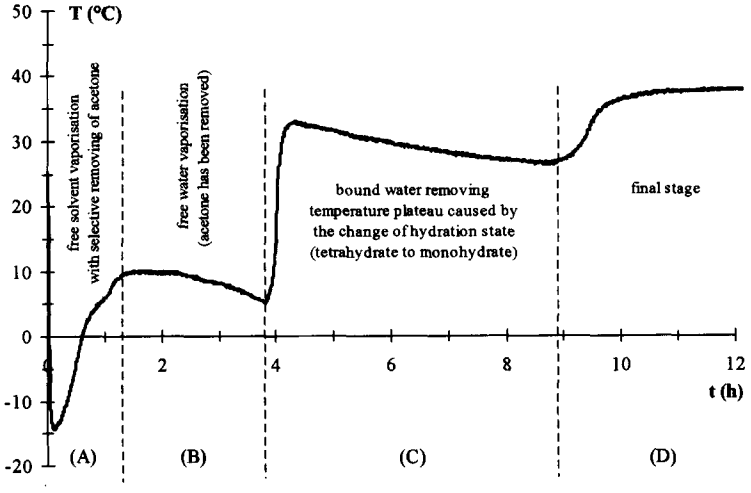

Figure 15. Different vacuum drying stages for the pharmaceutical product under investigation (P_{vessel} = 15 mbar and T_{res} = 50 °C).

Vacuum drying of a material impregnated with a water-acetone binary solvent is selective. Acetone is removed preferentially. In this case, the vaporisation stage of the operation does not result in a temperature plateau. Measuring temperature variations enables to determine the local evolution of the solvent composition within the material.

A change of hydration state during vacuum drying causes a temperature plateau. The whole energy provided by the heat resistor is consumed by the dehydration.

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