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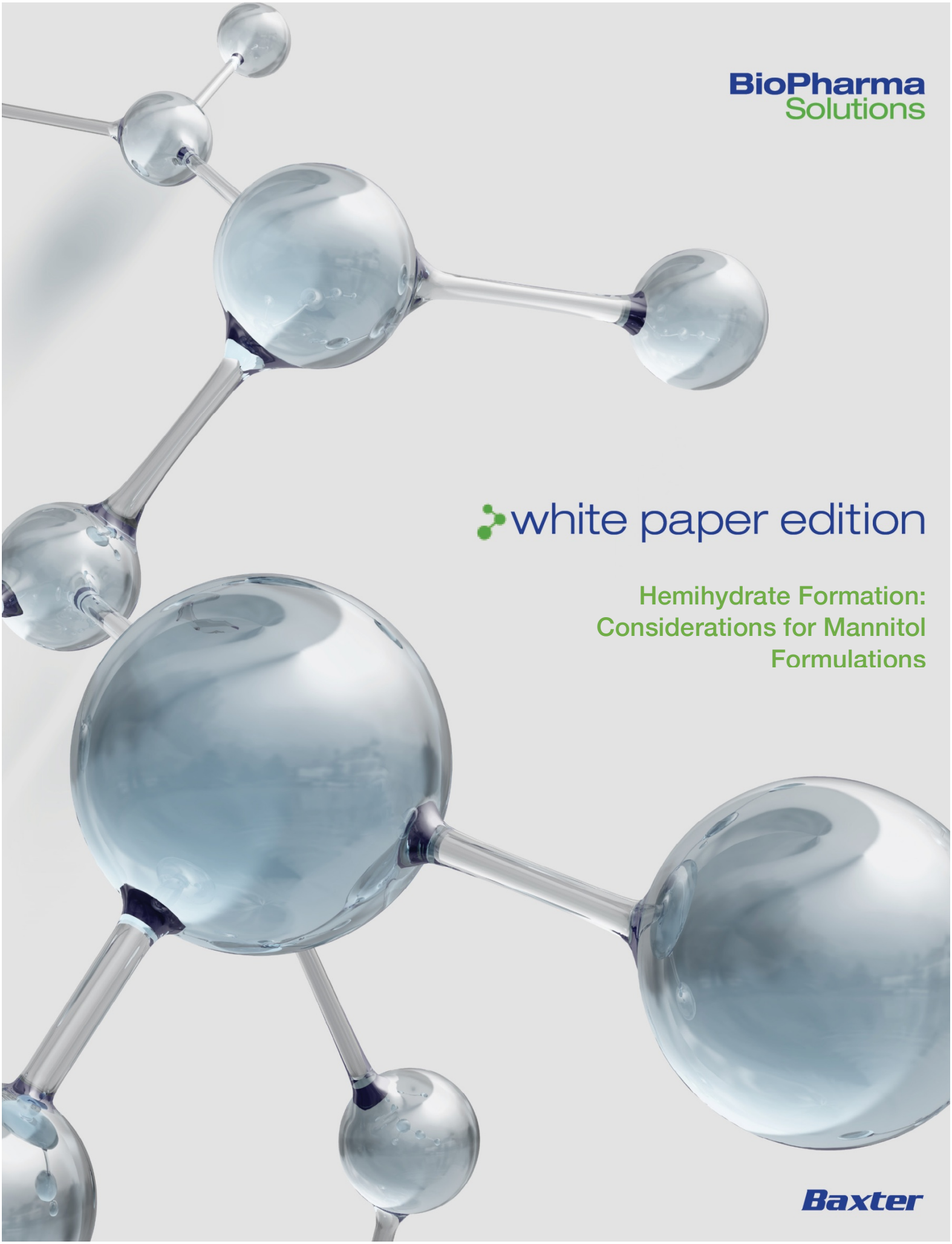
Hemihydrate Formation: Considerations for Mannitol Formulations



Baxter

Hemihydrate Formation: Considerations for Mannitol Formulations

Introduction

Mannitol is a versatile excipient used in freeze-dried injectables in the pharmaceutical industry due to its high eutectic melting point (~ -1.5°C) when it is crystallized. This allows for aggressive primary drying thereby considerably reducing the freeze-dry cycle time. The resultant freeze-dried solids are pharmaceutically elegant in appearance with cake uniformity. Reconstitution of the dried solids is generally rapid and complete. Due to the advantages that a crystalline mannitol presents, it is very common to include an annealing step, prior to primary drying, to ensure complete crystallization of mannitol.

The crystallization of mannitol during freezing relies on several factors: its concentration, other formulation components, and the freezing conditions. All these factors determine if mannitol stays amorphous, crystalline, or partially crystalline. If it remains amorphous or partially crystalline, mannitol has a propensity to crystallize during drug product stability, which might adversely affect the drug product stability due to changes to residual moisture redistribution.

In addition to the three stable forms of crystalline mannitol, namely, alpha, beta, and delta forms, mannitol can also crystallize into a metastable form called the hemihydrate.[1] There are several consequences to the hemihydrate mannitol formation: it can give rise to vial to vial variability in its formation and the residual moisture within a batch, variability in the primary drying duration, and the redistribution of the residual moisture after its release during storage.

For these reasons, it is important that the mannitol hemihydrate formation is inhibited during the freezing step, by adding sodium chloride or other additives to the formulation.[2] Hawe and Frieß found that annealing mannitol-containing formulations at less than -30°C promoted the hemihydrate formation and annealing at greater than -27°C inhibited its formation.[3] The hemihydrate can also be removed during secondary drying at a shelf temperature of ≥40°C.[4]

Mannitol Hemihydrate: A Case Study

An atypical water vapor dynamics during secondary drying of a commercial formulation containing mannitol (8% w/v), trehalose (2% w/v), sodium chloride (225 mM, 1.3% w/v), in addition to the active pharmaceutical ingredient, prompted the author of this report to investigate the crystallization behavior.[5] Typically, as the shelf temperature is elevated during secondary drying, the unfrozen water in the formulation gets released at once giving rise to a single peak in the Pirani response. But with this formulation, three “bursts’ of water vapor release was observed as the shelf temperature was ramped up to 40°C, 45°C, and 50°C and subsequently held for a few hours at each temperature (Figure 1).

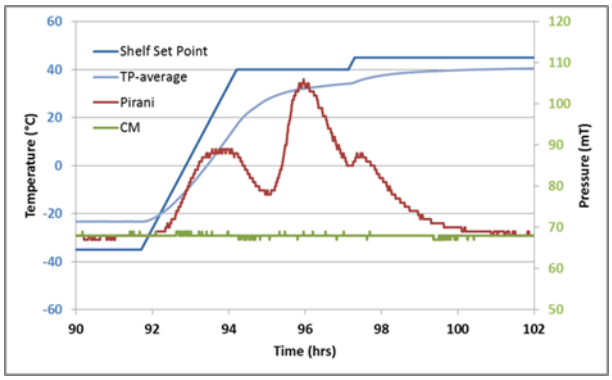


Figure 1. *Pirani Response During Secondary Drying of the Formulation.*

The formulation was freeze-dried using the recipe provided in Table I. After the initial freezing step, the formulation was first annealed at -23°C for mannitol crystallization and at -33°C to facilitate NaCl crystallization. Primary drying was conducted at -35°C. The first burst of water vapor release occurred, after primary drying, during the ramp to 40°C. The second burst occurred when the product was held for three hours at 40°C, and the third water vapor release occurred when the shelf was held at 45°C.

Table I. Freeze-drying Protocol

Step	Temp (°C)	Pressure (mT)	Hold Time (min)
Loading	20	Ambient	10
Freezing	-5	Ambient	30
	-40	Ambient	60
	-23	Ambient	180
	-50	Ambient	90
	-33	Ambient	240
	-50	Ambient	60
1° drying	-50	68	90
	-35	68	*
2° drying	40	68	180
	45	68	180
	50	68	180

*until the Pirani gauge equilibrated with the capacitance manometer set point.

Table II describes characteristic peaks observed in the X-ray Powder Diffraction (XRPD) diffractograms of different mannitol polymorphs. The δ polymorph has a crystallinity pattern with a peak at 9.7 and 20.4 °2θ (Table II). Mannitol hemihydrate, on the other hand, possesses a unique peak at 17.9 ° 2θ, which is not present in the other polymorphs (Table II). At higher temperatures, the more stable α- and β-forms are obtained.

Table II. XRPD Peaks Attributed to Different Polymorphs of Mannitol

Modification	Main Peaks [° 2θ]	Intensity (%)
α-mannitol	9.4	10
	13.6	20
	17.2	45
	18.7	100
β-mannitol	10.5	18
	14.6	65
	16.8	85
	18.8	100
	23.4	90
δ-mannitol	9.7	100
	20.4	50
Mannitol hydrate	9.6	80
	17.9	100

Thief samples were removed during freeze-drying of the formulation at the end of primary drying and subsequently when the shelf temperature was ramped to 40°C and during secondary drying. The samples were analyzed by XRPD to determine the crystallinity of

mannitol (see Figure 2 at the end of the document). The diffractograms indicated that at the end of primary drying, mannitol was present predominantly in the hemihydrate form (as indicated by the peak at 17.9 °2θ (labeled by a green star). As the shelf temperature was raised, the hemihydrate slowly converted to the more stable δ-form. After being held for ~80 minutes at 45°C, the hemihydrate fully converted in to the δ-form.

The thief samples that were removed throughout the cycle were analyzed by Differential Scanning Calorimetry (DSC) and Thermo Gravimetric Analysis (TGA) for thermal signature changes. DSC identified three thermal events when the samples were heated from 35°C to 180°C: an endothermic event at 63°C corresponding to the dehydration of the hemihydrate, an exothermic event at 103°C representing the crystallization of other polymorphs, a melting event at 132°C indicating melting of all anhydrous forms of mannitol. All three thermal events correlated well with those published by Nunes *et al*.[6]

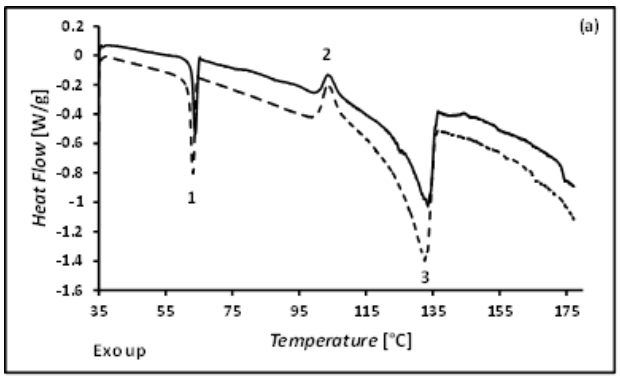


Figure 3. *DSC Total Heat Flow Thermogram of Thief Sample Removed at the End of Primary Drying.*

The DSC thermogram of a sample at the end of secondary drying showed the absence of peaks 1 and 2 observed in Figure 3 but contained only a melting event at 147°C, indicating the absence of the hemihydrate in the sample (Figure 4).

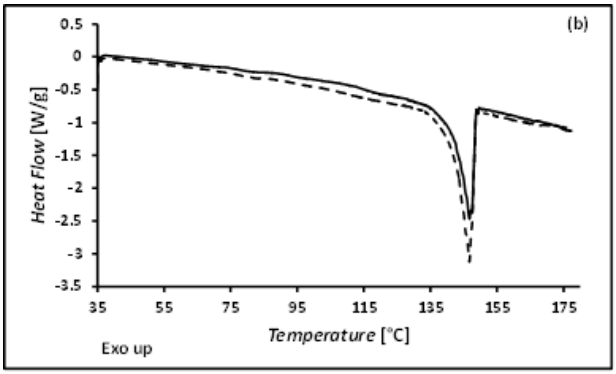


Figure 4. *Total Heat Flow Thermogram of a Sample After Secondary Drying.*

TGA analysis of the end of primary drying sample and end of cycle sample indicated a loss of 4.1% residual moisture in the sample removed at the end of primary drying, suggesting near stoichiometric water content (~90%) in the freeze-dried solid in the form of the hemihydrate (Figure 5).

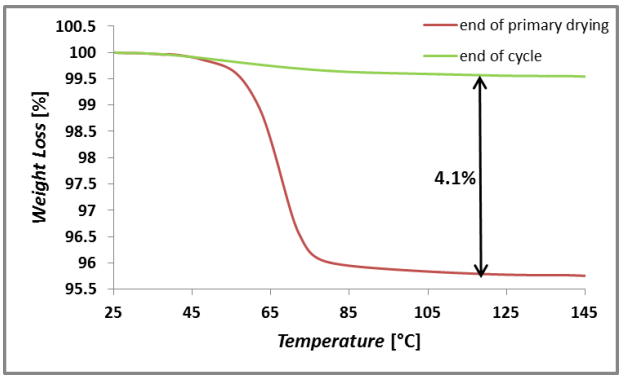


Figure 5. *TGA Thermograms Indicating Weight Loss Due to Dehydration of the Hemihydrate.*

Influence of Excipients on the Crystallization of Mannitol

The impact of other excipients on the crystallization mannitol hemihydrate was investigated since it is a routine practice to include a co-excipient in mannitol formulations. Other excipients considered for this study were NaCl at different concentrations and sucrose,

and trehalose both in the presence and absence of NaCl. The findings of this investigation suggested that sodium chloride promoted the mannitol hemihydrate formation and the hydrate formation depended on the concentration of co-excipient. When present at 225 mM, NaCl induced the hemihydrate and δ-mannitol formation in 1:1 ratio. At concentrations of NaCl closer to most parenteral drug formulations (150 mM and 75 mM), the ratio was much less, favoring the δ-form (Figure 6).[5]

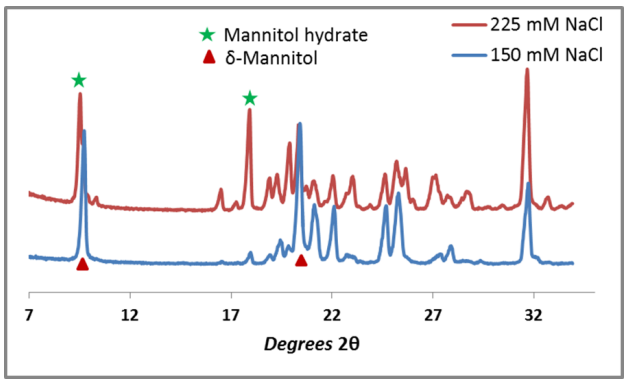


Figure 6. *Diffractograms of Mannitol at Different Concentrations of NaCl.*

When trehalose in the original formulation was replaced by sucrose, in addition to the hemihydrate, δ-mannitol was also present in the sample that was sampled at the end of primary drying, indicating that trehalose may promote the metastable form to a greater degree than sucrose (Figure 7).

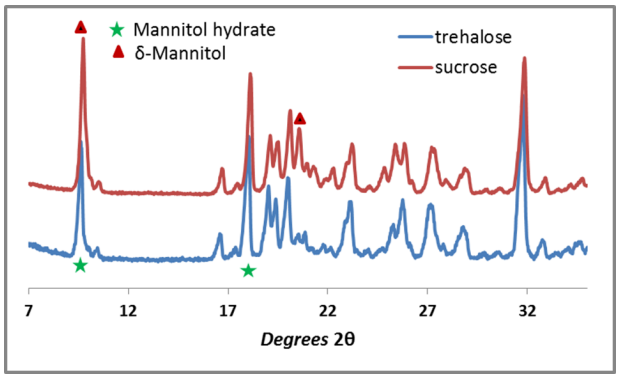


Figure 7. *Comparison of Diffractograms of Trehalose and Sucrose Formulations in the Presence of NaCl.*

Both sucrose and trehalose, when investigated independently in the absence of NaCl, were found to facilitate the δ-mannitol polymorph with the hemihydrate present as a minor component (data not shown).[5]

When mannitol (8% w/v) was freeze-dried alone, in the absence of co-excipients, no hemihydrate was detected when annealed at -25°C and a minor amount of the hydrate was present when annealed at -35°C (data not shown).

Practical Considerations

It is common practice in the pharmaceutical industry to conduct secondary drying at a shelf temperature of 30°C or even lower. The case study provided in this report illustrates that, if mannitol hemihydrate is formed during freezing, shelf temperatures less than 40°C may not be sufficient to remove the metastable form completely. The study also emphasizes the critical role played by the product temperature. Dehydration of mannitol occurs only when the product temperature exceeds 30 °C for the given formulation and under the process conditions employed.

References

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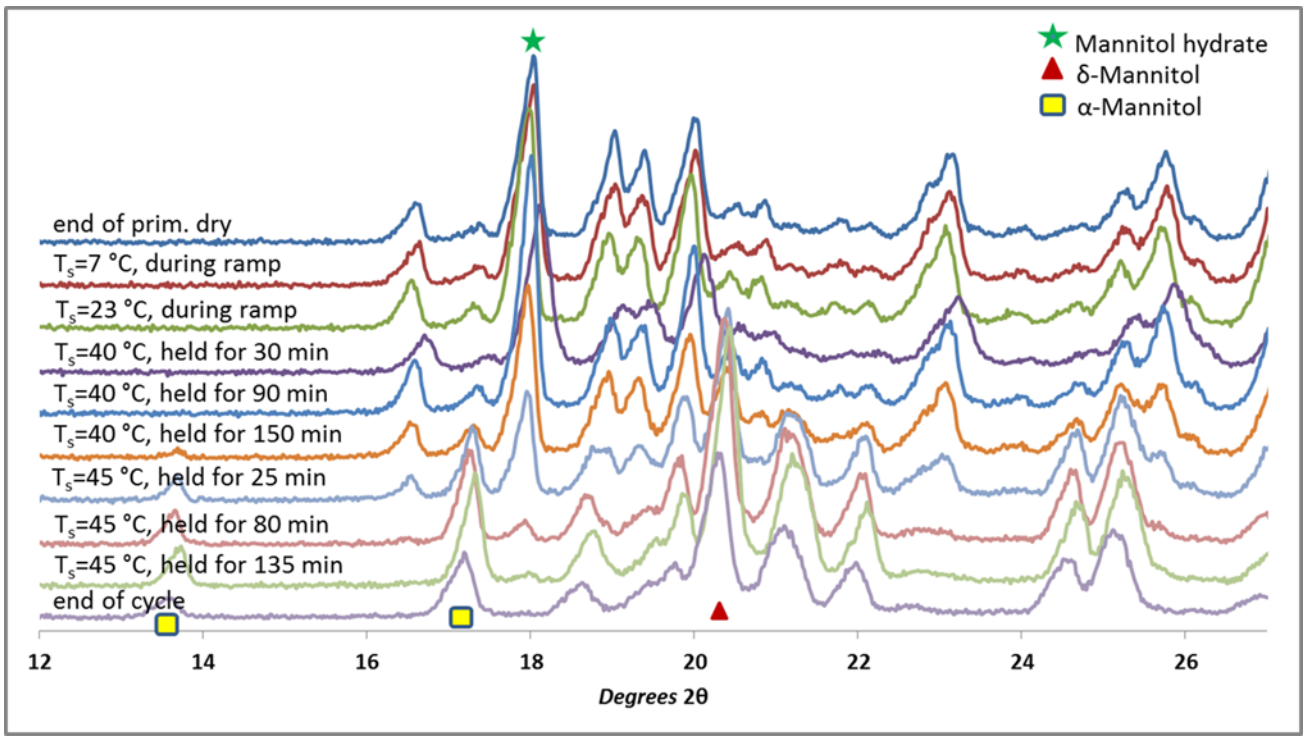

Figure 2. *X-ray Diffractograms of Thieved Samples During Drying. Samples were Removed at Various Stages of the Ramp to and During Secondary Drying as Labelled in the Figure.*

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