

An Examination of the Moisture Sorption Characteristics of Commercial Magnesium Stearate

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Submitted: August 22, 2001; Accepted: November 26, 2001; Published: December 3, 2001

ABSTRACT The objective of this study was to characterize the moisture sorption of magnesium stearate and the morphological changes, if any, resulting from moisture sorption. Six samples of commercial magnesium stearate USP were examined. Moisture sorption isotherms were obtained at 25°C and 5% to 98% relative humidity (RH) using a moisture balance. Changes in crystal form resulting from moisture sorption were determined by x-ray diffraction. There were differences in the shape of the isotherm, reversibility of moisture uptake, and shape of the hysteresis loop in the isotherms of crystalline and amorphous magnesium stearates. The isotherm of crystalline magnesium stearate was almost parallel to the pressure axis until and RH of ~ 80%. The isotherm of the amorphous sample was characterized by continuous uptake of water over the entire range of RH. Exposure of amorphous magnesium stearate to RH greater than 70% resulted in the formation of the trihydrate. The trihydrate was converted into the anhydrous form when heated to a temperature of 100°C to 105°C. The trihydrate could be generated by exposing the anhydrate to RH higher than 70%.

KEYWORDS: Moisture sorption, magnesium stearate hydrates, crystalline, amorphous magnesium stearate.

INTRODUCTION

The interaction of pharmaceutical solids with water can affect their chemical stability as well as their physical and mechanical properties. The importance of moisture on the solid-state stability of drugs is extensively documented [1,2]. Review of pharmaceutical literature to date reveals limited information on the interaction of poorly soluble and hydrophobic materials with water. Many drugs and excipients that are poorly soluble and, in some instances, hydrophobic can form hydrates that differ from the parent compound in their physical and mechanical properties. Magnesium stearate, although almost completely insoluble in water, forms hydrates; the crystal structure of magnesium stearate and its

moisture content have received attention recently as potential contributors to lubrication efficiency [3-7]. Four hydration states of magnesium stearate - the mono-, di-, and trihydrates and an anhydrous form - have been identified [3].

The objective of the study was to characterize the moisture sorption of commercial magnesium stearate. The specific aims were (1) to characterize moisture sorption and desorption isotherms at 25°C, (2) to determine morphological changes, if any, resulting from sorption of water, (3) to determine whether the morphological changes are reversible, and (4) to determine whether moisture sorption characteristics can be related to morphological changes.

MATERIALS AND METHODS

Materials

Six samples of commercial magnesium stearate from 3 vendors- Mallinckrodt (Hazelwood, MO), Witco (Petrolia, PA), and Faci (Carasco, Italy) corporations- were examined. The batches are referred to as M1, M2, and M3 (Mallinckrodt); W1 and W2 (Witco); and F (Faci). The samples were stored in screw-capped bottles at 25°C and 25% to 30% relative humidity (RH).

Physical Characterization of Magnesium Stearate

Moisture content: The moisture content of the samples was measured by Karl Fisher titration with coulometric endpoint determination (Accumet®150 titration controller made by Fisher Scientific (Pittsburgh, PA) using Hydranal® coulomat reagent).

X-ray powder diffraction: The x-ray powder diffraction patterns were obtained on the Siemens Diffraktometer-Kristalloflex (Nurnberg, Germany) with Cu K α_1 radiation of .15406 nm. Powder was packed into the back cavity of a square aluminum holder and its surface leveled with a glass slide to obtain reproducible packing. Samples were

continuously scanned between 4°C and 40°C at a scan rate of 10°C per minute. Measurements were made under ambient conditions. No attempt was made to quantify the crystalline and amorphous content of the samples.

Moisture sorption and desorption isotherms:

Moisture sorption and desorption isotherms were obtained by measurement of moisture uptake using a gravimetric moisture balance (VTI Instruments Inc, Hialeah, FL). Isotherms were obtained at 25°C and 5% to 98% RH in increments of 2% RH, following an initial drying period.

Moisture Exposure Studies

Samples of magnesium stearate were exposed to 11.2%, 54%, 75.5%, 84.3%, or 93.7% RH at 25°C. The relative humidity conditions were produced by saturated aqueous salt solutions [8]. By using dried silica and evacuating the glass jars, 0% RH was obtained; pure water was used to obtain 100% RH. Samples were equilibrated for 60 days in controlled-humidity chambers and subsequently analyzed for their powder diffraction patterns.

Dehydration and Rehydration Studies

Samples of magnesium stearate were dehydrated in a hot air oven (Baxter® DN63 Constant Temperature Oven, Deerfield, IL) at 40°C, 60°C, 80°C, 90°C, 100°C, or 105°C for 3 hours. Additionally, samples were exposed to 40°C, 60°C, or 80°C for 24 hours and the x-ray diffraction (XRD) patterns of the resulting material were compared with that of the control. The material dehydrated at 105°C was allowed to rehydrate at 100% RH for 7 days. The resulting material was subjected to another sequence of dehydration at 105°C followed by rehydration at 100% RH. The powder diffraction pattern of each of these samples was measured.

RESULTS AND DISCUSSION

Characterization of Magnesium Stearate

Moisture content: The moisture content of the samples was between 5.6% and 7%. Karl Fischer titrimetry cannot distinguish among the states of water in the material.

X-ray powder diffraction patterns of magnesium stearate: There was no difference in the XRD patterns

of magnesium stearate samples from the same vendor. Representative XRD patterns of a sample from each commercial source are shown in **Figure 1**. In general, the diffraction patterns do not have the sharp, intense peaks that are characteristic of inorganic compounds or highly symmetric organic crystals. This is reflective of low symmetry and large unit cells and can generally be problematic in qualitative x-ray powder diffraction [9].

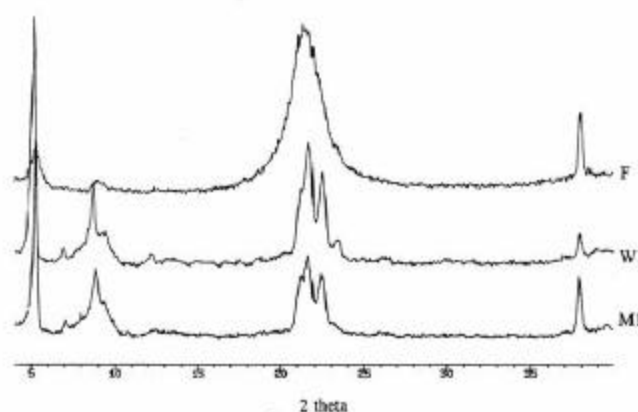


Figure 1. Representative x-ray powder diffraction patterns of magnesium stearate from the three sources - Mallinckrodt (M), Witco (W), and Faci (F).

The diffraction pattern of the sample from Faci indicated that it had considerably more amorphous content, as indicated by the broad, diffuse peaks (**Figure 1**). None of the patterns matched the standard pattern in the Powder Diffraction File. This is not unusual because the commercial material has much lower purity than the sample used to generate the standard diffraction pattern. The positions of the major peaks were within the 2 theta range of 0.5; there were variations in the relative intensities of the peaks in samples from a given vendor as well as from among the 3 vendors.

The prominent peaks in the crystalline materials were at 5.3, 8.8, 21.3, 21.7, 22.5, and 37.8. There were relatively well-defined, sharp peaks at 2 theta of 5.3 and 37.9 and a triplet (composite of 3 peaks) at 21 to 22.5. The crystalline magnesium stearate sample was identified as the dihydrate by comparison with published patterns. The powder from Faci had a single broad peak extending over 20 to 25 and smaller peaks at 5.3 and 37.8 and was identified as the amorphous form by comparison with a published pattern [3].

The variation in intensity of the major peaks may reflect differences in the processing history of the material, such as temperature of precipitation, size reduction techniques, and differences in the impurity profiles of the raw materials used in synthesis. The molecular weight of magnesium stearate, $\text{Mg}(\text{C}_{18}\text{H}_{35}\text{O}_2)_2$, is 591.27. The water of crystallization in the di- and trihydrates theoretically represents 5.74% and 8.37%, respectively, of the weight of the material, assuming it is pure magnesium stearate. The total water content in all of the batches, as determined by Karl Fisher analysis, was less than 8%. The batches examined could, in theory, consist of the dihydrate or a mixture of hydrates, along with adsorbed water. The moisture content of the amorphous material may represent adsorbed water.

Effect of relative humidity on the XRD pattern of amorphous magnesium stearate: The powder diffraction patterns of amorphous magnesium stearate samples that were exposed to a range of RH conditions are shown in **Figure 2**. There was no change in the XRD pattern of the amorphous material stored at 0%, 11.3%, and 54.4% RH. The broad peak centered at 20.9 split up, and discrete peaks appeared at 21.6, 22.37, and 23.38 in the diffraction pattern of the sample stored at 74.2% RH. There was an increase in the intensity of these peaks in the diffraction patterns of samples stored at 84.3%, 93.7%, and 100% RH. The positions of the major peaks were similar to those in the standard pattern of magnesium stearate trihydrate in the powder diffraction files, although there was considerable variation in intensity (**Figure 2**). It was inferred that incorporation of water into the lattice resulted in a change from the amorphous to a crystalline form.

Moisture adsorption and desorption isotherms: The water adsorption isotherm relates the equilibrium amount of water sorbed on a solid and the water activity at constant temperature and pressure. The amount of water associated with a solid at a particular relative humidity and temperature depends on its chemical affinity for the solid and the number of available sites for interaction. The general shape of the isotherm, the amount of moisture sorbed at low relative pressures in comparison with the specific surface area of the sample, the reversibility of moisture uptake, the presence of a hysteresis loop, and the shape of the hysteresis loop provide information on the manner of interaction of the solid with water.

Given the hydrophobic nature of magnesium stearate (contact angle $>90^\circ$), a type III isotherm in the Brunauer classification, which is characteristic of weak, nonspecific interaction between adsorbate and solid, is expected. This is because the hydrocarbon chains that make up a considerable proportion of the molecule interact through dispersion forces only.

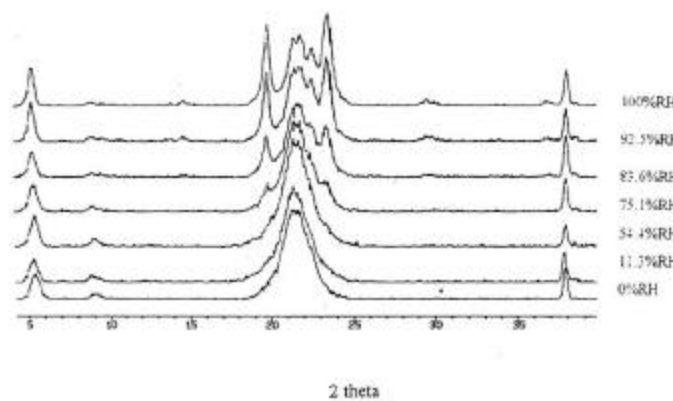


Figure 2. X-ray diffraction patterns of products formed by exposure of amorphous magnesium stearate to increasing relative humidity at 25°C.

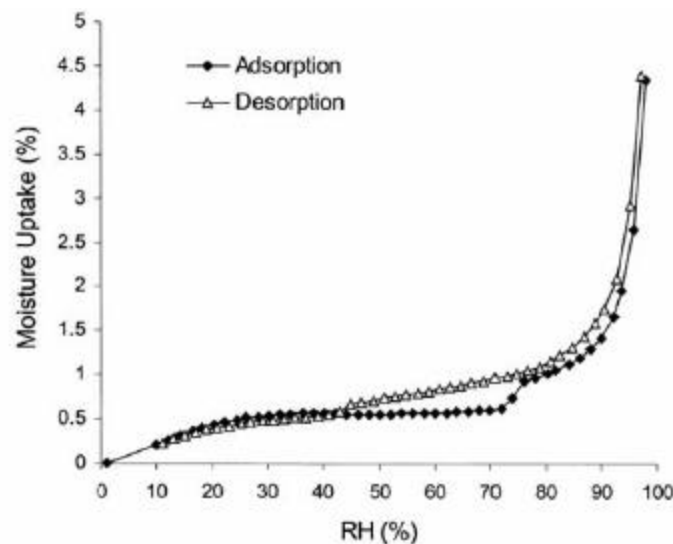


Figure 3. Moisture adsorption isotherm of crystalline magnesium stearate at 25°C.

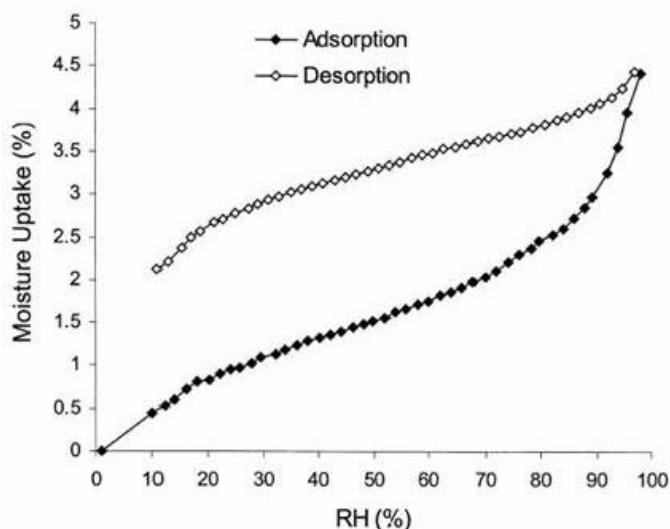


Figure 4. Moisture adsorption isotherm of amorphous magnesium stearate at 25°C.

The samples examined exhibited 1 of 2 types of isotherms: (1) an isotherm approaching type III or (2) a sigmoid isotherm. These are shown in **Figures 3** and **4**, respectively. Isotherms of magnesium stearate samples from Mallinckrodt (M) and Witco (W) belong in the former category, while that of the material from Faci (F) was sigmoidal - the latter is typical of predominantly amorphous material. The diffraction patterns of the Faci material indicated that it had considerably more amorphous content than the crystalline magnesium stearate samples, as evident from the broad, diffuse peaks in its diffraction pattern (**Figure 1**). The commercial samples in this study were broadly classified as crystalline and amorphous on the basis of their diffraction patterns. It must be pointed out that crystalline material may contain amorphous material in amounts too small to be reliably detected by x-ray powder diffraction.

Moisture adsorption isotherms of crystalline magnesium stearate: The water adsorption isotherms of crystalline magnesium stearates approached type III in behavior; the isotherm was almost parallel to the pressure axis until 80% RH was reached (**Figure 3**). On an expanded scale, however, a small inflection was observed at ~16% RH; such inflections are characteristic of type II isotherms. Similar isotherms have been described for polystyrene latexes and oxidized carbon blacks and have been termed pseudo type III [10].

Moisture was adsorbed to an extent of 0.54% and 0.6% of the weight of the solid at 30% and 70% RH, respectively. The moisture adsorbed at relative humidity greater than 80% accounted for much of the total uptake. The increased uptake at high relative pressures may represent adsorption onto pre-adsorbed sites. Given the hydrophobicity of the solid surface, a film of water is not expected to be formed. The small upward inflection at ~70% RH in the isotherms of crystalline magnesium stearate samples may be a result of moisture uptake by small amounts of amorphous material present in the sample. The adsorption-desorption isotherm of crystalline magnesium stearate showed a closed hysteresis loop. This has traditionally been associated with the presence of capillary-sized pores. The desorption branch is almost completely superimposed on the adsorption branch, indicating desorption of nearly all of the adsorbed water.

Moisture sorption isotherms of amorphous magnesium stearate: Water was sorbed continuously over the entire relative humidity range (**Figure 4**). The term "sorbed" here denotes uptake of water into the solid structure and not merely adsorption onto the surface. The isotherm showed a classical sigmoid shape. Larger amounts of water were sorbed at RH less than 40% and greater than 70% than were sorbed in the intermediate RH range.

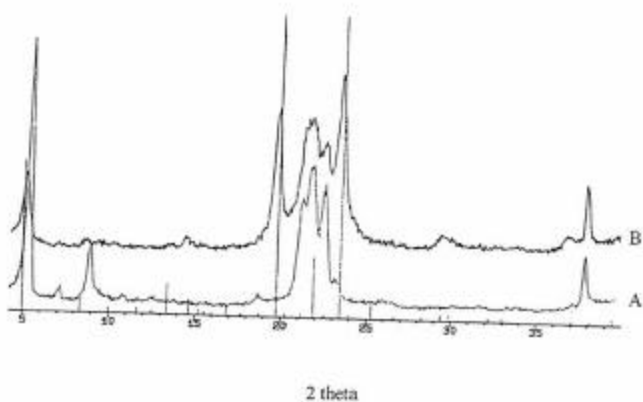
The isotherm of the amorphous material showed an open hysteresis loop (ie, a larger amount of water was associated with the solid at a given relative pressure on the desorption branch relative to the sorption branch). Open hysteresis loops have traditionally been associated with bottle-neck pores. In this case, the sorption of water was followed by the conversion of the amorphous into the crystalline form, as indicated by the change in diffraction pattern (**Figure 2**). The open hysteresis loop was attributed to the binding and physical fit of water in the lattice.

Given that magnesium stearate is practically insoluble in water, solubilization and recrystallization from solution is not a likely mechanism in the conversion of the amorphous magnesium stearate to the hydrate. The role of water here is likely to be that of a plasticizer rather than a solvent. Levine and Slade [11] have demonstrated that water, with a very low glass temperature, can act as a plasticizer, thereby lowering the glass temperature of amorphous polymers. Magnesium stearate has a low molecular weight (591.27) and can be expected to crystallize readily

because of an overall greater mobility relative to higher molecular weight polymers. Determination of the glass transition of magnesium stearate as a result of sorbed moisture using differential-scanning calorimetry was attempted; the low chemical purity of the commercial samples - which had variable quantities of the various organic acid components - gave rise to numerous overlapping transitions that could not be adequately resolved.

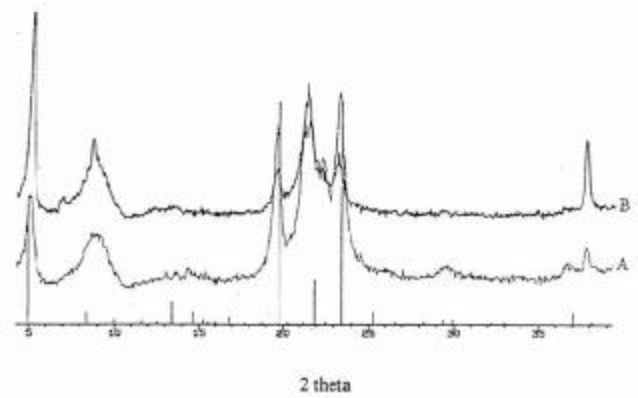
Exposure of magnesium stearate dihydrate to 100% RH resulted in the formation of the trihydrate (**Figure 5**); the XRD pattern of the trihydrate was the same as that of the product obtained by exposure of amorphous material to 70% RH (**Figure 6**). It was inferred that the plasticizing effect of sorbed moisture can facilitate the necessary molecular mobility crystallization of the trihydrate.

Dehydration of magnesium stearate trihydrate: To determine whether the formation of the trihydrate was reversible, the trihydrate obtained from the dihydrate was sequentially dehydrated and rehydrated and the diffraction patterns of the resulting material measured. Dehydration resulted in the disappearance of the peaks at 22.37 and 23.38 (**Figure 7**). A single diffuse peak was seen at 21.4. The peaks at 5.3 and 37.8 remained largely unaffected, although a slight broadening of the latter was observed.



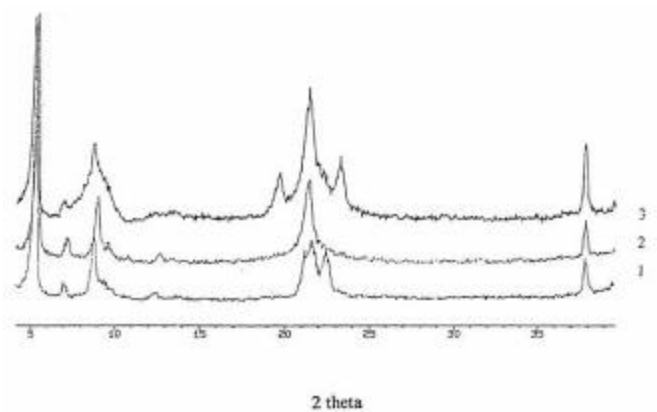
A: magnesium stearate dihydrate (control)
B: Product formed when the dihydrate was exposed to 100%RH

Figure 5. X-ray powder diffraction pattern of product formed by exposure of magnesium stearate dihydrate to 100% RH.



A: trihydrate obtained from amorphous magnesium stearate
B: trihydrate obtained from dihydrate

Figure 6. Comparison of x-ray powder diffraction patterns of products obtained by exposure of crystalline dihydrate and amorphous magnesium stearate to 100% RH.



1: Magnesium stearate dihydrate (starting material for formation of trihydrate(3))
3: Trihydrate
2: Anhydrate formed by dehydration of the trihydrate

Figure 7. X-ray diffraction powder pattern of product formed by dehydration of the trihydrate at 105°C.

Exposure of the dehydrated material to 100% RH resulted in the formation of the trihydrate (**Figure 7**). The peaks at 22.37 and 23.38 reappeared, and the XRD pattern of the product was identical to that obtained by initial exposure of the material to 100% RH. This observation was true of all the batches examined.

There was no change in the XRD pattern of the trihydrate after it was heated to temperatures as high as 90°C. A similar observation has been reported for the pure trihydrate [3].

Dehydration of magnesium stearate dihydrate:

The diffraction patterns of the dihydrate exposed to a range of temperatures from 40°C to 105°C are shown in **Figures 8 and 9**. There was no discernible change in the powder diffraction patterns of the samples that were heated to temperatures of up to 90°C. The threshold temperature at which a change in the XRD pattern was seen was around 100°C. The diffraction patterns of samples that were heated to 100°C and 105°C were characterized by the disappearance of the peak at 22.7. The XRD pattern of the resulting anhydrous material was different from that of the dihydrate or the trihydrate. Further, the same anhydrous form was obtained by dehydration of the crystalline dihydrate samples and of the trihydrate. The peaks at 5.3 and 37.8 remained unchanged. Exposure of anhydrous magnesium stearate to 100% RH resulted in the formation of the trihydrate.

The dehydration and rehydration sequence was reversible. The dihydrate was not an intermediate substance in the formation of the trihydrate from the anhydrous form under the experimental conditions in the study. Exposure of the anhydrate to 70% RH yielded the trihydrate. Conversely, dehydration of the trihydrate yielded the anhydrous form. The interconversion of the hydrates of magnesium stearate are summarized in the schematic in **Figure 10**. The possibility of the presence of small amounts of the trihydrate in the starting material cannot be excluded. While the trihydrate may have been present in too small an amount to be reliably detected by x-ray diffraction, it can act as a nucleus in crystallization during hydration. Further experiments on seeding the anhydrate with various pure hydrates prior to dehydration and rehydration are needed to exclude this possibility.

Generally, the strength of the water-solid interaction depends on the level of hydrogen bonding within the lattice. In hydrates such as theophylline and caffeine, in which the hydrogen bonding is weak, water molecules aid hydrate stabilization primarily by their space-filling capacity [12]. From the reversibility of the hydration-dehydration phenomenon in magnesium stearate, hydration of the lattice is likely to be nonspecific.

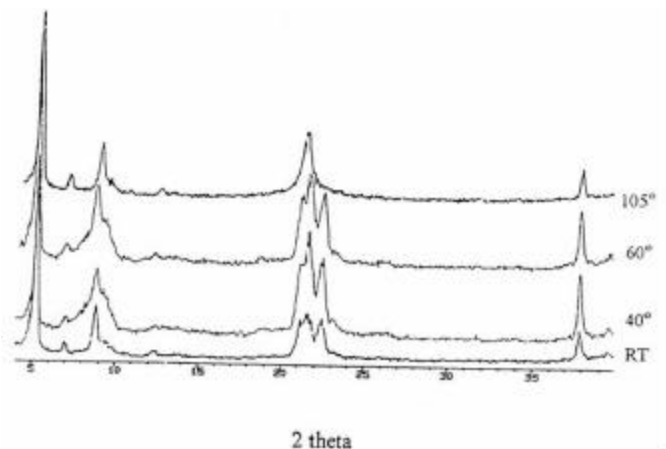


Figure 8. X-ray powder diffraction patterns of products formed by exposing magnesium stearate dihydrate to temperatures of 40°C, 60°C, and 105°C.

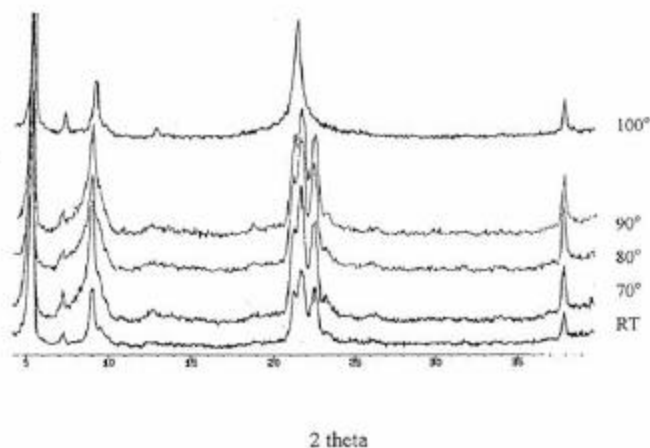


Figure 9. X-ray powder diffraction patterns of products formed by exposing magnesium stearate dihydrate to temperatures of 70°C, 80°C, 90°C, and 100°C.

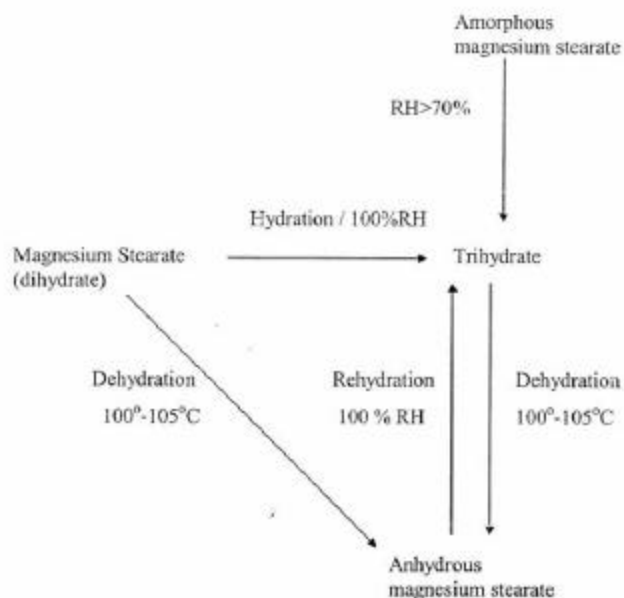


Figure 10. Schematic representation of interconversion of magnesium stearate hydrates.

CONCLUSION

The moisture sorption of crystalline and amorphous magnesium stearates and changes in crystal form as a result of sorbed water was characterized. Sorption of water by amorphous magnesium stearate resulted in the trihydrate. The trihydrate was converted into the anhydrous form when dehydrated. The conversion was reversible and the trihydrate was formed by exposure of the anhydrate to RH > 70%. From the reversibility of the hydration-dehydration phenomenon, it was inferred that water molecules aid stabilization in a space-filling capacity.

Further study: the effect of hydration on the functional characteristics of the material-lubrication efficiency-merits study. The relative lack of chemical purity of the commercial material is likely to be a significant factor affecting die-wall lubrication because of the effect of the impurities on the melting point of the material and on the crystal state. Both of these factors, along with particle size distribution and surface area, would be expected to have an effect on the dissolution of solid dosage forms. To assess the effect of the state of hydration, the use of hydrates of the pure material of comparable particle size distribution is recommended.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support provided by the Purdue Research Foundation.

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