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Thermal analysis of water and magnesium hydroxide content in commercial pharmaceutical suspensions milk of magnesia

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Abstract A standard protocol was developed to determine the water content by thermal analysis of milk of magnesia (MoM). Differential scanning calorimetry (DSC) and thermogravimetry (TG) were used in a novel manner for examining the physical characteristics of the commercial pharmaceutical suspensions. Moisture analyzer and oven-dry methods validate the proposed protocol. MoM consists primarily of water and magnesium hydroxide [$Mg(OH)_2$]. Experimental design of the thermal analysis parameters were considered including sample size, flowing atmosphere, sample pan, and heating rate for both DSC and TG. The results established the optimum conditions for minimizing heat and mass transfer effect. Sample sizes used were: (5–15 mg) for DSC and (30–50 mg) for TG. DSC analysis used crimped crucibles with a pinhole, which allowed maximum resolution and gave well-defined mass (water) loss. TG analysis used a heating rate of 10 °C/min^{-1} in an atmosphere of nitrogen. The heat of crystallization, heat of fusion, and heat of vaporization of unbound water are 334, 334, and 2,257 Jg^{-1}, respectively (Mitra et al. Proc NATAS Annu Conf Therm Anal Appl 30:203–208, 2002). The DSC average water content of (MoM) was 80 wt% for name brand and 89.5 wt% for generic brand, based on the relative crystallization, melting and vaporization heats/Jg^{-1} of distilled water in the recently purchased (2011) MoM samples. The TG showed a two-step process, losing water at 80–135 °C for unbound water and bound water ($MgO{\cdot}H_2O$) at 376–404 °C, yielding a total average water loss of 91.9 % for name brand and 90.7 % for generic brand by mass. The difference between the high-temperature TG and the lower-temperature DSC can be attributed for the decomposition of magnesium hydroxide or $MgO{\cdot}H_2O$. Therefore in performing this new approach to water analysis by heating to a high temperature decomposed the magnesium hydroxide residue. It was determined that the TG method was the most accurate for determining bound and unbound water.

Keywords Milk of magnesia (MoM) · Differential scanning calorimetry (DSC) · Thermogravimetry (TG) · Unbound water and bound water

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Introduction

In general, water can be organized by phases of matter: liquid, solid, and gas. The liquid phase is the most common among all the water phases on the surface of the earth, and this phase is noted as "water". The solid phase of water is a physically hard structure, which is commonly known as ice. The gas phase of water is recognized as vapor or the "vapor phase" of water. The physical chemistry of water is denoted as one molecule of water where two hydrogen atoms are covalently bonded to a single oxygen atom. Liquid water has no taste or odor and, at normal atmospheric temperature and pressure water is colorless; however, it can have a very light blue hue. Ice is colorless: water vapor or steam cannot be seen as a gas. At standard

conditions, 25 °C and pressure 1 atm, water is a liquid [1]. The water molecule has a net positive charge on the hydrogen atoms and a net negative charge on the oxygen atom. The net result is that each water molecule has a dipole moment. Water is a polar liquid that can form a hydronium ion (H_3O^+) and is interactive with hydroxide ion (OH^-).

$$2H_2O(l) \rightleftharpoons H_3O^+(aq) + OH^-(aq)$$

The heat of vaporization, (ΔH_v), is the energy required to change a given quantity of water into its gas phase at the standard temperature and pressure. Heat of vaporization for water is 2,257 J g^{-1}. The heat of fusion (ΔH_f) is the result of the change in the phase of water from solid to liquid, which occurs at the melting temperature (T_m). Heat of fusion for water is 334 J g^{-1}. The heat of crystallization (ΔH_c) is the result of the change in the phase of water from liquid to a solid, which occurs at the crystallization temperature (T_c). Heat of crystallization for water is 334 J g^{-1}. The following is a summary from W.J. Sichina's paper "Characterization of Water of Hydration of Pharmaceuticals Using the DSC", in which a test was developed to characterize the properties associated with the water in a pharmaceutical material. The method includes automated sample pan-puncturing accessory for the study of free and bound waters in pharmaceuticals. An additional protocol for determining hydrated pharmaceuticals materials is DSC. Sichina's DSC protocol includes a thermal program: heat from room temperature at 10 °C min^{-1}, sample mass approximately 4 mg, sample pan 30 µl aluminum pan with a hole, and purge gas nitrogen [2].

Milk of magnesia (MoM) is a suspension of magnesium hydroxide $Mg(OH)_2$ in water. It is widely used as an antacid to neutralize stomach acid and laxatives. Low solubility of $Mg(OH)_2$ in water makes it a weak base and considered as a strong electrolyte. The United States Pharmacopeia states that single strength MoM should contain not less than 90.0 % and not more than 115.0 % of the labeled amount of 80 mg of $Mg(OH)_2$ mL^{-1}. It is commercially produced by the precipitation of magnesium hydroxide paste from seawater. The paste can have varying degrees of viscosity, which determines whether a suspending agent is required or not. Water, melting/crystallization temperature and enthalpy of which are not significantly different from those of normal (bulk) water, is called free water or freezing water or unbound water. Those water species exhibiting large differences in transition enthalpies and temperatures, or those for which no phase transition can be observed calorimetrically are referred to as bound water. Recent investigation has proven that the ideal conditions for minimizing heat and mass transfer effects were a small sample size (between 15 to 20 mg), a heating rate of 5° min^{-1}, and an atm. of nitrogen. Crimped crucibles without pinholes allowed maximum resolution and gave relatively well-defined mass losses, and the DSC studies characterized the presence of 19–22 % non-freezing water [3].

The purpose of these experiments is to find the best analytical method to determine bound and unbound water. Oven-dry and moisture analyzer methods are traditional methods, which are used in this experiment as controls. They are used to determine the total water lost from the test samples. Since both traditional methods can only determine the total amount of water lost, these methods cannot be used to determine bound and unbound water, but can be used to check the accuracy of the TG and DSC methods [4–10]. TG rapidly measures changes in mass as a sample is heated and is eventually vaporized. This can be used to create a water loss profile that can show the different temperature ranges in which water and other components of a sample vaporize. DSC analyzes the phase changes in matter and can also be used to determine a water loss profile. Both methods can be used to determine the amounts of bound and unbound water, which can be used to determine the total amount of water lost in a sample. This will be compared with the traditional controls to determine if the novel methods can be accurately used to determine bound, unbound, and total water in a sample of MoM.

Experimental methods

The laxatives used in the study were a brand name MoM and a generic brand MoM. Each product was tested for water content using two conventional methods: 110 °C oven, and moisture analyzer and two novel methods: Differential scanning calorimetry and thermogravimetry.

110 °C Oven method

This method used small aluminum pans, a vacuum oven set to 110 °C, and desiccators. First, the mass of the aluminum pans were recorded to three decimal places. Next, the masses of two samples of each product were recorded and varied from 1.5 to 2.0 g and placed onto separate preweighed pans to three decimal places, and the masses were recorded. Then the pans were placed into the vacuum oven. The oven used was a Fisher Scientific Isotemp® vacuum oven model 282A. Pans and samples were left in the oven for 3 h at 15 kPa vacuum. After 3 h, the pans were removed from the oven and immediately placed into desiccators under vacuum for 1 h. After 1 h, the pans were removed from the desiccators, and the masses were recorded to three decimal places.

Moisture analyzer method

Samples of each product were analyzed for moisture content using the Lab wave 9000 Moisture Analyzer. The moisture analyzer uses an analytic balance inside a microwave oven, which dries the sample, while recording a change in mass. At the end of the test, the percent moisture of the sample is automatically calculated. First, two absorbent pads are placed on the analytic balance inside the moisture analyzer, and the balance is tarred. Next, 1.0–1.5 g of sample is placed in between the absorbent pads. Then the moisture analyzer is activated, using 80 % power. The sequence is completed, when the moisture analyzer no longer records a change in mass. The instrument then displays the percent moisture, percent solids, and the amount of time it took to complete the analysis.

Thermogravimetric method (TG)

The TA Instruments Hi-Res Thermogravimetric Analyzer Model 2950 was used to measure bound and unbound water in MoM samples. The samples were prepared by placing one drop of material on to a pre-tarred platinum TG pan. The pan was placed onto the auto-loading mechanism of the TG analyzer, and an automated loading sequence was initiated. The sample is placed into a furnace which heats the sample, while measuring the mass of the sample every 0.5 s. The TG experimental conditions were Ramp 10 °C per minute to 500 °C in nitrogen. 30–50 mg of sample was used in each run.

Differential scanning calorimetry method (DSC)

The Mettler DSC 823e 20 instrument was used to measure the heat flow properties of the MoM samples which involve exothermic or endothermic processes as a function of time and temperature. Samples were placed in solid fat index (SFI) aluminum pans with sampling size ranging from 5 to 15 mg, covered with a lid and were sealed. The samples were cooled from 25 to −50 °C and then heated to 120 °C at 5 °C min^{-1} heating rate with nitrogen gas purge of 50 mL min^{-1}. Closed pans were used in this study. The DSC scan provided data of the following properties: Heat of fusion (ΔH_f), melting temperature (T_m), peak melt temperature (T_{mp}), heat of crystallization (ΔH_c), crystallization temperature (T_c), peak crystallization temperature (T_{cp}), heat of vaporization (ΔH_v), vaporization temperature (T_v), and peak vaporization temperature (T_{vp}).

Results and discussion

The results of % water from the 110 °C pan method are shown in Table 1.

The results were obtained by subtracting the mass of the pan and sample after testing, from the initial mass of the pan. The difference was the amount of solids left in the pan. From thio value, the mass of the material left in the pan was subtracted from the initial mass of the sample. The data show that the amount of water in the commercial brand of MoM was 91.8 % and the generic brand of MoM was 90.6 %. The moisture analyzer results were virtually identical to the results obtained from the 110 °C pan method as seen in Table 2.

The TG data were analyzed using Universal Analysis 2000, by TA Instruments, version 4.4A. The data were plotted and analyzed using the first derivative of the percent (%) mass loss versus temperature in °C. From the graph, each peak was identified, and the percent material loss was calculated. Also identified were the initial and end points at which mass loss began and ended. All remaining materials in the sample were calculated as percent residue. The results are shown in Figs. 1 and 2.

In comparison to the conventional methods, TG analysis showed both bound and unbound water. Water vaporization results are shown in Table 3. The unbound water vaporized between 80 and 119 °C in the name brand MoM. The unbound water in generic brand MoM vaporized between 91 and 135 °C. The bound water in the name brand MoM vaporized between 376 and 398 °C and in the generic brand MoM between 374 and 404 °C.

DSC results are summarized in the Figs. 3, 4 and 5 as well as Tables 4 and 5. The free water concentrations were determined based on the cool and heat DSC curves. The heat of crystallization, ΔH_c (from the cooling curve) and the heat of fusion, ΔH_f (heating curve after crystallization), were calculated for pure water and the commercial suspensions of MoM produced by a name brand and a generic pharmaceutical contract packager. The free unbound water

Table 1 Results of % water from pan method

Source drug suspension	Sample	Water/%	Average/%	SDEV
Milk of magnesia/name brand	1	91.8	91.8	0.0
	2	91.7		
Milk of magnesia/generic brand	1	90.6	90.6	0.1
	2	90.7		

Table 2 Comparison of two conventional methods for water content in milk of magnesia

	Total water (oven)/%*	Total water (analyzer)/%*
Milk of magnesia/name brand	91.8	91.9
Milk of magnesia/generic brand	90.6	90.8

* Average values

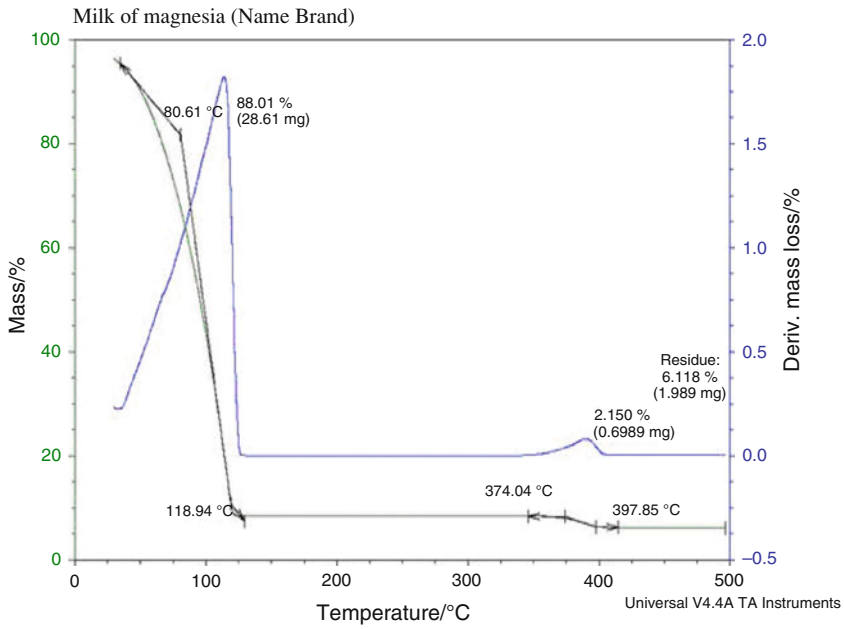

Fig. 1 TG analysis for name brand

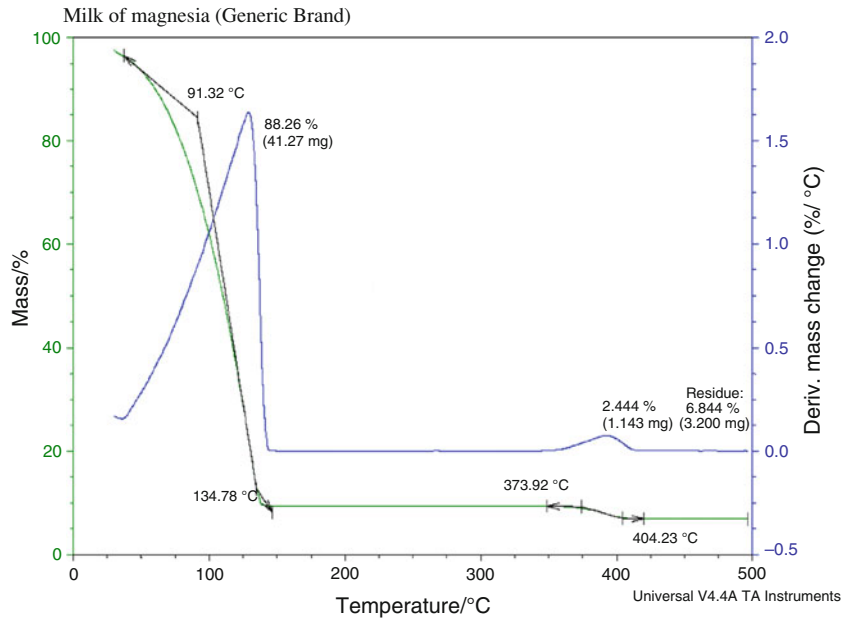

Fig. 2 TG analyses for generic brand

Table 3 % of unbound water and bound water for test samples by TG

	Unbound water/%	Bound water/%	Total water/%
Milk of magnesia/name brand	88.0	2.2	90.2
Milk of magnesia/generic brand	88.3	2.4	90.7

is the focus of this study and is the difference of the amount of water relative to the "pure" water. Assuming a two-component suspension of water and magnesium hydroxide [$Mg(OH)_2$ suspended in the water],various samplings of the commercial suspensions were evaluated by the DSC curves. The average, standard deviation, and percent relative error were calculated from the ΔH_c and ΔH_f measured and are reported in Table 4. The standard deviation was ± 17 to ± 22 and the % relative error was from 5.3 to 7.6 % for the heat measurements. The heats of vaporization were recorded during the DSC run, but due to baseline variations and sampling techniques, they were not used for the calculation of the water content.

The final summary of the DSC analysis includes the temperature profile of the free or unbound water, its water content relative to the ΔH_f and ΔH_c, and the average results

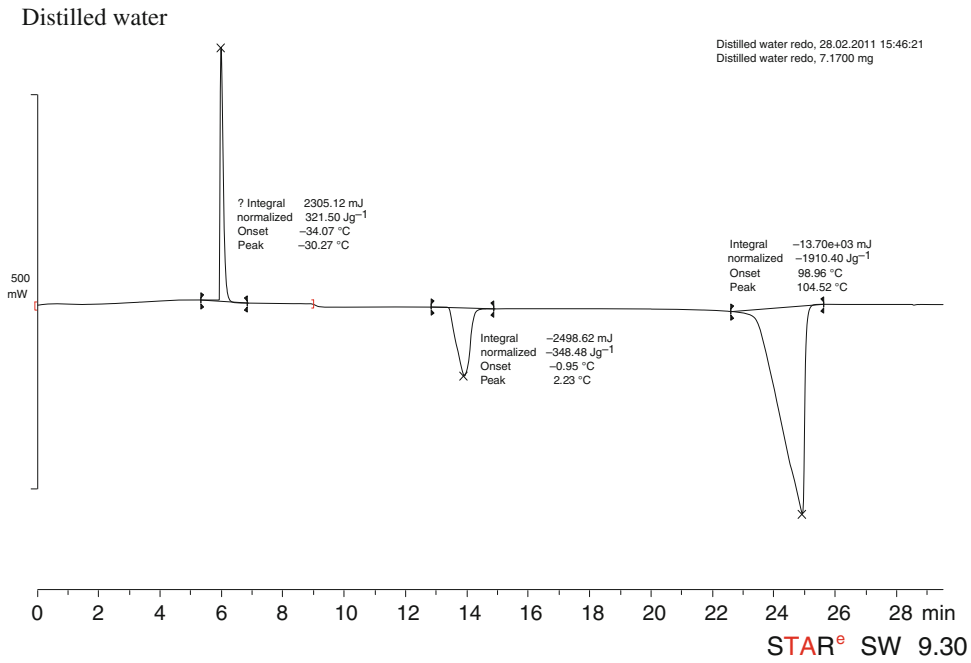

Fig. 3 DSC analyses for distilled water

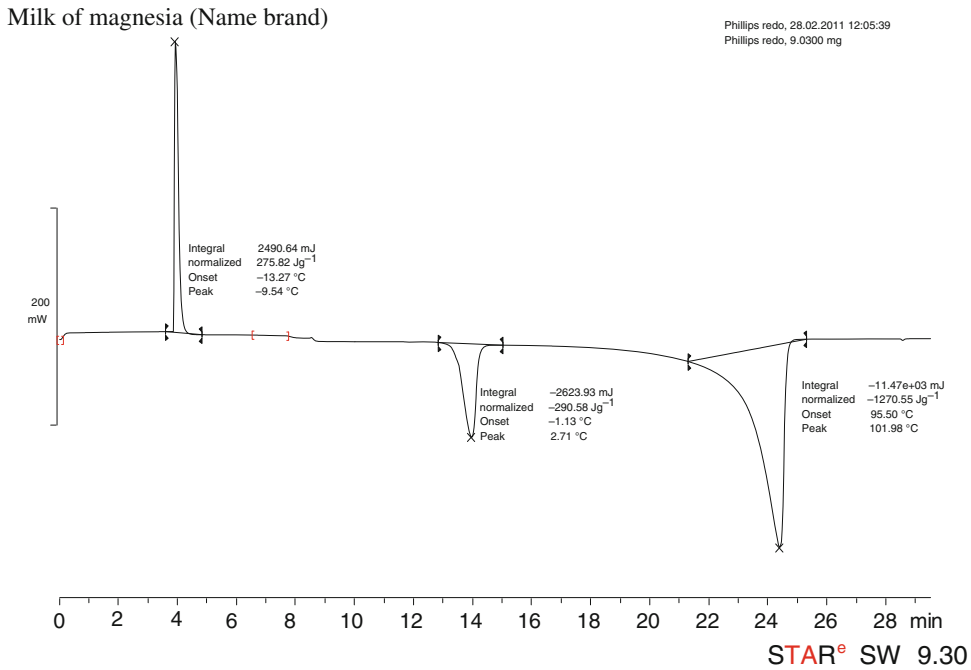

Fig. 4 DSC analyses for name brand MoM

of the water by both analytic techniques, see Table 6. The MoM, name brand and generic brand, were 80.0 and 89.5 %, respectively, by DSC. Therefore, there appears to be a 10 % variation between the two MoM commercial samples. An overview of the water content by four analytic techniques is reported in Table 6.

The differences between the name brand and generic MoMs were the same for the oven, moisture analyzer, and TG methods. There was a repeatable difference based on the DSC analysis of 10 % more water in the generic sample. Further, there was a sizable viscosity difference of 88 % between the name brand and generic. The generic had more water and a higher viscosity according to DSC. The latter may be due to the additional additives denoted by 20 mg calcium and 2 mg sodium in the generic product. There is also a difference

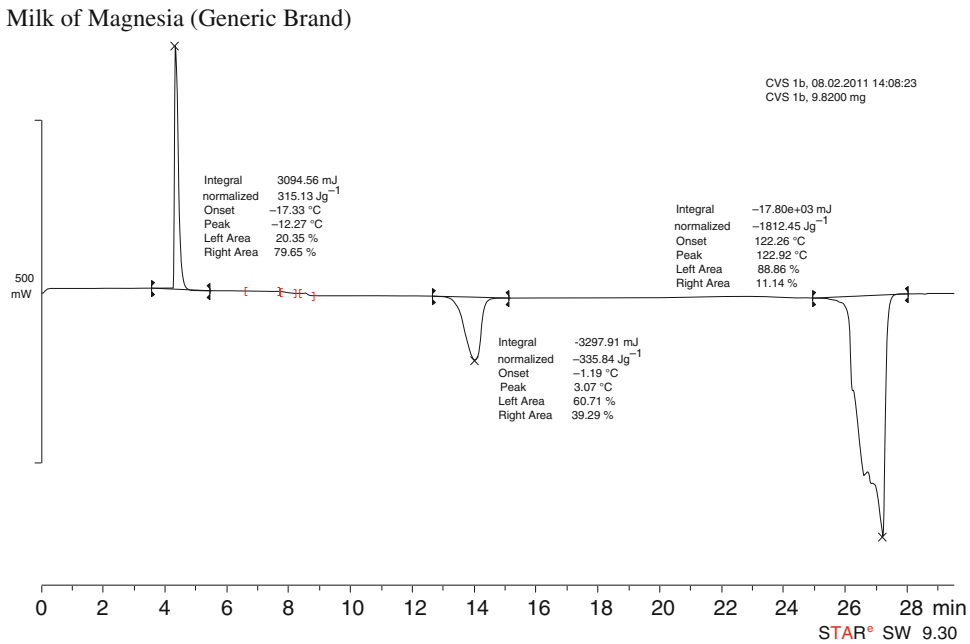

Fig. 5 DSC analysis of generic brand

Table 4 Average, standard deviation and % relative error of ΔH_c and ΔH_f*

Drug/liquid	Average ΔH_c/J g^{-1}	Standard deviation/±	Relative error/%	Average/ ΔH_f/J g^{-1}	Standard deviation/±	Relative error/%
Distilled water	338	19	5.5	373	20	5.3
Milk of magnesia/name brand	276	17	6.1	291	18	6.2
Milk of magnesia/generic brand	312	18	5.4	326	22	7.6

* All values H_c and H_f are based on three samplings

Table 5 Relative ΔH_c, ΔH_f and average of ΔH_c and ΔH_f

Drug/liquid	T_c/°C	T_{cp}/°C	ΔH_c/J g^{-1}	Relative ΔH_c/%	T_m/°C	T_{mp}/°C	ΔH_f/J g^{-1}	Relative ΔH_f/%	Average of ΔH_c and ΔH_f
Distilled water	−18	−14	338	100	0	3.0	373	100	100
Milk of magnesia/name brand	−17	−13	276	82	−1.2	2.0	291	78	80
Milk of magnesia/generic brand	−17	−12	312	92	−1.3	2.0	326	87	89.5

between the naturally mined sodium hydroxide and synthetic sodium hydroxide, which is made from magnesium chloride. It is possible that differences in the preparation of magnesium hydroxide may play a role in the thermal differences shown in the DSC. The results show that the DSC was able to determine that the name brand MoM and the generic MoM are chemically different from each other. Figure 6 shows the thermal differences between the two products using distilled water for comparison.

Water activity is a measure of the energy status of the water in a system [3, 10–12]. It is defined as the vapor pressure of a liquid divided by that of pure water at the same temperature, yielding a value of one or 100 %. It is interpreted that the difference noted in the DSC analysis may also be due to the differences between the water activities of the two samples.

The study of the thermal decompositions of magnesium salts of organic acids such as Mg acetate, Mg lactate, Mg citrate, and Mg hydrogen aspartate were analyzed by

Table 6 Percent of water content from all the techniques and viscosity for test samples

Source suspension	Oven 110/°C	Moisture analyzer/%	TG/%	Mettler DSC/%	Viscocity/mPa s*
Milk of magnesia/name brand	91.8 %	91.9	90.2	80.0	1,585
Milk of magnesia/generic brand	90.6 %	90.8	90.7	89	2,980

* Brookfield DV II+ Viscometer (#3 RVT spindle at 20 rpm)

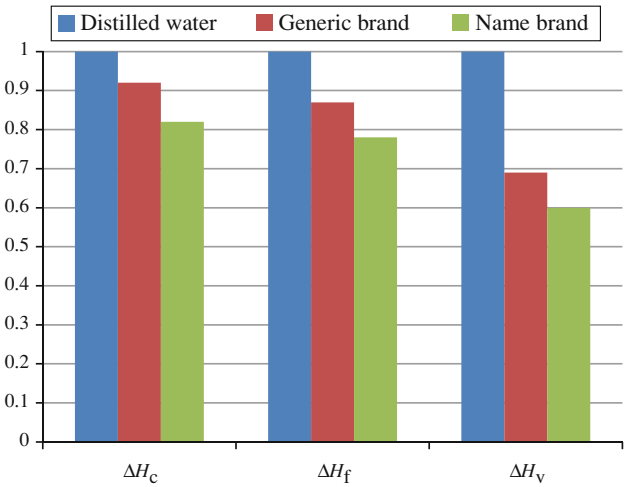

Fig. 6 DSC thermal properties of name brand and generic compared to distilled water

thermo-analytic, and calorimetrical methods and, this study showed that the values of transitions heats and enthalpies of dehydration for the investigated salts varied with the increase of heating rate [13].

Conclusions

The control methods could not effectively determine bound, and unbound water in the test samples, but were effective in determining total water concentration. TG was determined to be the best method to determine both bound and unbound water. DSC was not effective in determining bound, unbound, or total water concentration, but showed that the commercial and generic brands were chemically different from each other.

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