Pharmaceutical Sciences, November 2015, 21(Suppl 1), 127-135
doi: 10.15171/PS.2015.27
http://journals.tbzmed.ac.ir/PHARM

Research Article

Determination of Water Content of Crystalline Pharmaceutical Solids under Different Percentages of Relative Humidity

Kazam Kargosha, Zahra Shirazi*
Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran.

Article Info

Article History:
Received: 29 June 2015
Accepted: 30 July 2015
ePublished: 18 November 2015

Keywords:
Water Content
Water in Solids
Moisture Sorption
Pharmaceutical Crystalline Salts

ABSTRACT

Background: It is reported that the change in the number of water molecules in the crystalline mineral salts which is used as pharmaceutical ingredients, can cause variations in their physicochemical and pharmaceutical properties. The number of water molecules of these pharmaceutical ingredients is subordinate to Relative Humidity (RH) and temperature of the maintenance environments of the medicines. The aim of the present study was to investigate variation in water content of pharmaceutical solids including ferrous sulfate, barium sulfate and magnesium chloride in different percentage of RH and temperature. ***Methods:*** For this purpose, the pharmaceutical solids (both inside and outside the packaging) were subjected to various relative humidity at constant temperature for a given period of time, then change in their water content was determined with Thermo Gravimetry Analysis (TGA). To create a variety environments with different RH in constant temperature, the saturated salt solutions were put in a desiccator and the RH above mixtures of solids was determined with a Hygroscope at 25°C. ***Results:*** According to the results obtained from TGA, the water content of pharmaceutical solids studied in this research (ferrous sulfate, barium sulfate and magnesium chloride) changed in different RH and temperatures. ***Conclusion:*** It is necessary to determine water uptake of Active Pharmaceutical Ingredients (APIs) and excipients in each stage of pharmaceutical development process. Furthermore, these results could be used to select an appropriate packaging to avoid adverse effects caused by water absorption by pharmaceutical solids. In cases where this is not possible, the allowable range of relative humidity for each pharmaceutical solid should be noted on its package.

Introduction

When a crystalline pharmaceutical solid is subjected to different levels of relative humidity (RH), water vapor molecules in the atmosphere can be attached to its surface through van der Waals, ion-dipole or hydrogen bonding interactions. Study of water molecules absorbed on the well-defined crystalline surfaces, specifies the high tendency of water to form hydrogen bonds. The main cause for extensive interactions observed between water molecules and pharmaceutical solids, is thought to be the ability of water to act as both Lewis acid and base.[1-5]

Several research conducted on pharmaceutical solids indicates that changes in water content and number of water molecules in the pharmaceutical solids can cause extensive variations in their physical and chemical properties, thereby reducing their pharmaceutical contributions.[6-10] For this reason, it is necessary to measure water content of pharmaceutical solids within each stage of the development process. Accordingly, water contents of Active Pharmaceutical Ingredients (APIs) and excipients are measured before and after mixing them together.[11]

The tendency of solids to take up water vapor from the atmosphere with changes in RH at constant temperature, is often referred to as "hygroscopicity", the measurement of which is now a routine preformulation activity intended to provide an early assessment of the potential effects of moisture on the physical and chemical properties of drug candidates.[11-13]

Once hygroscopicity was measured, one must select a suitable coating for drug package, so as to avoid moisture to penetrate into the pharmaceutical solids; thereby preventing possible changes to occur in the drug's characteristics.[14,15] However, it is a point that seems to be neglected, as the findings of this research indicate that even packed pharmaceutical solids start to absorb water vapor from the atmosphere under high levels of relative humidity, representing ineffectiveness

***Corresponding Author:** Zahra Shirazi , Tel: (+98) 21 44787720, E-mail: zshirazi69@yahoo.com

of their packaging. As a result, it seems to be necessary to measure water uptake not only in the early stages of the pharmaceutical development process, but also after the packaging step was completed to ensure a proper packaging through which water may not penetrate.[16]
Investigated in this study are the amounts of water uptake for two pharmaceutical formulations, namely ferrous sulfate tablet and barium sulfate powder, measured both inside and outside the packaging, together with the amounts of water uptake for two active pharmaceutical ingredients, namely magnesium chloride and ferrous sulfate, before reporting the obtained results.
Water uptake in pharmaceutical solids is typically measured using gravimetric method, where solid sample is subjected to various levels of relative humidity at a constant temperature for a given period of time. The change in the weight of the solid, measured as a function of relative humidity, is then translated into a water vapor sorption.[11] To put it in simple terms, a pre-weighed sample is placed in a closed desiccator containing a saturated solution of an electrolyte (i.e., at a constant RH). Then the sample is periodically removed and weighted until a constant weight is attained.[17]
Thermo Gravimetric Analysis (TGA) was used to determine moisture content of the solids, before and after being subjected to different levels of relative humidity. This technique measures the mass loss of the samples as a function of temperature or time.[18,19]

Materials and Methods

Water vapor uptake in pharmaceutical solids (ferrous sulfate, barium sulfate and magnesium chloride) was measured in a desiccator. Various substances can be used to establish different levels of relative humidity inside a desiccator: saturated and unsaturated salt solutions, solutions with different percentages of sulfuric acid, solutions with different percentages of glycerol and etc. The advantages of using saturated salt solutions for humidity control is that they are, mostly, simple and inexpensive chemicals, available at an acceptable level of purity while, are not volatile.[1,20] Accordingly, saturated salt solutions were used to establish different levels of relative humidity in this research. Table 1 presents the used salts and the required amount of each one for the preparation of the saturated solutions.

Table 1. Percentage of RH generated by different salt with required amount of each salt.[1]

Saturated salt solution	RH%	Amount of salt (gr) for the preparation of saturated solution (25 ml)
NaOH	9.5	30.32
$MgCl_2$	33.8	60
KI	66.4	35
K_2CO_3	46	34
$Mg(NO_3)_2$	54.5	31
$NaNO_3$	63	28
NaCl	73.5	10.39
KCl	83	10.15

The percentage of relative humidity depends on the temperature and salt concentration. Therefore, measurements must be performed at constant temperature so as to avoid changes in the established relative humidity.
Pharmaceutical solids investigated in this study include $FeSO_4,7H_2O$ APIs, $FeSO_4$ tablets (inside and outside the packaging), $BaSO_4$ powder (inside and outside the packaging) and $MgCl_2$, $6H_2O$ APIs were exposed to different percentages of relative humidity inside the desiccator. In the following, each sample will be separately described.

Ferrous sulfate, hepta hydrate APIs

$FeSO_4,7H_2O$ powder was exposed to different percentages of relative humidity (9.5, 33.8, 54.5, 66.4, 73.5 and 83.0%) at 25˚C for 4 days, during which time changes in its weight (due to sorption or desorption of water) were recorded.
After a constant weight was reached, changes in the number of molecules of water were determined by using TGA.

Ferrous sulfate tablets

Ferrous sulfate tablets, both inside and outside the packaging, were subjected to different percentages of relative humidity (34, 46, 63 and 83%) at 25˚C. Storage time was 10 days for those tablets out of the packaging, while it was 3 months for those packed. The samples were analyzed thermo gravimetrically.

Barium sulfate

Barium sulfate was studied, again inside and outside the packaging. Moistures levels employed in were 34, 46, 63 and 83%. Time to reach an equilibration with water vapor was 3 months for the packed barium sulfate, while it was 10 days for unpacked barium sulfate.

Magnesium chloride, hexa hydrate

$MgCl_2,6H_2O$ has also been studied as an API. Same amounts of $MgCl_2,6H_2O$ were placed in a desiccator of relative humidity of 34, 46, 63 and 83% at 25˚C, and their water sorption was investigated. The relative humidity inside the desiccator was measured by a Lutron AM-4205A hygrometer.

It should be noted that the time listed for each drug is the time required to reach equilibrium with water vapor in the atmosphere. A number of factors influenced this time: 1) the ratio of open surface of the solution to volume of the chamber, 2) air flow rate, 3) absorption characteristics of the sample, and 4) activity of saturated salt solution.[20] Based on the four factors mentioned, the time to reach equilibrium varied for different solids. After reaching equilibrium, TGA was used to determine sorption of the samples with the mass loss observed in the TGA spectra directly linked to the water content of the solids.

Results and Discussion

Ferrous sulfate

Figure 1 presents TGA spectrum of $FeSO_4,7H_2O$ as is obtained in the laboratory. The spectrum indicates that $FeSO_4,7H_2O$ loses three moles of water at 70˚C when it is converts into $FeSO_4,4H_2O$ which then loses additional three moles of water at around 120˚C and becomes $FeSO_4,H_2O$. Finally, a last mole of water is lost at around 400˚C. The dehydration temperatures are reported in Table2.

Mass loss observed at higher temperatures is related to the oxidation of $FeSO_4$ to Fe_2O_3. Accordingly, in the subsequent analysis of the ferrous sulfate, the temperature range was set to 20-500˚C.

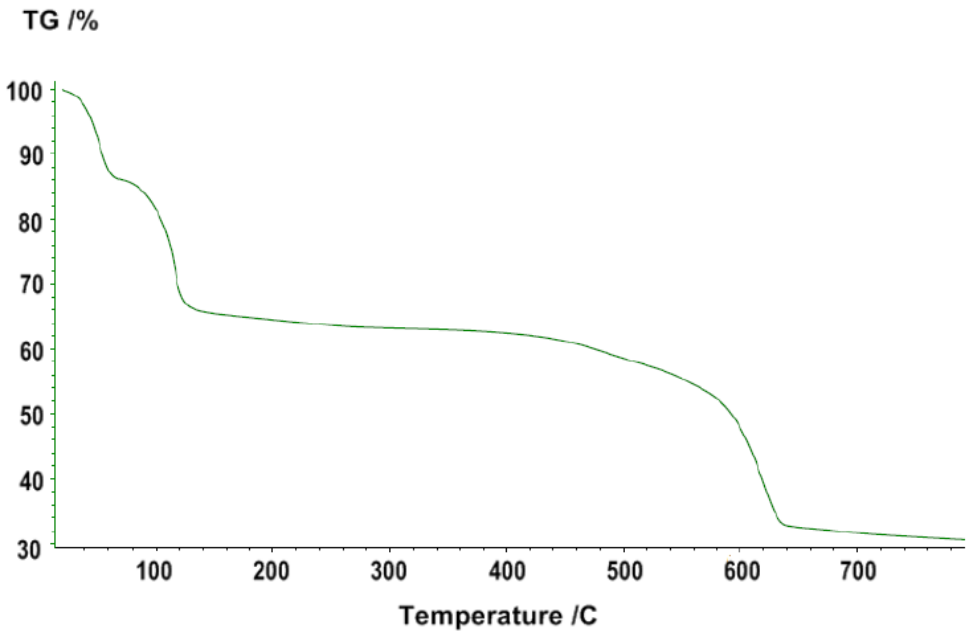

Figure 1. TGA spectra of FeSO4,7H2O kept at lab condition.

Table 2. Temperature and reaction of hydrate losing for $FeSO_4$, $7H_2O$.

Temperature of hydrate losing (˚C)	Reaction of hydrate losing
70	$FeSO_4$, $7H_2O \rightarrow FeSO_4$, $4H_2O + 3\ H_2O$ (g)
120	$FeSO_4$, $4H_2O \rightarrow FeSO_4$, $H_2O + 3H_2O$ (g)
400	$FeSO_4$, $H_2O \rightarrow FeSO_4 + H_2O$ (g)

The TGA spectra of the $FeSO_4,7H_2O$ stored under various percentages of relative humidity (9.5, 33.8, 54.5, 66.4, 73.5 and 83.0%) are shown in Figure2. Figures 2a and 2b represents ferrous sulfate stored at relative humidity of 9.5 and 33.8%, respectively. In these two spectra, the no mass loss was detected to be associated with the loss of three moles of water at around 70˚C. Thus, it can be concluded that maintaining $FeSO_4,7H_2O$ under relative humidity of 9.5 and 33.8% have led three moles of water to be desorbed while $FeSO_4,7H_2O$ has been converted into $FeSO_4,4H_2O$.

But no significant change is seen in the TGA spectra of $FeSO_4,7H_2O$ sample stored under relative humidity of 54.5, 66.4, 73.5 and 83.0% (shown in Figure2c, 2d, 2e and 2f, respectively), so that one can conclude that the a relative humidity above 50% is suitable for storing $FeSO_4,7H_2O$.

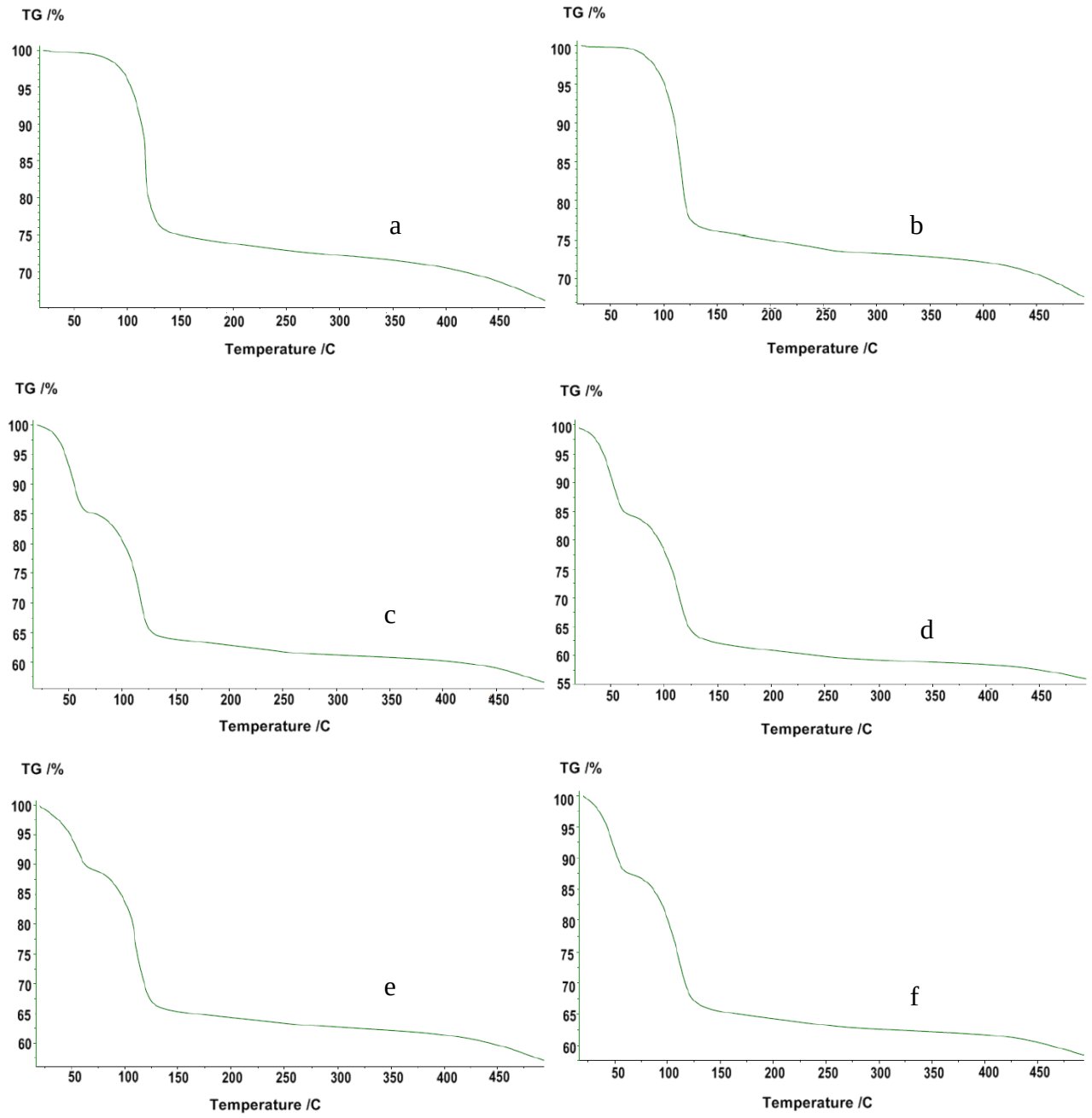

Figure 2. TGA spectra of FeSO4,7H2O kept at RH a) 9.5%, b) 33.8%, c) 54.5%, d) 66.4%, e) 73.5% and f) 83.0%.

Ferrous sulfate tablet

Continuing with this study, ferrous sulfate tablets were investigated both inside and outside the packaging, the results of which are indicated in terms of TGA spectra shown in Figure4 (for tablets out of the pack) and Figure5 (for tablets inside the pack), Presenting ferrous sulfate tablets stored under relative humidity of 83.0%, Figure 4d shows a greater mass loss compared to that in Figure 4a-c which present tablets stored under relative humidity percentages of of 34, 46 and 63%, respectively. In addition, showing a mass loss at lower temperatures, the shape of the spectrum in Figure 4d is different from those of the other spectra. These observations express that the tablet uptakes moisture at a relative humidity of 83%.

Shown in Figure 3 is the image of ferrous sulfate tablet after being placed under a relative humidity of 83%.

Figure 3. Image of ferrous sulfate tablet maintained at RH 83%.

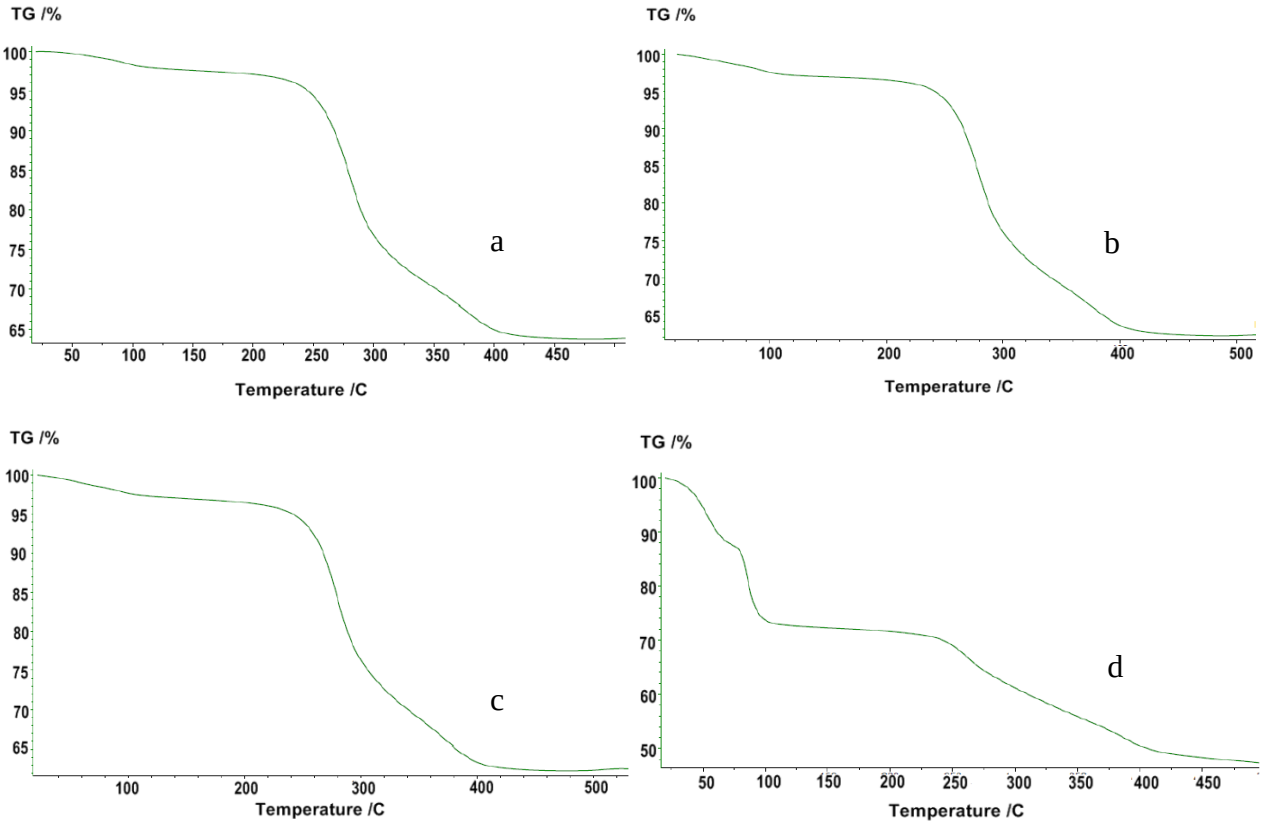

Figure 4. TGA spectra of out of the package ferrous sulfate kept at RH: a)34%, b) 46%, c) 63% and d) 83%.

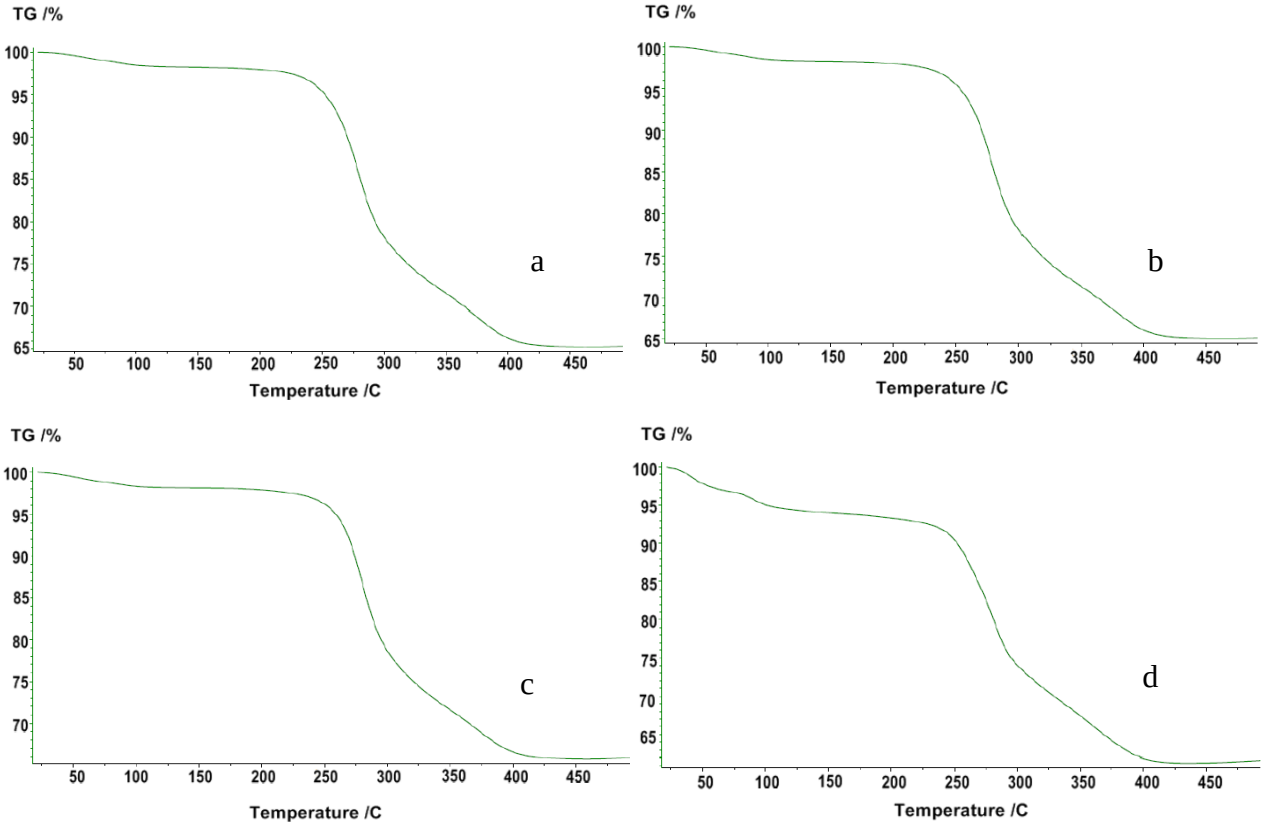

Figure 5. TGA spectra of coated ferrous sulfate kept at RH: a) 34%, b) 46%, c) 63% and d) 83%.

This difference can be seen even in the packed ferrous sulfate tablets placed under different percentages of relative humidity (34, 46, 63 and 83%). Comparing the spectrum of the tablet stored under relative humidity of 83% (Figure 5d) to other spectra, shows a greater mass loss. The results obtained from this investigation proved unsuitability of the selected packaging through which the moisture has penetrated and absorbed by the pharmaceutical solid.

Therefore, in order to avoid adverse effects of water uptake by the pharmaceuticals, more appropriate material should be chosen for the packaging of tablets with the allowable range of relative humidity written on the package; this range should be less than 80%.

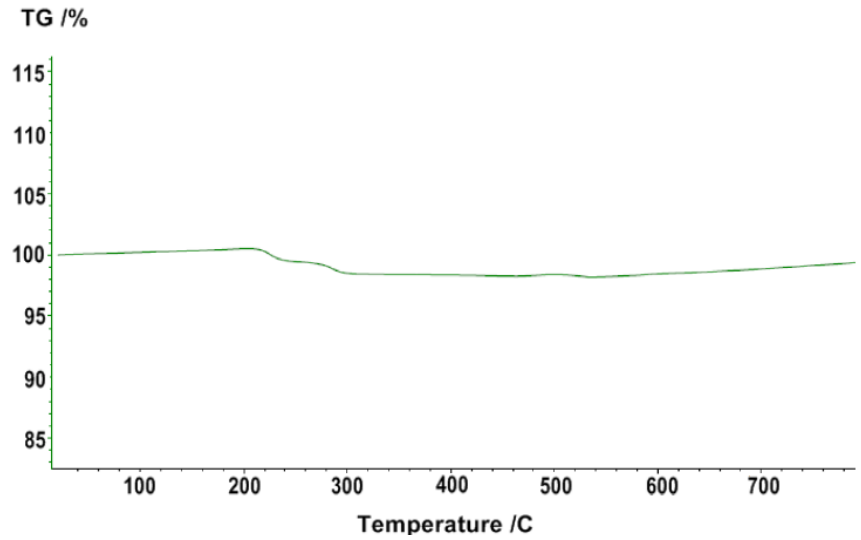

Figure 6. TGA spectra of barium sulfate kept at lab condition.

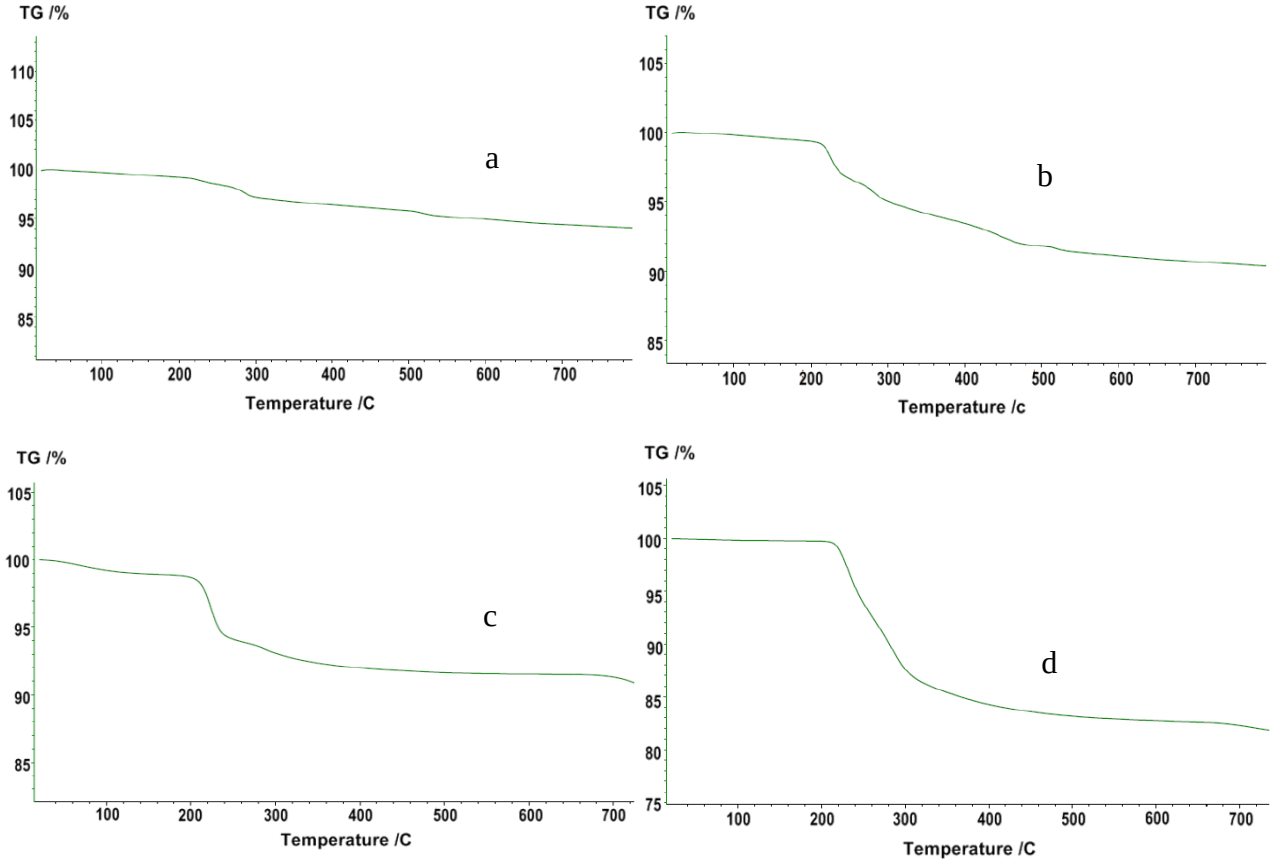

Figure 7. TGA spectra of out of package barium sulfate kept at RH: a) 34%, b) 46%, c) 63% and d) 83%.

Barium sulfate

Figure 6 shows TGA spectrum of the barium sulfate stored in the lab where due to absence of water molecules in the structure of $BaSO_4$, as well as its stability against heat, a little mass loss is observed in the spectra. However, when different levels of relative humidity (34, 46, 63 and 83%) are applied to the drug at 25˚C, a greater mass loss is observed in TGA spectra. See Figure7a-d.

Continuing with the investigation, the packed barium sulfate was placed under different percentages of relative humidity while water uptake behavior of the drug was being monitored. The results are presented in Figure8. Increased amount of mass loss in Figures8a-d shows that some amount of moisture is absorbed by barium sulfate even when it is inside the package, so that the packaging provides inappropriate means to prevent the moisture from penetrating into the drug.

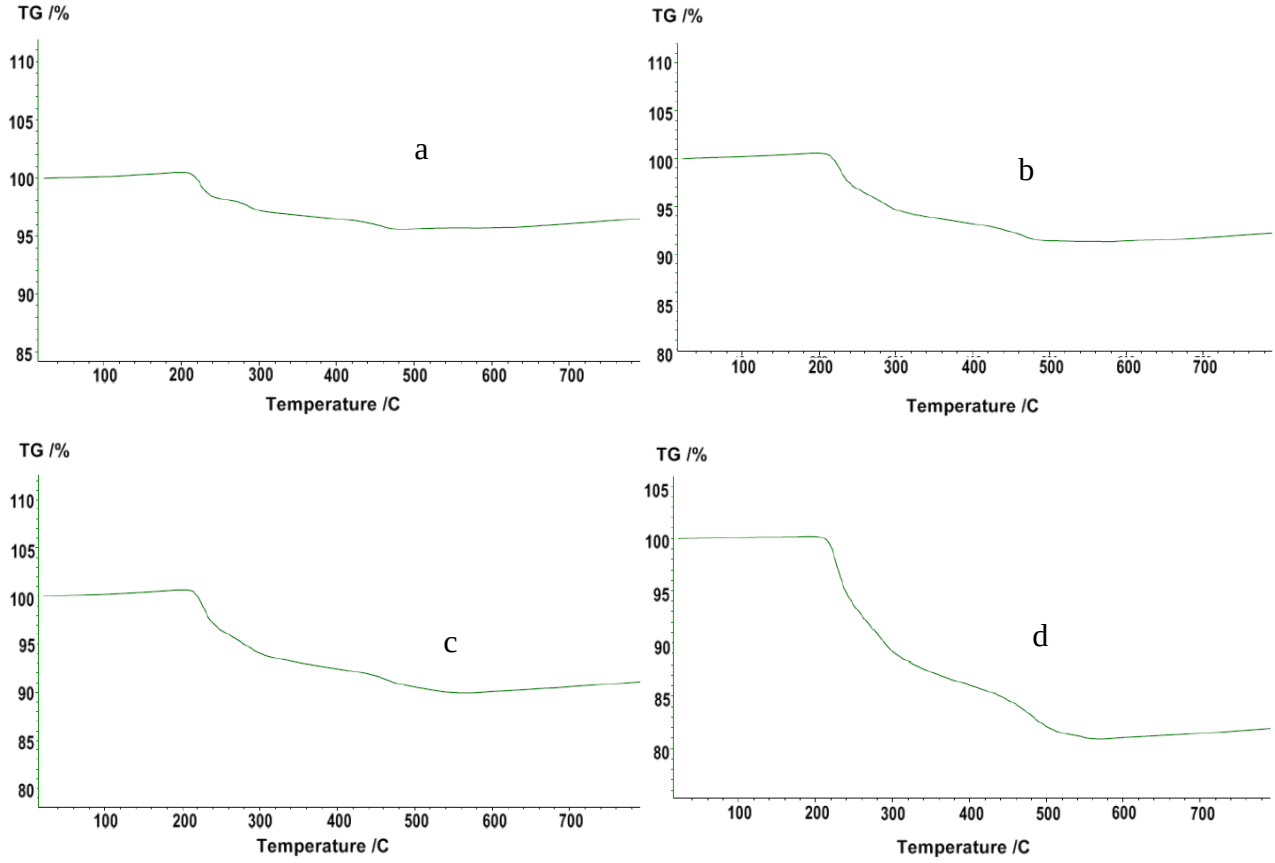

Figure 8. TGA spectra of coated barium sulfate kept at RH: a) 34%, b) 46%, c) 63% and d) 83%.

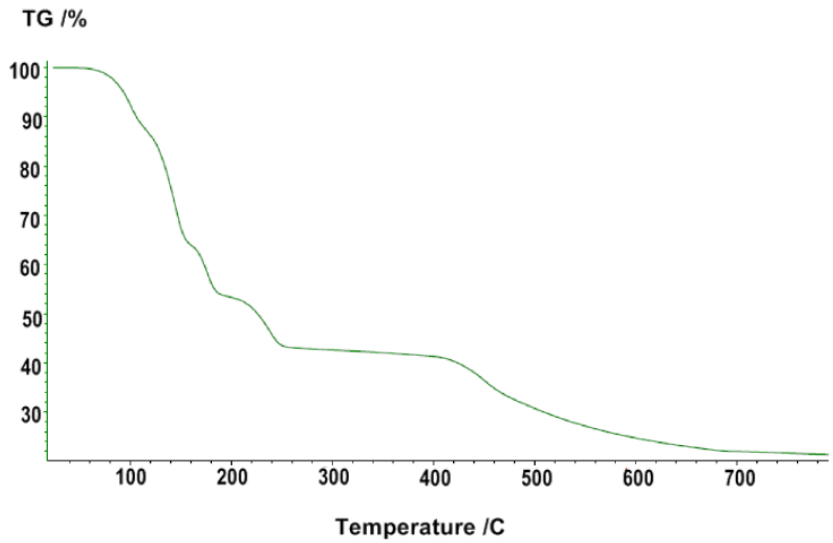

Figure 9. TGA spectra of magnesium chloride kept at lab condition.

Table3. Temperature and reaction of hydrate losing for magnesium chloride.

Temperature of hydrate losing (˚C)	Reaction of hydrate losing
100	$MgCl_2$, $6H_2O \rightarrow MgCl_2$, $4H_2O + 2\ H_2O$ (g)
150	$MgCl_2$, $4H_2O \rightarrow MgCl_2$, $2H_2O + 2H_2O$ (g)
190	$MgCl_2$, $2H_2O \rightarrow MgCl_2$, $H_2O + H_2O$ (g)
250	$MgCl_2$, $H_2O \rightarrow MgCl_2 + H_2O$ (g)

Magnesium chloride, hexa hydrate APIs

$MgCl_2,6H_2O$ was resolved in the absorbed water after being exposed to different percentages of relative humidity (34, 46, 63 and 83%) with different times to dissolve for different percentages of relative humidity. The time intervals required for complete dissolution of $MgCl_2,6H_2O$ were 160 min at relative humidity of 83%, 170 min at relative humidity of 63%, 10 days at relative humidity of 46% and 15 days at relative humidity of 34%. Because of the high rate of water uptake by this pharmaceutical solid, it is necessary to use a moisture-resistant coating for that.

TGA spectrum of $MgCl_2,6H_2O$ is given in Figure9 while dehydration temperatures are reported in Table3.

It is worth mentioning that magnesium chloride, as a pharmaceutical solid, is usually sold without any packaging; however, as demonstrated in this study, this compound tends to absorb a large amount of moisture from the environment even at as low relative humidity percentages as 34%. So, it is necessary to wrap it in an appropriate package and keep it under relative humidity percentages of less than 34%.

Conclusion

A change in the number of water molecules in pharmaceutical solids can cause variations in their physicochemical and pharmaceutical properties. Investigated in this study were the effect of two major factors, namely relative humidity and temperature, on the number of water molecules in three pharmaceutical solids including ferrous sulfate, barium sulfate and magnesium chloride. For this purpose, they were placed under different percentages of relative humidity before incorporating thermo gravimetric analysis. The results of investigations show that the water content of pharmaceutical solids can change under different percentages of relative humidity, so that it is necessary to determine water uptake of APIs and excipients in each stage of pharmaceutical development process. Furthermore, these results could be used to select an appropriate packaging to avoid adverse effects caused by water absorption by pharmaceutical solids. In cases where this is not possible, the allowable range of relative humidity for each pharmaceutical solid should be noted on its package. The appropriate ranges of relative humidity were found to be less than 80% for ferrous sulfate tablets, 50-80% for ferrous sulfate APIs, and less than 34% for barium sulfate and magnesium chloride.

Conflict of Interest

The authors report no conflicts of interest.

References

1. Greenspan L. Humidity fixed points of binary saturated aqueous solutions. *J Res Nat Bur Stand* 1977;81A:89-96. doi:10.6028/jres.081a.011
2. Campen LV, Amidon GL, Zografi G. Moisture sorption kinetics for water-soluble substances.1. Theoretical considerations of heat-transport control. *J Pharm Sci* 1983;72:1381-1388. doi:10.1002/jps.2600721204
3. Campen LV, Amidon GL, Zografi G. Moisture sorption kinetics for water-soluble substances.II. Experimental verification of heat-transport control. *J Pharm Sci* 1983;72:1388-1393. doi:10.1002/jps.2600721205
4. Campen LV, Amidon GL, Zografi G. Moisture sorption kinetics for water-soluble substances.III. Theoretical and experimental studies in air. *J Pharm Sci* 1983;72:1394-1400. doi:10.1002/jps.2600721206
5. Kontny MJ, Zografi G. Moisture sorption kinetics for water-soluble substances.1. Theoretical considerations of heat-transport control . *J Pharm Sci* 1985;74:124-127. doi:10.1002/jps.2600721204
6. Ahlneck C, Zografi G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int J Pharm* 1990;62:87-95. doi:10.1016/0378-5173(90)90221-o
7. Khankari RK, Grant DJ. Pharmacetical hydrates. *Thermochim Acta* 1995;248:61-79. doi:10.1016/0040-6031(94)01952-d
8. Kontny MJ, Mulski CA. Gelatin capsule brittleness as a function of relative humidity at room temperature. *Int J Pharm* 1989;54:79-85. doi:10.1016/0378-5173(89)90168-3
9. Badawy SIF, Gawronski AJ, Alvarez FJ. Application of sorption-desorption moisture transfer modeling to the study of chemical stabil-ity of a moisture sensitive drug product in different packaging con-figurations. *Int J Pharm* 2001;223:1-13. doi:10.1016/s0378-5173(01)00693-7
10. Waterman KC, Grest P, Macdonald BC. Relative humidity hysteresis in solid-state chemical reactivity: A pharmaceutical case study. *J Pharm Sci* 2012;101:610-615. doi:10.1002/jps.22789
11. Newman AW, Reutzel-edens SM, Zografi G. Characterization of the hygroscopic properties of

active pharmaceutical ingredients. *J Pharm Sci* 2008;97:1047-1059. doi:10.1002/jps.21033
12. Murikipudi V, Gupta P, Sihorkar V. Efficient thoroughput method for hygroscopicity classification of active pharmaceutical ingredients by water vapor sorption analysis. *Pharm Dev Technol* 2013;18:348-358. doi:10.3109/10837450.2011.618947
13. Reutzel-edens SM, Newman AW. *Polymorphism: in the Pharmaceutical Industry*. Chapter 9. Weinheim: Wiley-VCH; 2006:235–258.
14. Ahlneck C, Alderborn G. Moisture adsorption and tableting .I. effect on tensile strength and air permeability of the relative humidity during storage of tablets of three crystalline materials. *Int J Pharm* 1989;56:143-150. doi:10.1016/0378-5173(89)90007-0
15. Ahlneck C, Alderborn G. Moisture adsorption and tableting .II. the effect on volume reduction properties and tablet strength for some crystalline materials. *Int J Pharm* 1989;54:131-141. doi:10.1016/0378-5173(89)90332-3
16. Dalton CR, Hancock BC. Processing and storage effects on water vapor sorption by some model pharmaceutical solid dosage formula-tions. *Int J Pharm* 1997;156:143-151. doi:10.1016/s0378-5173(97)04983-1
17. Nyqvist H. Saturated salt solutions for maintaining specified relative humidities. *Int J Pharm Tech Prod Mfr* 1983;4:47-48.
18. Khankari RK, Law D, Grant DJ. Determination of water content in pharmaceutical hydrates by differential scanning calorimetry. *Int J Pharm* 1992;82:117-127. doi:10.1016/0378-5173(92)90080-l
19. Komatsu H, Yoshii K, Okada S. Application of thermogravimetry to water content determinations of drugs. *Chem Pharm* 1994;42:1631–1635. doi:10.1248/cpb.42.1631
20. Young JF. Humidity control in the laboratory using salt solutions. *J Appl Chem* 1967;17:241-245. doi:10.1002/jctb.5010170901