Sudarshan Publications

Available online at https://s-epub.in/index.php/trp/index

Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2022.v14.i01.pp1-8

MOISTURE SORPTION BEHAVIOUR OF HYGROSCOPIC EXCIPIENTS UNDER ACCELERATED STABILITY CONDITIONS

IOANNA KYRIAKOU[1]*, ELENA MARCHETTI[2], BAVO DUBOIS[3]

Affiliation

[1]Department of Pharmaceutics, Macedonia Plain Institute of Pharmacy, Serres, Greece
[2]Department of Pharmaceutical Technology, Valtellina Centre for Pharmacology, Sondrio, Italy
[3]Department of Pharmaceutics, Kempen Centre for Pharmaceutical Analysis, Geel, Belgium

*Corresponding author: Ioanna Kyriakou, i.kyriakou@mpip.gr
ORCID iD: Ioanna Kyriakou 0000-0001-0662-9385; Elena Marchetti 0000-0001-0501-8478; Bavo Dubois 0000-0001-3593-2922

Article info

Received date:23-10-2021
Accepted date:20-02-2022
Published date:29-05-2022
ISSN;0975-8216

Keywords:

Moisture sorption, Hygroscopic excipients, Accelerated stability, Water activity, Solid dosage forms

Abstract

Hygroscopic excipients take up water from the surrounding air, and the amount they hold at the humidity and temperature of accelerated stability testing can decide whether a solid dosage form stays acceptable. This short review brings together published work on how water is bound by excipients, how sorption isotherms are measured and modelled, how microcrystalline cellulose, lactose, polyols and polymers behave, and what moisture does to powder flow, compaction and drug stability. It reports no new experimental data. The literature agrees on the broad ranking of materials but is patchy on kinetics, temperature dependence and mixtures, and most isotherms are collected near 25 °C rather than at the 40 °C used in accelerated studies.

1. INTRODUCTION

Solid dosage forms are rarely dry. Even a tablet that looks inert on the bench exchanges water vapour with its surroundings, and the excipients, which usually make up most of the mass, do most of the exchanging [1, 2]. Accelerated stability conditions of 40 °C and 75% relative humidity, set out in the ICH guideline for new drug substances and products, push that exchange hard [3]. Stability programmes for hot and humid climatic zones adopt similarly severe storage conditions [4]. The logic is practical: such conditions compress months of ordinary storage into weeks of observation and expose weak formulations early [5]. The cost is that the outcome depends heavily on how each excipient in the blend responds to water.

Hygroscopicity is not a single property. Pharmacopoeial and industry schemes sort materials into broad classes by the mass

gained after storage at a fixed humidity, but a single weight gain figure says little about where the water sits or what it does [1, 6]. Water adsorbed on a surface, absorbed into an amorphous matrix, held as a crystal hydrate or dissolved in a deliquesced film behaves very differently towards a drug that is prone to hydrolysis [7, 8]. A useful picture of an excipient therefore needs the full isotherm, not one point on it, and some indication of how fast equilibrium is reached.

This short review gathers published work on the moisture sorption of widely used hygroscopic excipients, with attention to what happens at the temperature and humidity of accelerated testing. It covers the physical basis of uptake, the way isotherms are measured and fitted, the reported behaviour of cellulosic, sugar, polyol and polymer excipients, and the downstream effects on powder handling, compaction and chemical stability. It reports no new experimental measurements. Where the literature is thin, particularly on mixtures and on temperatures above 25 °C, the text says so rather than extrapolating.

Regulatory stability programmes treat humidity as a storage variable, yet formulators often meet it first as a manufacturing problem. Granules that cake in a humid suite, tablets that cap on the press and capsules that go soft in the bottle all trace back to the same sorption behaviour [9, 10]. Seeing the two views together helps explain why a product that passes release testing can drift out of specification at the six-month accelerated time point.

2. MECHANISMS OF MOISTURE UPTAKE

Zografi's classic account divides sorbed water into several states: tightly bound monolayer water at polar sites, loosely held multilayer water, and bulk-like condensed water in pores or amorphous regions [8]. For crystalline materials with no hydrate form, uptake below a critical relative humidity is essentially a surface effect and is small, often below a percent by weight [11]. Above that humidity a water-soluble crystal begins to dissolve in its own adsorbed film, which is deliquescence, and uptake rises steeply [12, 13]. Mixtures of water-soluble components can deliquesce at humidities well below that of either component alone, a point easily missed when excipients are screened one at a time.

Amorphous and partly disordered materials behave differently again. Their open, disordered structure lets water penetrate the bulk, so uptake scales with mass and not just surface area [14, 15]. The absorbed water acts as a plasticiser and lowers the glass transition temperature, sometimes by tens of degrees, so a solid that is glassy at 25 °C and 30% relative humidity may be rubbery at 40 °C and 75% [7, 14]. Once mobility rises, crystallisation can follow and the water is expelled, which shows as a loss in the desorption branch of the isotherm [16]. Spray-dried lactose and some freeze-dried bulking agents illustrate the pattern.

Hydrate formation is a third route. Some excipients and many drugs exist as stoichiometric hydrates whose water is part of the lattice and is lost or gained at defined humidities [17, 18]. Lactose monohydrate keeps its lattice water through ordinary storage, whereas anhydrous forms of lactose pick up water readily and convert, with a change in compaction behaviour [18, 19]. The distinction matters in practice because a hydrate that is stable at 25 °C may lose water at 40 °C when the surrounding vapour pressure is low, releasing it into the blend where a neighbouring ingredient can take it up.

Co-solutes and impurities complicate the simple picture. Residual salts, low-molecular-weight sugars and traces of acids lower the deliquescence point of an otherwise stable crystalline excipient, and a few tenths of a percent of such material can change the isotherm visibly at high humidity [11, 12]. This helps explain why different suppliers of nominally the same excipient give different results in a stability study. Pharmacopoeial monographs control identity and purity, but they seldom control sorption behaviour, and users often learn of the difference only when a batch behaves oddly at the 40 °C time points [6, 18].

Temperature enters twice. Sorption is exothermic, so equilibrium uptake at a given

relative humidity usually falls as temperature rises, yet the absolute water vapour pressure rises sharply, and so does the rate of every moisture-driven reaction [5, 20]. At 40 °C and 75% relative humidity the vapour pressure is more than twice that at 25 °C and the same relative humidity. An excipient may hold slightly less water at the higher temperature, but whatever it does hold is chemically far more active. This opposition is one reason why isotherms taken at room temperature predict accelerated behaviour only loosely [5, 17].

Desorption deserves a comment of its own. Water bound in micropores or within polymer chains leaves more slowly than it arrived, and a tablet moved from a humid chamber to a dry laboratory can keep a measurable fraction of its water for hours or days [7, 8]. The practical lesson is that the history of a sample, including the transport and handling between chamber and balance, may bias moisture results, so assay protocols should specify how long samples are exposed to room air before testing.

Particle size and surface area change the picture for kinetics more than for equilibrium. Fine, high-surface-area grades reach equilibrium within hours, while coarse granules and compacts may take days because water must diffuse through a tortuous pore network [10, 21]. Reported studies on tablets show that a compact can lag behind the loose powder it was made from by a wide margin, so a moisture content measured after a short exposure can be a poor guide to what the tablet will eventually hold.

3. ISOTHERMS AND MEASUREMENT

Three approaches dominate the literature. Saturated salt solutions in desiccators give fixed humidities that have been tabulated carefully, and they remain the reference method for long exposures [20, 22]. Gravimetric dynamic vapour sorption instruments step the humidity automatically and record mass continuously, which allows an entire isotherm from a few milligrams in a day [16, 21]. Thermogravimetry and Karl Fischer titration then give the absolute water content, and the two are often combined because loss on drying cannot distinguish water from other volatiles [6, 20]. Each method has blind spots, and the choice affects what a published isotherm means.

Fitting a model turns the curve into a few parameters. The Brunauer, Emmett and Teller equation estimates monolayer capacity and is reliable only over the lower part of the isotherm, roughly 5 to 35% relative humidity [23]. The Guggenheim, Anderson and de Boer extension, known as the GAB model, reaches up to about 90% and is the form most often used for food and pharmaceutical solids [24, 25]. Parameters from these fits allow comparisons between excipients, but they carry an uncertainty that is rarely reported. Two laboratories fitting the same data with different humidity windows can obtain monolayer values that differ appreciably.

Dynamic vapour sorption has also been used to quantify amorphous content, since the uptake of a partly amorphous crystalline powder shows a characteristic step as the disordered fraction crystallises and expels water [15, 16]. Detection limits in the low single-digit percent range have been reported, which is relevant because quite small amounts of disorder can dominate the early sorption of an otherwise crystalline excipient. The method needs care, as the humidity ramp, sample history and particle size all alter the transition, but it provides a sensitive link between processing, such as milling, and stability behaviour.

Classification schemes try to condense the isotherm into a label. The European Pharmacopoeia scheme assigns slightly hygroscopic, hygroscopic and very hygroscopic categories from weight gain after 24 hours at 80% relative humidity and 25 °C, while later proposals use dynamic vapour sorption to classify many materials in a single run [1, 21]. Such labels are useful for triage, but they were designed for drug substances. Applied to excipients they hide the difference between a material that reaches 10% water reversibly and one that reaches the same figure by irreversible deliquescence [1, 2].

Hysteresis between the sorption and desorption branches is informative and often ignored. A closed loop with a narrow gap suggests reversible surface and capillary processes, whereas a wide, persistent loop

points to structural change such as swelling of cellulose fibres, collapse of an amorphous matrix or conversion between hydrates [8, 9, 26]. Because accelerated studies run for months and the humidity of a real store fluctuates, the desorption branch may be the more relevant one for deciding how much water a product actually carries into its last months of shelf life [5, 7].

Practical reporting also deserves mention. Pre-drying a sample over desiccant or under vacuum sets the starting point for the isotherm, yet drying itself can alter hydrates or collapse amorphous regions, so published curves that start from different dry states are not strictly comparable [16, 20]. Sample mass matters too, because small samples in a dynamic vapour sorption pan respond faster than the bulk powder in a bottle. Workers who wish to apply isotherm data to packaging calculations are therefore advised to confirm key points with the saturated salt method on larger samples [22, 27].

Equilibrium is also less certain than it appears. Published protocols vary in the mass change per minute that counts as equilibrium, and slow sorbers can look finished when they are not. Differences in sample history, such as prior drying, milling or compaction, can shift an isotherm by an amount comparable to the differences between excipient grades, so direct comparison across papers needs care. A sensible habit is to read the methods section before the numbers, noting the temperature, the equilibrium criterion and whether the sample was dried first [16, 20].

4. BEHAVIOUR OF COMMON EXCIPIENTS

Published equilibrium moisture data for the main excipient families are collected in table 1 and grouped by chemical class in fig. 1. The Handbook of Pharmaceutical Excipients and the early compilation by Callahan and colleagues remain the usual starting points, and later dynamic vapour sorption work has confirmed their ranking while adding detail on kinetics [2, 18, 21]. Cellulosics, starches and synthetic polymers hold water mainly through hydrogen bonding to hydroxyl and amide groups. Sugars and polyols are mostly crystalline and take up little until a critical humidity is reached, with the exception of sorbitol, whose polymorph and purity strongly influence its behaviour.

Table 1: Reported moisture behaviour of common excipients

Excipient	Reported sorption behaviour	Ref.
Microcrystalline cellulose Cellulosic	Reversible uptake with hysteresis; water plasticises fibrils and alters flow and compactibility	[9, 10, 26]
Hypromellose Cellulose ether	Moderate uptake with little hysteresis; swelling polymer in matrix systems	[2, 18]
Lactose monohydrate Crystalline sugar	Low surface uptake to high humidity; lattice water retained in storage	[18, 19]
Spray-dried lactose Partly amorphous	Amorphous fraction absorbs water, may crystallise and release it to the blend	[14, 15, 16]
Mannitol Polyol	Crystalline forms remain essentially non-hygroscopic under ordinary conditions	[18, 28]
Sorbitol Polyol	More water-avid than mannitol; can liquefy at high humidity	[18, 19]
Povidone and crospovidone Synthetic polymer	Large uptake at high humidity; reduces glass transition temperature	[2, 7, 18]
Croscarmellose sodium Cross-linked cellulose	Swells and takes up water readily; may affect later disintegration	[2, 18]
Starch Native polysaccharide	Settles near ten to fifteen percent at ambient conditions, source dependent	[2, 28]
Colloidal silicon dioxide Inorganic	Adsorbs much water on silanol surface, weakly bound; can act as scavenger	[6, 18]

Microcrystalline cellulose is the best studied. It adsorbs water reversibly, typically reaching several percent by weight at 50% relative humidity and appreciably more at 75%, with measurable hysteresis [9, 26]. The water acts as a plasticiser between cellulose fibrils, improving compactibility up to a point and then weakening the tablet, and it changes powder flow, with cohesion rising as the surface water layer thickens [9, 10]. Sun reported that true density and compaction properties of the material vary with moisture

in a way that tracks the water held in the amorphous regions [26]. Grades differ in particle size and crystallinity, so the numbers are not interchangeable [29].

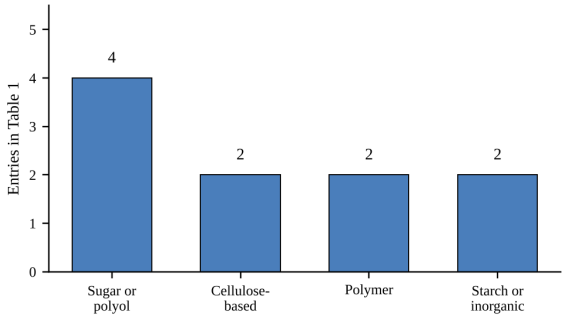


Fig. 1: Number of excipients in table 1 by chemical class

Moisture-driven flow problems show up long before chemical ones. Cohesion rises with surface water because liquid bridges form between particles, and powder flow through hoppers and feed frames deteriorates in a manner that has been measured with shear cells for several excipients [9, 10]. Fine lactose grades and MCC with small particle size are the most affected, and glidants such as colloidal silica recover only part of the loss. Anyone interpreting a stability failure in a tablet batch should consider whether the press had a flow problem on the day of compression [10, 29].

Hygroscopic behaviour also depends on the form in which the excipient is supplied. Co-processed products, such as cellulose combined with lactose or silicified cellulose, are marketed for better flow and compaction, and their sorption is not a weighted average of the parts, because the intimate association changes the accessible surface and the proportion of disordered material [18, 29]. Granulated and spray-dried grades of the same chemical often show distinct isotherms from their milled counterparts. For this reason a grade-specific isotherm is worth more than a monograph value when a formulation is being designed for hot, humid markets [4, 21].

Among sugars, lactose monohydrate is the benchmark of low hygroscopicity. Its crystalline lattice takes up very little surface water up to high humidity, which is part of its popularity as a diluent [18, 19]. Problems arise from its amorphous content. Even a small fraction of disordered lactose, produced by milling or spray drying, absorbs water quickly and can crystallise on storage, releasing heat and water to the blend [14, 15, 16]. Mannitol is similarly stable and non-hygroscopic in its crystalline forms, whereas sorbitol and xylitol are noticeably more water-avid and can liquefy at high humidity [18, 19, 28].

Polymeric binders and disintegrants show the largest and most variable uptake. Povidone and crospovidone can hold more than a quarter of their weight in water at high humidity, and croscarmellose sodium and sodium starch glycolate swell and take up water readily [2, 18]. Hypromellose grades sorb moderately and with relatively little hysteresis, and starches settle at roughly ten to fifteen percent at ambient conditions, depending on source [2, 18, 28]. A tablet disintegrant that has already absorbed its fill from the atmosphere in the bottle may disintegrate more slowly, a link rarely tested directly under accelerated storage.

Inorganic and lubricant excipients are often overlooked. Colloidal silicon dioxide adsorbs substantial water on its silanol surface yet binds it weakly, and in some formulations it serves as a moisture scavenger that draws water away from a labile drug [6, 18]. Magnesium stearate exists in several hydrate forms, and its water content and the hydrate present depend on the supplier and the history of the batch [18]. Because it is used at low levels its sorption is small in absolute terms, but its hydrophobic film can slow water uptake by the surrounding material.

5. CONSEQUENCES FOR FORMULATION STABILITY

The chemical effects of sorbed water follow from the work of Ahlneck and Zografi, who argued that moisture raises molecular mobility and acts as solvent, reactant and plasticiser [17]. Hydrolysis of esters, amides and lactams is the obvious consequence, but moisture also speeds oxidation, Maillard reactions between amines and reducing sugars, and some solid-state transformations [5, 7, 30]. A key point from that literature is that total water content is a poor predictor. Water activity, the effective availability of the

water, correlates better with degradation rate, and two blends with the same percent moisture can behave quite differently [7, 20].

Excipients influence this by competing for water. In a blend, the more hygroscopic component acts as a sink, and the drug's local water activity reflects the combined equilibrium of everything in the tablet [7, 27]. This can protect a labile drug, as when starch or silica draw water away, or it can harm it, as when a polymer pre-loaded with water releases it at the higher temperature of accelerated testing. Both outcomes appear in the compatibility literature, which is why a binary screen at 40 °C and 75% relative humidity is a standard first test and why its findings are never universal [5, 30].

Physical properties change in parallel. Moisture reduces the glass transition temperature of amorphous polymeric components, and soft films of coating polymer may become tacky or permeable [7, 14]. Tablet hardness can rise or fall with moisture depending on whether water forms bridges between particles or weakens them, and friability and disintegration time shift accordingly [9, 28]. Dissolution is less consistently affected, but reports describe slower release from matrix tablets when swelling polymers have already hydrated and from tablets in which a hard crust has formed by partial dissolution and recrystallisation of a soluble component [2, 26].

Interactions between the drug and the excipient surface add a further layer. Polymers with basic or acidic groups can raise or lower the microenvironmental pH of the adsorbed water film, and so change the rate at which a pH-sensitive drug degrades even when total moisture is low [5, 17]. Reducing sugars such as lactose react with primary and secondary amines through the Maillard route, a reaction that needs only traces of water to proceed and is clearly accelerated at 40 °C [7, 30]. Case reports of discoloured tablets in warm, humid stores are consistent with this mechanism, although the individual drug and the grade of lactose both matter [5, 18].

Study design for accelerated programmes can build on these observations. Placing excipient blends and placebo tablets in the same chamber as the drug product helps separate water effects from chemical ones, and monitoring water content or activity over time, not only potency, shows whether the formulation is simply equilibrating or continuing to drift [5, 30]. Open-dish exposure is useful as a worst case, but the packaged product is the true test of the system, because the pack, rather than the tablet, then controls the rate of ingress [4, 27]. Interpreting accelerated data in this way avoids over-reacting to changes that reflect a simple equilibrium.

Packaging is the formulator's principal control. High-density polyethylene bottles, aluminium blisters and desiccant canisters trade off protection against cost, and Waterman and MacDonald showed that package selection can be modelled from the product isotherm, the permeability of the container and the humidity of the market [27]. The same approach shows why a pack that is adequate at 25 °C and 60% relative humidity may be inadequate under accelerated conditions, where the driving force for ingress is much higher [4, 5, 27]. Designing the formulation and the pack together, rather than in sequence, is generally the more economical route.

6. LIMITATIONS AND FUTURE DIRECTIONS

Several gaps stand out. Most published isotherms were collected near 25 °C, and relatively few report sorption at 40 °C, the temperature actually used for accelerated testing [5, 17, 20]. Data on mixtures are sparse, which is awkward because tablets contain several hygroscopic components that compete for water, and additive models can mispredict the result where deliquescence or hydrate formation intervenes [12, 13]. Reported kinetics are often given without grade, particle size or sample history, limiting reuse. The literature also leans on a small number of well-known excipients, with little on newer co-processed materials.

Better practice is within reach. Authors could report temperature, drying history, equilibrium criteria and fitting range alongside every isotherm, and journals could ask for them [16, 20]. Water activity

measurements on real blends at the accelerated condition would give formulators a direct predictor [7]. Combining dynamic vapour sorption with solid-state methods such as X-ray diffraction would show whether sorbed water is accompanied by structural change [15, 16]. Until such data accumulate, accelerated stability results for hygroscopic excipients are best read as informative stress tests and not as quantitative predictions of shelf life [3, 4, 5].

7. CONCLUSION

Hygroscopic excipients do not all respond to humid heat in the same way, and the published evidence helps explain why. Crystalline sugars and polyols hold little water until a critical humidity is passed, polymers and cellulosics take up water steadily and reversibly, and amorphous fractions behave as small reservoirs that can release water on crystallising [2, 14, 18]. The way that water is held, and its activity, count for more than the total percentage found by loss on drying [7, 17, 20].

For practice, formulators should obtain isotherms for each excipient grade at both 25 °C and 40 °C, test mixtures as well as single materials, and choose packaging with the isotherm in hand [5, 21, 27]. Accelerated results then become a more reliable guide to what will happen in the market pack. More systematic reporting of method, sample history and temperature would make the existing literature considerably easier to use [3, 4, 16, 30]. The case for mixture data and for sorption measurements at the temperature of testing is strong.

8. ABBREVIATIONS

DVS-Dynamic vapour sorption, GAB-Guggenheim, Anderson and de Boer, BET-Brunauer, Emmett and Teller, ICH-International Council for Harmonisation, RH-Relative humidity, HDPE-High-density polyethylene, MCC-Microcrystalline cellulose

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

1. Newman AW, Reutzel-Edens SM, Zografi G. Characterization of the 'hygroscopic' properties of active pharmaceutical ingredients. J Pharm Sci 2008;97:1047–59.
2. Callahan JC, Cleary GW, Elefant M, Kaplan G, Kensler T, Nash RA. Equilibrium moisture content of pharmaceutical excipients. Drug Dev Ind Pharm 1982;8:355–69.
3. Grimm W. Extension of the International Conference on Harmonisation tripartite guidelines for stability testing of new drug substances and products to countries of climatic zones III and IV. Drug Dev Ind Pharm 1998;24:313–25.
4. Kommanaboyina B, Rhodes CT. Trends in stability testing, with emphasis on stability during distribution and storage. Drug Dev Ind Pharm 1999;25:857–68.
5. Waterman KC, Adami RC. Accelerated aging: prediction of chemical stability of pharmaceuticals. Int J Pharm 2005;293:101–25.
6. United States Pharmacopeial Convention. General chapter 1241 Water-solid interactions in pharmaceutical systems. In: United States Pharmacopeia. Rockville: USP; 2012.
7. Airaksinen S, Karjalainen M, Shevchenko A, Westermarck S, Leppänen E, Rantanen J, *et al.* Role of water in the physical stability of solid dosage formulations. J Pharm Sci 2005;94:2147–65.
8. Zografi G. States of water associated with solids. Drug Dev Ind Pharm 1988;14:1905–26.
9. Amidon GE, Houghton ME. The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. Pharm Res 1995;12:923–9.
10. Crouter A, Briens L. The effect of moisture on the flowability of pharmaceutical excipients. AAPS PharmSciTech 2014;15:65–74.
11. Kontny MJ, Grandolfi GP, Zografi G. Water vapor sorption of water-soluble substances: studies of crystalline solids below their critical relative humidities. Pharm Res 1987;4:104–12.
12. Mauer LJ, Taylor LS. Water-solids interactions: deliquescence. Annu Rev Food Sci Technol 2010;1:41–63.

13. Burnett DJ, Thielmann F, Booth J. Determining the critical relative humidity for moisture-induced phase transitions. Int J Pharm 2004;287:123–33.
14. Craig DQM, Royall PG, Kett VL, Hopton ML. The relevance of the amorphous state to pharmaceutical dosage forms: glassy drugs and freeze dried systems. Int J Pharm 1999;179:179–207.
15. Buckton G, Darcy P. Assessment of disorder in crystalline powders: a review of analytical techniques and their application. Int J Pharm 1999;179:141–58.
16. Sheokand S, Modi SR, Bansal AK. Dynamic vapor sorption as a tool for characterization and quantification of amorphous content in predominantly crystalline materials. J Pharm Sci 2014;103:3364–76.
17. 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.
18. Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of Pharmaceutical Excipients. 6th ed. London: Pharmaceutical Press; 2009.
19. Hancock BC, Shamblin SL. Water vapour sorption by pharmaceutical sugars. Pharm Sci Technol Today 1998;1:345–51.
20. Bell LN, Labuza TP. Moisture Sorption: Practical Aspects of Isotherm Measurement and Use. 2nd ed. St Paul: American Association of Cereal Chemists; 2000.
21. Murikipudi V, Gupta P, Sihorkar V. Efficient throughput method for hygroscopicity classification of an active and inactive pharmaceutical ingredients by water vapor sorption analysis. Pharm Dev Technol 2013;18:348–58.
22. Greenspan L. Humidity fixed points of binary saturated aqueous solutions. J Res Natl Bur Stand A 1977;81A:89–96.
23. Brunauer S, Emmett PH, Teller E. Adsorption of gases in multimolecular layers. J Am Chem Soc 1938;60:309–19.
24. Van den Berg C, Bruin S. Water activity and its estimation in food systems: theoretical aspects. In: Rockland LB, Stewart GF, editors. Water Activity: Influences on Food Quality. New York: Academic Press; 1981. p. 1–61.
25. Anderson RB. Modifications of the Brunauer, Emmett and Teller equation. J Am Chem Soc 1946;68:686–91.
26. Sun C. Mechanism of moisture induced variations in true density and compaction properties of microcrystalline cellulose. Int J Pharm 2008;346:93–101.
27. Waterman KC, MacDonald BC. Package selection for moisture protection for solid, oral drug products. J Pharm Sci 2010;99:4437–52.
28. Zhang Y, Law Y, Chakrabarti S. Physical properties and compact analysis of commonly used direct compression binders. AAPS PharmSciTech 2003;4:Article 62.
29. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment: a review. Int J Pharm 2014;473:64–72.
30. Carstensen JT, Rhodes CT, editors. Drug Stability: Principles and Practices. 3rd ed. New York: Marcel Dekker; 2000.