ORIGINAL ARTICLE

Hygroscopicity Categorization of Pharmaceutical Solids by Gravimetric Sorption Analysis: A Systematic Approach

Ravikiran Allada, Arthanareeswari Maruthapillai, Kamaraj Palanisamy, Praveen Chappa

Department of Chemistry, SRM University, Kattankulathur, Kanchipuram, Tamil Nadu, India

Abstract

Context: Hygroscopicity is the ability of a material to absorb or adsorb moisture from surrounding environment. Hygroscopicity of pharmaceutical solids is often evaluated due to the fact that the up-taken moisture can impact physical and chemical stability of the pharmaceutical products. In pharmaceutical industry, the most commonly used conventional method for hygroscopicity is as per the European Pharmacopeia (Ph. Eur.). The Ph. Eur. method relies on equilibrium for 24 h at 25°C – 80% relative humidity and it does not take the initial moisture content of the material into consideration, but the initial moisture content is critical in interpreting the hygroscopicity of any material. **Aim:** In this current work, we emphasize the necessity of sample pretreatment, by which the sample achieves a dry reference initial state, which plays an important role in deriving calculations required for accurate interpretation, and thereby right hygroscopicity categorization. **Materials and Methods:** The proof-of-concept experiments were performed on seven pharmaceutical solids (four antihypertensive drugs and three commonly used excipients). The studies are conducted using gravimetric sorption analyzer, an instrument, which is capable of controlling humidity and measuring weights accurately. Each of the pharmaceutical solid was subjected to the pretreatment followed by equilibrating at 25°C – 80% RH. Separately, the seven pharmaceutical solids were evaluated using conventional Ph. Eur. Method, and the results from both approaches are compared. **Results:** The results show that the proposed method not only enables higher throughput but also gives a more accurate interpretation when compared with that of Ph. Eur. method. **Conclusion:** Finally, we present a systematic approach to examine samples to establish the right hygroscopicity categorization of pharmaceutical solids.

Key words: Drugs, European pharmacopeia, excipients, hygroscopicity, pharmaceutical, relative humidity

INTRODUCTION

Hygroscopicity is a physicochemical property and it can be described as the ability of a material to take up moisture from surrounding atmosphere. In other words, hygroscopicity is a measure of interaction between water and a material. Often, this property is measured at a constant temperature with variations in relative humidity (RH).[1-4] The extent of ability to take up moisture may vary depending on the material under study.[5] In fact, hygroscopicity is one of the critical material attributes as per quality by design terminology.[6] Hence, it turns out to be essential to to conduct experiments to describe how much hygroscopic a given material is. However, it is important to ensure that the solid-state of the sample does not undergo any transformation, during the experiment, so that the property of hygroscopicity is particular to the solid-state of that material only and not of a different solid-state occurred after moisture sorption.[7-10] It is well-known that the water content of solid drug substance and excipients, individually and when formulated in pharmaceutical dosage forms, is an important parameter that should be monitored throughout the process of drug product development.[11-15]

In recent years, hygroscopicity has become one of the most important criteria in selecting solid form of a drug substance

Address for correspondence:
Ravikiran Allada, Department of Chemistry, SRM University, Kattankulathur, Kanchipuram - 603 203, Tamil Nadu, India. Phone: +91-8884744099.
E-mail: ravianalytical@gmail.com

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for development. Moisture sorption data are frequently used even during initial salt screening process; This is because the sorption data is useful to identify solid forms with "adequate" stability.[16-20] The moisture sorption analysis is usually performed early in development to find out material handling requirements and the need for drug substance potency calculations in assay methods that principally depend on the error that can be tolerated in the analytical result, during weighing of standards, due to the sorbed water.[21] If a particular drug substance is known to be sensitive to moisture, the sorption data of constituent excipients becomes crucial; the vapor sorption data may also be used to guide excipient selection, to define operational and procedural conditions that ensure both physical and chemical stability or to identify suitable packaging requirements that control moisture permeation into the drug product.[22-25]

A conventional and simple method, for determining degree of hygroscopicity, is prescribed in European Pharmacopeia (Ph. Eur.).[26] Moreover, this is the most widely used in the pharmaceutical industry, due to its ease and cost effectiveness when compared with advanced methods. As per the Ph. Eur., there are total four categories of hygroscopicity: Non-hygroscopic, slightly hygroscopic, moderately hygroscopic, and very hygroscopic as shown in Table 1. The Ph. Eur. method categorization relies on the amount of weight gain, when a material is equilibrated at 25°C ± 1°C and 80% ± 2% RH for 24 h. Although the Ph. Eur. method is a simple tool to evaluate many of the pharmaceutical solids, it has many limitations as the chosen RH value: 80% may not be suitable to all pharmaceutical solid selected, many anhydrous solid forms might transform to hydrated state with changes in crystal lattice there by solid form.[27,28] More importantly, the Ph. Eur. method does not prescribe any sample pretreatment and the study starts with some amount of moisture already present with the material being studied, because the initial weighing happens in laboratory environment which is usually maintained at about 60% RH. Due to the initial moisture, for any given material, the amount of weight gain as Ph. Eur. method will be always lesser than the maximum amount of moisture that the materials can up-take when exposed to 25°C - 80% RH right from its dried state. Thus, the result of Ph. Eur. method depends on the initial weight, which is vulnerable to undergo changes due to the varying laboratory RH. Thereby, the interpretation or categorization as per Ph. Eur. Method may change depending on laboratory RH at the time of analysis.

The aim of the present work is to provide a systematic approach to categorize materials based on their hygroscopicity. A comparative evaluation is given, demonstrating how the proposed approach can overcome the problems associated with Ph. Eur. method. In this work, we used a highly sensitive gravimetric sorption analyzer (GSA), which comprises ultra-sensitive thermo-balance, precise and accurate humidity control chamber, and a reliable auto-sampler.[29] This advanced instrument generally requires only few milligram quantities of sample and is, therefore, very useful for early solid form screening studies wherein the availability of drug substance is very limited. In this GSA, the sample is placed on a microbalance, and then exposed to a continuous flow of humidified air or nitrogen of a pre-determined RH, and the weight is continually measured *in situ*.[30] The methodology used in this work: Each sample, under the study, is subjected to a pre-treatment step before it is actually subjected to 25°C – 80% RH, the desired condition. During the pre-treatment step, the material is kept in suitable drying conditions like 40°C – 0% RH until it reaches a stable weight. A separate evaluation is done to ensure that the pre-treatment step does not result in change in solid form. The proposed GSA methodology is applied to study four anti-hypertensive drugs, namely, valsartan [Figure 1], acetazolamide [Figure 2], olmesartan medoxomil [Figure 3], and carvedilol phosphate [Figure 4] and the three commonly used excipients (microcrystalline cellulose [MCC], hydroxypropyl methyl cellulose [HPMC], and croscarmellose sodium [CCS]). The same materials (the four APIs and three excipients) are also studied as per Ph. Eur. method. The results and time taken for the study are compiled.

MATERIALS AND METHODS

Materials

The chosen active pharmaceutical ingredients (APIs) - valsartan [Figure 1], acetazolamide [Figure 2],

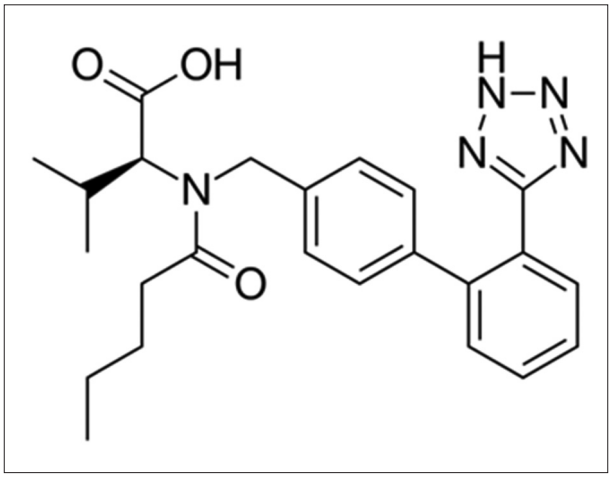

Figure 1: Molecular structure of valsartan. Molecular formula: $C_{24}H_{29}N_6O_3$, Molecular mass: 435.5 g/mol

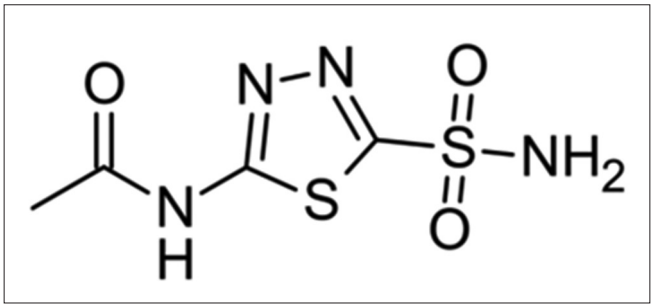

Figure 2: Molecular structure of acetazolamide. Molecular formula: $C_4H_6N_6O_3S_2$, Molecular mass: 222.2 g/mol

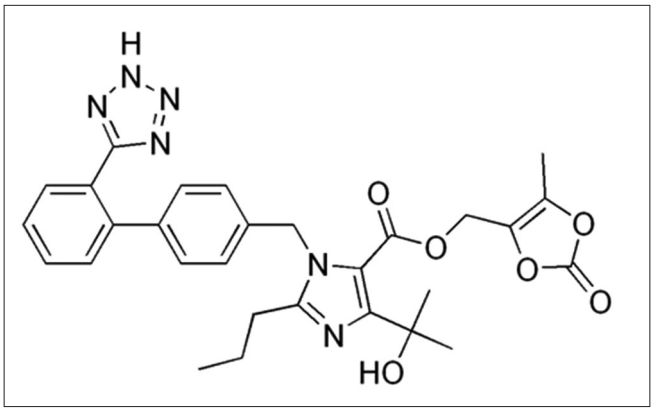

Figure 3: Molecular structure of olmesartan medoxomil. Molecular formula: $C_{29}H_{30}N_6O_6$, Molecular mass: 558.6 g/mol

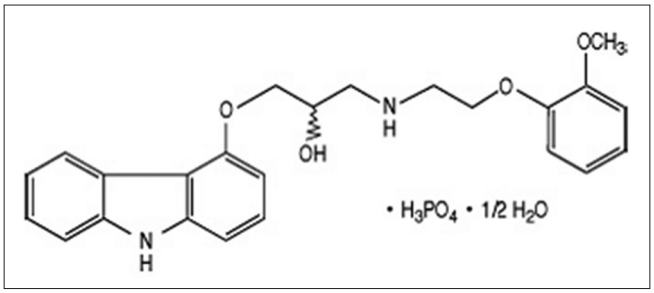

Figure 4: Molecular structure of carvedilol phosphate. Molecular formula: $C_{24}H_{26}N_2O_4 \bullet H_3PO_4 \bullet ½\ H_2O$, Molecular mass: 513.5 g/mol

olmesartan medoxomil [Figure 3], and carvedilol phosphate [Figure 4] are the gift samples from"Pharma Train," Hyderabad, India. The chosen excipients, Avicel® PH102- a particular grade of MCC, HPMC and CCS are procured from Sigma-Aldrich and used as obtained. The choice of the APIs for this study was done in order to exemplify compounds varying in their hygroscopicity. Further, the excipients were carefully chosen to represent commonly used excipients used for preparing solid dosage forms. For example, binding agent, diluent, bulking agent, anticaking agent, disintegrant and emulsifier chip resisting agent, and superdisintegrant. It was ensured that the certificates of analysis of the materials used, contain very minimum (within ICH limits) of residual solvents, and all the weight losses during pretreatment were only due to moisture or water present. General "Loss on drying" (LOD) values of the above said excipients - MCC, HPMC and CCS are readily available as ≤7.0%, ≤5.0% and ≤10.0%, respectively, the values were obtained from handbook of excipients.[31-33] The LOD values further emphasizes the need of sample pretreatment.

Methods

Hygroscopicity assessment by gravimetric sorption analysis (GSA) method

Q5000 SA GSA (TA Instruments, USA) has been used for this purpose. The instrument used was calibrated for accurate weight measurements and humidity creation. Samples were subjected to pre-designed instrument method program, and responses were gravimetrically measured. Each method program was designed in such a way that each sample undergoes three steps, those are: (Step I) Equilibration at 25°C – 60% RH, (Step II) pre-treatment step (drying at 40°C – 0% RH and (Step III) Equilibration 25°C – 80% RH. The purpose of Step I is to equilibrate the sample in the usual long tern condition as per ICH. Step II is the pretreatment condition chosen for drug substances is 40°C – 0% RH until it attains a stable weight, which is considered as a reference weight for initial dry state. Moreover, finally Step III is the measurement criterion equivalent to that of Ph. Eur. method. It was ensured that the pretreatment condition (Step II) was not compromised on the solid state being measured and this was done using powder X-ray diffraction (PXRD) studies. Detailed results and discussion of the PXRD studies is beyond the scope of this article. Initial weight loss during pretreatment step was calculated using Equation 1. Total weight gain (Sorption from its dried state) of each material was calculated using Equation 2.

$$W_{PT} = \frac{W_i - W_{min}}{W_i} \times 100 \quad (1)$$

Where,
W_{PT}=Weight loss during pre-treatment step
W_i=Initial weight of the material
W_{min}=Minimum weight that was attained, during drying, in the pre-treatment step.

$$W_{GSA} = \frac{W_{max} - W_{min}}{W_{min}} \times 100 \quad (2)$$

Where,
W_{total}=Total weight gain using GSA approach
W_{min}=Minimum weight that was attained, during drying, in the pre-treatment step.
W_{max}=Maximum weight that was attained, during sorption step, at 25°C-80% RH.

$$W_{Ph.\ Eur.} = \frac{W_2 - W_1}{W_1} \times 100 \quad (3)$$

Where,
$W_{Ph.\ Eur}$=Total weight gain using Ph. Eur. method.
W_1=Initial weight of the material, before loading into desiccator (containing well of the salt solution, to maintain 80% RH)
W_2=Weight of the sample after exposing to 25°C–80% RH, in the desiccators per Ph. Eur.

Hygroscopicity categorization as per Ph. Eur.

In this method, moisture sorption has been measured gravimetrically by placing a pre-weighed material in a closed desiccator, which contains a well filled with saturated

solution of ammonium chloride salt.[34] A calibrated thermohygrometer is placed inside desiccator for monitoring temperature and humidity. About 300-500 mg of each sample quantity is transferred into dry Petri-dish and kept in the desiccator maintained at 25°C–80% RH. After keeping for 24 h, the samples were removed from the desiccator, and the final weight of each sample was determined with the help of a calibrated balance.The percentage weight gain of each sample was calculated using Equation 3.

RESULTS

GSA

The GSA method results of the drugs and three excipients are compiled in Tables 2 and 3, respectively. Figures 5-11 depict the GSA graphs of the pharmaceutical solids that were studied: Valsartan, acetazolamide, olmesartan medoxomil, carvedilol phosphate, MCC, HPMC and CCS. The graphs indicate that the curve shape of each event (adsorption/desorption) is very much specific to the material being

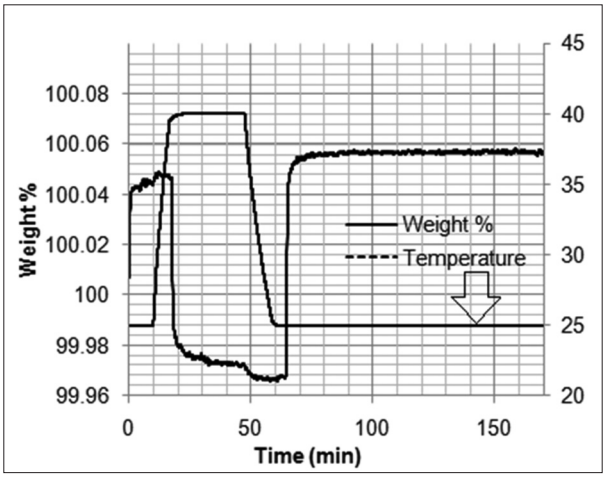

Figure 7: Gravimetric sorption analyzer study graph of olmesartan medoxomil

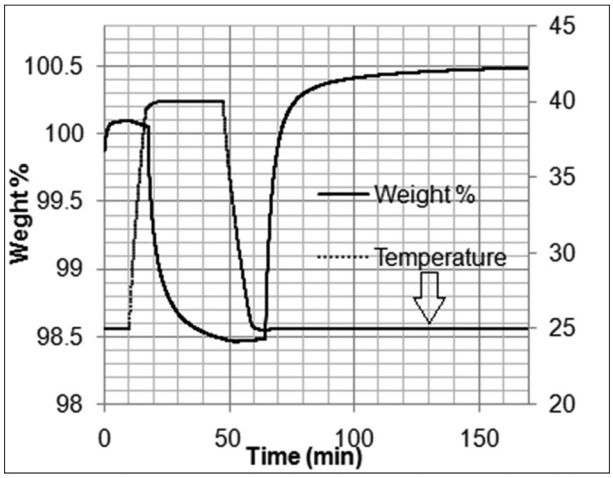

Figure 5: Gravimetric sorption analyzer study graph of valsartan

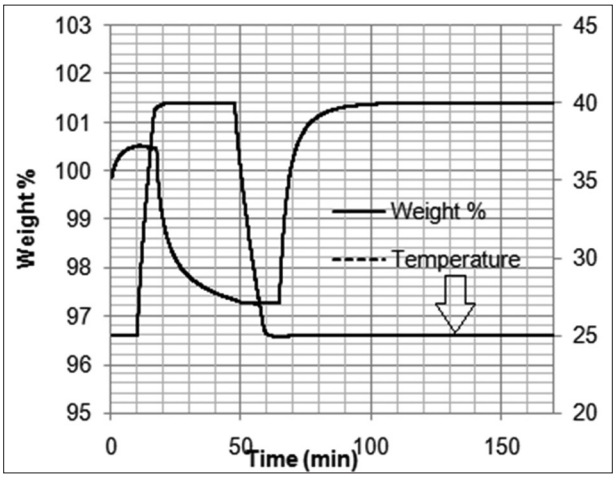

Figure 8: Gravimetric sorption analyzer study graph of carvedilol phosphate

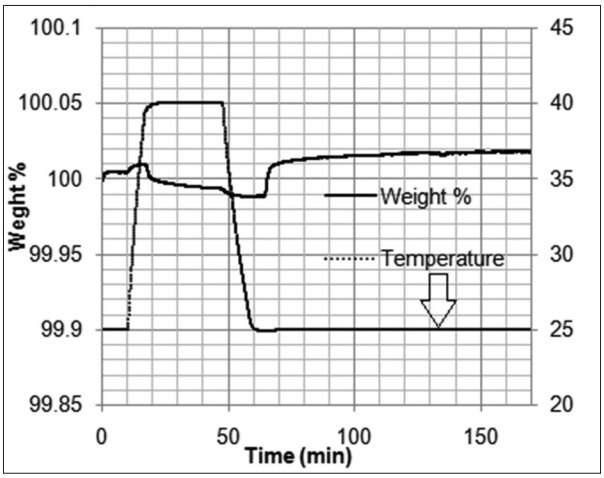

Figure 6: Gravimetric sorption analyzer study graph of acetazolamide

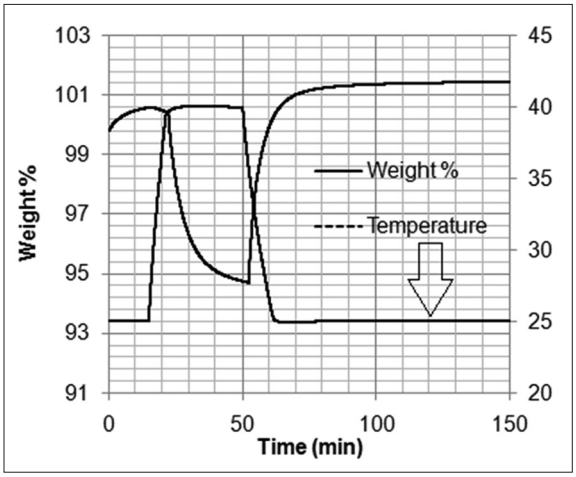

Figure 9: Gravimetric sorption analyzer study graph of microcrystalline cellulose

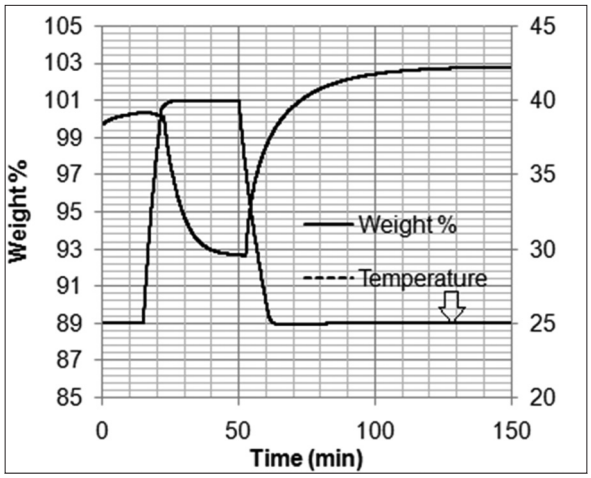

Figure 10: Gravimetric sorption analyzer study graph of hydroxypropyl methyl cellulose

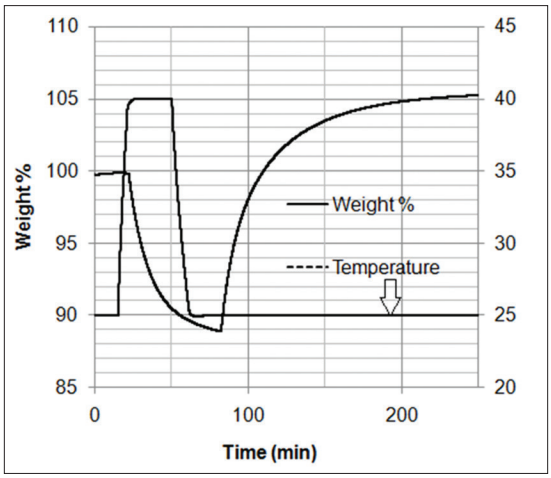

Figure 11: Gravimetric sorption analyzer study graph of croscarmellose sodium

Table 1: Categorization/classification as per Ph. Eur. method

Material category	Criteria as per Ph. Eur.*
NH	0-0.012% w/w
SH	0.2-2% w/w
MH	2-15% w/w
VH	More than 15% w/w

*Weight gain due to moisture sorption at 25°C-80% RH.
Ph. Eur.: European Pharmacopeia, RH: Relative humidity, NH: Non-hygroscopic, SH: Slightly hygroscopic, MH: Moderately hygroscopic, VH: Very hygroscopic

studied. The pre-treatment step time for each of the API and excipient was about 60 and 50 min, respectively; this was done till the material achieved relatively stable weight, which was considered the end of pre-treatment step. The pre-treatment step weight loss values were compiled in Tables 2 (drugs) and 3 (excipients). The subsequent sorption steps weight gain values were also compiled in Tables 2 (drugs) and 3 (excipients). Looking at the pre-treatment weight losses and weight gain at sorption step, it is clearly evident that the pre-treatment step weight loss is very significant when compared with total weight gain, thereby in categorization. In other words, all the materials studied have lost moisture significantly during pre-treatment step. Based on the total weight gain, each material is categorized as per the nomenclature and criteria as represented in Table 1. Category of each the material determined with this method and is compiled in Tables 2 and 3.

Ph. Eur. method

The results as per Ph. Eur. method for the drugs and three excipients are compiled in Tables 2 and 3, respectively. The weight gain values for the materials studied were obtained using Equation 2. The hygrometer readings have shown that the 25°C-80% RH is well maintained. Based on the total weight gain each material is categorized as per the nomenclature and criteria as represented in Table 1. Category of each material, determined with this method, is compiled in Tables 2 (drugs) and 3 (excipients).

DISCUSSION

Comparative evaluation

The results of hygroscopicity classification of four drugs, and three excipients determined by both sorption analysis and Ph. Eur. method are compiled in Tables 2 and 3, respectively. These results do not correlate each other. This is because the EP method only considers the percentage of increase in mass occurring on storage at 25°C and 80% RH for 24 h and has it included the initial moisture content. The results may, therefore, depend profoundly on the thermal history (W1) of the material, and there lies a possibility for a material being categorized at different class of hygroscopicity under differ experimental conditions. In contrast, the proposed method has a pre-treatment step, using which it is clearly ensured that the results are independent of initial moisture of the material. Looking at the weight gain results [Tables 2 and 3] from both the methods, it is clearly evident that the weight gain values obtained using Ph. Eur. method are always lesser than that of proposed methodology, in other words, the Ph. Eur. method under reports the weight gain values. The same observation is represented graphically in Figure 12. Ph. Eur. method relies on 24 h equilibration time. On the other side, the study as per proposed method can be completed in maximum of 3-4 h [Tables 2 and 3] for time taken as per proposed method for different materials studied.

CONCLUSIONS

In the introduction, we have highlighted the importance of understanding hygroscopicity nature of a material,

Table 2: Hygroscopicity categorization of the four drugs by proposed method and Ph. Eur. method

Drug substance	%Weight loss during pre-treatment (W_{PT})	%Weight gain as per proposed method (W_{GSA})	Category as per proposed method	Time taken for proposed method (about)	%Weight gain as per Ph. Eur. method ($W_{Ph. Eur.}$)	Category as per Ph. Eur. method
Valsartan	1.4	2.1	MH	175 min	1.5	SH
Acetazolamide	0.0	0.0	NH	175 min	0.0	NH
Olmisartan medoxomil	0.1	0.1	NH	175 min	0.0	NH
Carvedilol Phosphate	3.2	4.3	MH	175 min	1.8	SH

Ph. Eur.: European Pharmacopeia, NH: Non-hygroscopic, SH: Slightly hygroscopic, MH: Moderately hygroscopic

Table 3: Hygroscopicity categorization of the three excipients by proposed method and Ph. Eur. method

Excipient	%Weight loss during pre-treatment (W_{PT})	%Weight gain as per proposed method (W_{GSA})	Category as per proposed method	Time taken for Proposed method (about)	%Weight gain as per Ph. Eur. method ($W_{Ph. Eur.}$)	Category as per Ph. Eur. method
MCC	5.2	7.1	MH	150 min	2.3	MH
HPMC	7.1	11.0	MH	150 min	4.2	MH
CCS	10.9	18.5	VH	250 min	9.6	VH

Ph. Eur.: European Pharmacopeia, NH: Non-hygroscopic, MH: Moderately hygroscopic, MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methyl cellulose, CCS: Croscarmellose sodium

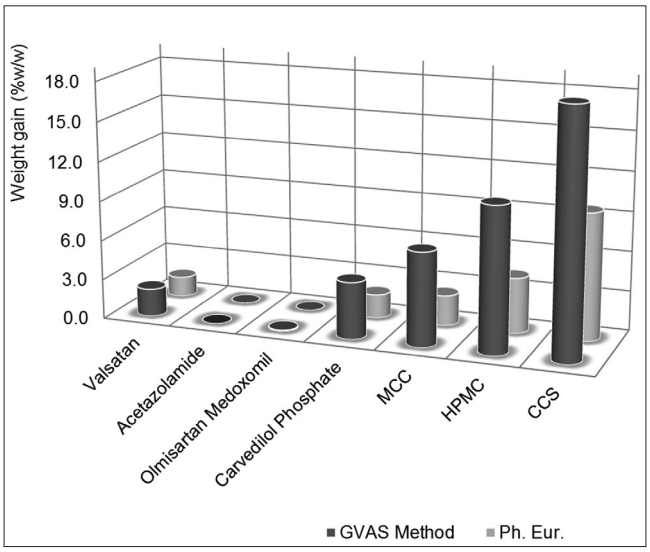

Figure 12: Comparative evaluation of gravimetric sorption analyzer (GSA) and European Pharmacopeia (Ph. Eur) methods. Total weight gain of each the material using GSA and Ph. Eur. methods are represented as cylinder shape with black and grey colours, respectively

particularly in the pharmaceutical industry. Furthermore, we discussed about limitations of most widely used Ph. Eur. method for determination of hygroscopicity. Experiments were conducted on four selectedAPIs and three excipients, to determine their hygroscopicity using Ph. Eur. method and with the proposed systematic GSA method. Given emphasis on "pre-treatment step," an integral part of the proposed GSA method, it was demonstrated that how this method could make possible accurate interpretation of hygroscopic nature of a material, thereby appropriate categorization. A comparative evaluation has been put forwarded and discussed how the Ph. Eur. method has under-reported degree of hygroscopicity of the substances evaluated. Alongside accurate interpretation, the GSA method analysis time is based on in-situ data, and so is very less when comparison with Ph. Eur. method (24 h). The sorption analysis curves provide real-time information about sample changes. Hence, the proposed methodology is very useful, accurate, and reproducible. With minimum efforts to optimize pre-treatment step, this methodology can be applied to all pharmaceutical solids. This systematic approach is more helpful even in the case of early stages of drug development, wherein sample quantity is often very limited. On tops of the method's advantages like less sample quantity and rapid, it also provides most realistic interpretation and categorization; this is useful for experimental design or operations conditions design as per the pharmaceutical solids' hygroscopicity.

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