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Moisture Sorption by Polymeric Excipients Commonly Used in Amorphous Solid Dispersions and its Effect on Glass Transition Temperature: II. Cellulosic Polymers

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A B S T R A C T

Moisture sorption by polymeric carriers used for the development of amorphous solid dispersions (ASDs) plays a critical role in the physical stability of dispersed drugs since moisture may decrease glass transition temperature (T_g) and thereby increase molecular mobility of drugs leading to their crystallization. To assist the selection of appropriate polymers for ASDs, we conducted moisture sorption by five types of cellulosic polymers, namely, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), and ethyl cellulose (EC), as functions of relative humidity (10 to 90% RH) and temperature (25 and 40 °C). The moisture sorption was in the order of HPC>HPMC>HPMCP>HPMCAS>EC, and there was no significant effect of the molecular weights of polymers on moisture uptake. There was also less moisture sorption at 40 °C than that at 25 °C. Glass transition temperatures (T_g) of the polymers decreased with the increase in moisture content. However, the plasticizing effect by moisture on HPC could not be determined fully since, despite being amorphous, there were very little baseline shifts in DSC scans. There was also very shallow baseline shift for HPMC at >1% moisture content. In contrast, T_g of HPMCAS and HPMCP decreased in general agreement with the Gordon-Taylor/Kelley-Bueche equation, and EC was semicrystalline having both T_g and melting endotherm, with only minor effect of moisture on T_g. The results of the present investigation would lead to a systematic selection of polymeric carriers for ASDs.

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Introduction

Amorphous solid dispersions (ASDs), where drugs are dispersed either molecularly or in the amorphous state in polymeric carriers, are commonly used to improve dissolution rate and oral bioavailability of poorly water-soluble drugs.[1–3] ASDs are generally prepared by spray drying of drug-polymer mixtures from organic solutions or by melt extrusion at elevated temperatures. Physicochemical properties of polymeric carriers play major roles in formulation, manufacturing, stability, and performance of ASDs, and it is, therefore, critically important that polymeric carriers are carefully selected for the development of such dosage forms. For this reason, we have undertaken a systematic investigation of the physicochemical properties of different polymeric carriers commonly used in ASDs.

Previously, we reported thermal and viscoelastic properties of different polymers commonly used in ASDs, such as polyvinylpyrrolidones (PVP) and related polymers,[4] celluloses,[5] and methacrylates.[6]

In addition to these properties, the hygroscopicity of polymers used also plays a critical role in the formulation of ASDs, since the moisture sorption plasticizes ASDs and, consequently, decreases their T_g.[7] There are numerous reports in the literature demonstrating that such a decrease in T_g of ASDs by moisture sorption leads to physical instability of formulations due to amorphous-amorphous and amorphous-crystalline phase transformations.[8–11] In general, polymeric carriers constitute the larger fraction of the ASDs and they are also more hygroscopic than amorphous drugs, and, therefore, they play more dominant roles in moisture sorption by ASDs and potentially their physical instability.

Different PVPs, celluloses, and methacrylates have extensively been investigated for the development of ASDs. It has been reported by Solanki et al.[12] that among 20 ASDs marketed in the USA between 2007 and 2018, eight contain PVP and related polymers and 11 contain cellulosic polymers as carriers. Certain methacrylates (Eudragit®) also have great potential as carriers for ASDs as they can produce supersaturated solutions of poorly water-soluble drugs in aqueous media.[13,14] However, despite the importance of such polymers in the formulation of ASDs, there are only limited reports in the literature

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on their moisture sorption as the function of relative humidity. Even when moisture sorption data for some polymers are available in the literature, they are often variable and differ from one report to the other.[15−18] In Part I of the present series of papers, we reported the moisture sorption by PVP and related polymers as the function of humidity and its effects on their glass transition temperatures.[18] That report also describes the identification of experimental parameters for the determination of moisture sorption that produces highly reproducible data without any significant difference in moisture sorption between sorption and desorption modes or evidence of hysteresis loop.

The primary objective of the present Part II of the studies was to determine moisture sorption by several commonly used cellulosic polymers, such as hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), and ethyl cellulose (EC). Since each of these polymers exists in different grades depending on chemical and physical properties, any possible difference in moisture sorption among different grades of each polymer was also investigated. Although ASDs are usually developed and stored at room temperature of around 25 °C, their accelerated stability testing is conducted at elevated temperatures (for example, 40 °C/75% RH), and, therefore, we have also investigated the effects of temperature on moisture sorption by the polymers by conducting experiments at 25 °C vs 40 °C. Additionally, the effects of moisture contents on T_g of the polymers were studied to analyze what impact a decrease in T_g may have on product stability.

Materials and Methods

Materials

Table 1 lists all polymers used in the present investigation along with their chemical name, trade name, and manufacturers. The polymers belong to 5 different categories (e.g., EC, HPC, HPMC, HPMCAS and HPMCP), and several polymers from each category that differ in their molecular weights or chemical structures were used. They were donated by their respective manufacturers. All materials were used as received from the manufacturers, and no considerations were made for their particle sizes or surface areas since Zografi et al.[19] reported that the interaction between moisture and celluloses occurs by hydrogen bonding and does not depend on specific surface areas. In another study, Ocieczek et al.[20] observed that the moisture sorption by a cellulose with three widely different particle sizes obtained by micronization were essentially superimposable.

Moisture Sorption Study

Moisture sorption studies at 25 and 40 °C were conducted using an automated dynamic vapor sorption analyzer (VTI SA, TA Instruments, Wilmington, DE, USA) by applying the experimental parameters previously developed in our laboratory for the moisture sorption of PVP and related polymers.[18] Essentially, the method involves the production of relative humidity by combining dry nitrogen and the nitrogen saturated with water vapor by passing through a water reservoir, which can create any desired relative humidity at any temperature. VTI SA can produce RH between 0 to 98% with ±1% RH at any temperature (isothermal stability ± 0.1 °C).

Each sample was first subjected to a drying step to remove any residual moisture. For this purpose, 25±5 mg of a polymer was placed on a quartz pan, which was then mounted on the microbalance of the VTI instrument. The sample was then dried at 40 °C for 1h using the dry nitrogen flow. It was established separately that the drying was complete in <1h since any weight loss during such drying levels off in <30 min, and there was no additional weight loss when the dried material was subjected to thermogravimetric analysis at

higher temperature. The drying was followed by the determination of moisture sorption isotherm at relative humidity ranging from 10 to 90%. For each step of the moisture sorption (or desorption) isotherm, the weight change threshold was set at 0.004% w/w in 5 min, and a maximum period of 1440 min (24h) was given to reach the threshold. For selected polymers, both moisture sorption and desorption profiles were also generated at two humidity ranges of 10 to 90% RH and 10 to 80% RH to determine what effects, if any, the exposure to different high humidity conditions might have on hysteresis loops produced by moisture sorption-desorption profiles.
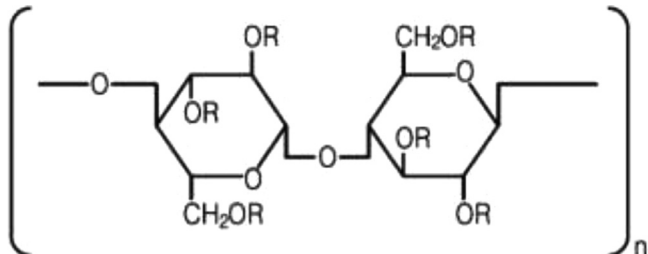
Thermal Analysis of Polymer

Selected cellulosic polymers were subjected to thermal analysis by differential scanning calorimetry (DSC) to determine the decrease in T_g as a function of increasing moisture content. It was not possible to accurately determine the effect of moisture sorption on the T_g by heating samples in open or non-hermetically sealed DSC pans as is normally done in most DSC analyses. This is because the moisture may escape the sample during heating before it reaches the T_g. Therefore, as described earlier,[18] we developed a novel method where a predetermined amount of moisture is absorbed into the sample and the sample is then sealed hermetically in a DSC pan to prevent moisture loss. Essentially, ∼5 mg of sample was taken on a Tzero aluminum DSC pan, and the DSC pan was then placed on the flat-bottomed aluminum pan used for moisture sorption analysis. The flat-bottomed aluminum pan with the DSC pan placed on it was mounted on the VTI microbalance. Another flat-bottomed aluminum pan containing an empty Tzero DSC pan was used as a reference. To remove any residual moisture, the sample was dried at 50 °C for 15 min under dry nitrogen flow, followed by the continuation of purging of dry nitrogen for another 60 min when the sample cooled down to 25°C. It was confirmed by separate thermogravimetric (TG) analysis that the sample was completely dry as there was no additional weight loss upon heating. The dry sample was then subjected to 25 °C/90% RH until a pre-defined weight gain due to moisture sorption was observed. Once the sample was equilibrated with the requisite amount of moisture, the door of the moisture sorption analyzer was opened and the lid was placed immediately on the Tzero aluminum pan, and the pan was then hermetically sealed by removing quickly from the moisture sorption analyzer. Modulated DSC of the sealed sample was performed using a Q200 modulated DSC analyzer equipped with a refrigerated cooling accessory (TA instruments, DE, USA). The ramping rate of 2.5 °C per 60 s with the modulation of ±1.5 °C in 60 s was used. A step change in reversible heat flow signal was taken as the T_g. Although this technique had the advantage that the predetermined amount of adsorbed moisture remained within the DSC pan, there could still be a potential limitation that the moisture might partially escape the sample mass during heating and be trapped in the headspace of the sample pan. Nonetheless, as will be shown later, definite changes in T_g were observed due to moisture sorption.

Results and Discussion

Identification of Optimal Experimental Conditions for Moisture Sorption

As detailed earlier,[18] there are major discrepancies in moisture sorption values for different polymers reported in the literature as there could be as much as 50% w/w difference in moisture content at a particular humidity and temperature[17] depending on experimental conditions used and whether the values were recorded during moisture sorption or desorption modes. Often, moisture contents during sorption are lower than that during desorption, thus giving hysteresis loops. Therefore, one of the goals of our previous investigation[18] as well as the present one is to identify experimental conditions that would provide reliable and consistent moisture sorption profiles

Table 1
Cellulosic Polymers used for Moisture Sorption Analysis.

General Structure of Celluloses

Chemical name	Trade name	Manufacturer	Aqueous solubility	Reported T_g (°C)	Comments	Substituents (R)
			ETHYL CELLULOSE (EC)			
Ethyl Cellulose (EC) (MW 63,800)[21]	ETHOCEL™ Std. 7 P	Dow (Croydon, PA, USA)	Practically water insoluble	130		R = —H, —CH$_2$CH$_3$
Ethyl Cellulose (EC) (MW 79,200)[21]	ETHOCEL™ Std.10 P	Dow	Practically water insoluble	129		
Ethyl Cellulose (EC) (MW-124,400)[21]	ETHOCEL™ Std.20 P	Dow	Practically water insoluble	115		
			HYDROXY PROPYLCELLULOSES (HPC)			
Hydroxy propyl cellulose (HPC) (MW 80,000)	Klucel™ EXF	Ashland (Wilmington, DE, USA)	Water soluble	-		R = —H, —CH$_2$CH(OH)CH$_3$
Hydroxy propyl cellulose (HPC) (MW 850,000)	Klucel™ MXF	Ashland	Water soluble	-		
Hydroxy propyl cellulose (HPC) (MW 1,150,000)	Klucel™ HXF	Ashland	Water soluble	-		
			HYDROXY PROPYLMETHYLCELLULOSES (HPMC)			
Hydroxypropyl methylcellulose (HPMC) (MW 80,000)	Affinisol™ 15cP HME	Dow	Water soluble	104.7		R = —H, —CH$_3$, —CH$_2$CH(OH)CH$_3$
Hydroxypropyl methylcellulose (HPMC) (MW 180,000)	Affinisol™ 10cP HME	Dow	Water soluble	109.7		
Hydroxypropyl methylcellulose (HPMC) (MW 550,000)	Affinisol™ 4M HME	Dow	Water soluble	107.8		
			HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE (HPMCAS)			
Hydroxypropyl methylcellulose acetate succinate (HPMCAS) (MW 18,000)	HPMCAS LF	Shin-Etsu (Tokyo, Japan)	Dissolving at pH>5.5	121.7	Acetyl content: 8% Succinoyl content: 15%	R= —H, —CH$_3$, —COCH$_3$, —CH$_2$CH(OH)CH$_3$ —CH$_2$CH(CH$_3$)OCOCH3
Hydroxypropyl methylcellulose acetate succinate (HPMCAS) (MW 18,000)	HPMCAS MF	Shin-Etsu	Dissolving at pH>6.0	123.0	Acetyl content: 9% Succinoyl content: 11%	—CH$_2$CH(CH$_3$)O COCH$_2$CH$_2$COOH
Hydroxypropyl methylcellulose acetate succinate (HPMCAS) (MW 18,000)	HPMCAS HF	Shin-Etsu	Dissolving at pH>6.5	121.8	Acetyl content: 12% Succinoyl content: 7%	

Table 1 (*Continued*)

Chemical name	Trade name	Manufacturer	Aqueous solubility	Reported T_g (°C)	Comments	Substituents (R)
HYDROXYPROPYL METHYLCELLULOSE PHTHALATE (HPMCP)						
Hydroxypropyl methylcellulose phthalate (HPMCP) (MW 37,900)	HPMCP HP 50	Shin-Etsu	Dissolving at pH>5.0	140.8	Phthalyl content: 24%	
Hydroxypropyl methylcellulose phthalate (HPMCP) (MW 45,600)[22]	HPMCP HP 55	Shin-Etsu	Dissolving at pH>5.5		Phthalyl content: 31%	

independent of whether they were determined during moisture sorption or desorption. We first determined moisture sorption-desorption profiles of cellulosic polymers belonging to 5 different chemical types (HPC Klucel EXF, HPMC Affinysol 15CP, HPMCAS MF, HPMCP HP55, EC Ethocel 10P) at 25⁰C and in the humidity ranges of 0 to 90% RH, when certain hysteresis loops, although relatively narrow, were observed for all the polymers tested. To further investigate this behavior, we also determined moisture sorption-desorption profiles between 0 to 80% RH and observed that there was no hysteresis loop in any of the polymers. Representative moisture sorption-desorption profiles of one of the polymers, HPC Klucel EXF, in the humidity ranges of 0 to 90% RH and 0 to 80% RH are shown in Fig. 1. Visual examination of materials exposed to different humidity conditions revealed that they converted to aggregates and formed lumps at 90% RH, while they remained loose free-flowing powders at 80% RH. Therefore, the difference in moisture sorption profiles observed in Fig. 1 could be attributed to slow and incomplete desorption of moisture following exposure to 90% RH in Fig. 1A, and no such hysteresis loop was observed and the equilibrium was reached rapidly in the humidity range of 0 to 80% RH in Fig. 1B. Essentially, equilibrium moisture sorption up to 80% RH occurred in ∼9h, and it took additional 10h for equilibration when the humidity was changed from 80% RH to 90% RH. It is the moisture sorption at the high humidity that changed the consistency of powder, caused slow moisture desorption, and produced hysteresis loops. It could be concluded from these results that all moisture sorption values up to 80% RH are equilibrium values as no hysteresis loop exists, and the values at 90% RH during the moisture sorption mode are also equilibrium values as the experimental

parameters were met. For these reasons, all moisture sorption data reported in the present investigation were generated during moisture sorption modes.

Moisture Sorption by Cellulosic Polymers

Physicochemical properties and pharmaceutical applications of cellulose and various cellulose derivatives have been reported in the literature.[23,24] Chemically, cellulose is a linear polymer of anhydroglucose units (AGU) linked by 1,4-β-glycosidic bonds that are derived from a variety of naturally occurring materials, such as wood pulp, cotton, etc. Since it has a relatively stiff backbone with many hydroxyl groups, cellulose undergoes inter-chain hydrogen bonding resulting in the formation of crystalline and water-insoluble material. Thus, by itself, cellulose is not a suitable carrier for ASDs; however, it can be converted to the amorphous form by reacting its hydroxyl groups with alkyl halides or epoxides to form cellulose ethers that are not capable of inter-chain hydrogen bonding like cellulose itself. Such cellulose ethers as hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), and hydroxypropyl methylcellulose phthalate (HPMCP) have been used in ASDs. Although all of them are amorphous, only HPC and HPMC are water-soluble throughout the gastrointestinal pH range of 1 to 7.5 because of the presence of -OH groups in hydroxypropyl moieties, while HPMCAS and HPMCAP are soluble only under intestinal pH conditions above pH 5.5 as they dissolve when their respective substituents succinic acid and phthalic acid moieties are ionized. Another cellulose ether, ethyl cellulose (EC), is also used in ASDs; however, it is water-insoluble and, therefore, may be used in combination with other polymers or when a slower release from of ASD is intended. As indicated in Table 1, different grades of polymers are available for each chemical type of cellulosic polymers depending on their molecular weights or differences in the number or ratio of substituent moieties. The results of moisture sorption by different chemical types of cellulosic polymers are described in the following sections.

Hydroxypropyl Cellulose (HPC)

Three different grades of HPC, marketed as Klucel™ EXF, Klucel™ MXF, and Klucel™ HXF by Ashland, have been used in the present investigation for moisture sorption as a function of relative humidity, and the results are given in Table 2. They are also shown graphically in Fig. 1 to facilitate visual comparison among different profiles.

In Table 1, the main difference among the three grades of HPC used is their molecular weight; otherwise, they are of linear chains with similar structures. The moisture sorption profiles of HPC are highly reproducible as indicated by the average (±s.d.) values of triplicated determinations for Klucel™ HPC EXF presented in Table 2. It may also be observed in the table that moisture sorption by the three grades of HPC at each temperature is also similar, which reflects the similarity in their chemical structures. When the data are plotted in Fig. 2, the moisture sorption profiles are essentially superimposable; although the three different grades of the polymer were used 'as received' from the manufacturer and could have differences in their physicochemical properties, such as particle size, specific surface area, bulk density, etc., there does not appear to be any influence of such factors on moisture sorption. Therefore, these results indicate that the moisture sorption occurs by hydrogen bonding with the -OH groups in hydroxypropyl moieties in anhydroglucose units (AGU) of the chain, and it is not dependent on the chain length, molecular weight, and physical properties.

It is apparent from the moisture sorption results that HPC is quite hygroscopic with, for example, 6.45%, 6.31% and 5.83% w/w moisture uptake at 25 °C/60% RH by Klucel™ EXF, Klucel™ MXF, and Klucel™
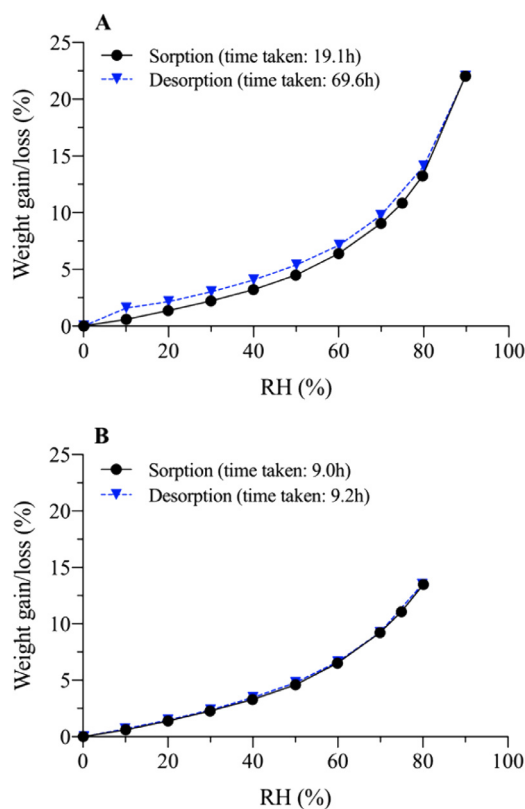

Figure 1. Moisture sorption and desorption isotherms of one representative polymer (HPC; Klucel™ EXF) at 25 °C and in the humidity ranges of (A) 0 to 90% RH and (B) 0 to 80% RH. There was hysteresis loop in A, indicating that complete desorption of powder could not be readily reached when the polymer was first exposed to 90% RH, while no hysteresis loop was observed in the free-flowing powder in the 0 to 80% RH range.

Table 2
Moisture Sorption by Different Grades of HPC (Klucel[TM]) as a Function of Relative Humidity (RH) at 25 and 40 °C.

| | %Weight Gain by Klucel[TM] HPC | | | | | |
| | 25 °C | 25 °C | 25 °C | 40 °C | 40 °C | 40 °C |
RH	EXF[a]	MXF	HXF	EXF	MXF	HXF
0	0	0	0	0	0	0
10	0.61±0.06	0.62	0.59	0.53	0.55	0.55
20	1.39±0.02	1.35	1.29	1.18	1.21	1.17
30	2.27±0.04	2.20	2.10	1.92	1.96	1.91
40	3.29±0.06	3.21	3.06	2.82	2.89	2.80
50	4.57±0.09	4.53	4.20	3.99	4.07	3.96
60	6.45±0.11	6.31	5.83	5.56	5.60	5.52
70	9.11±0.15	8.74	8.30	7.80	7.72	7.71
80	13.36±0.26	12.58	12.25	11.25	10.93	11.00
90	21.28±1.15	20.36	20.06	17.55	16.77	16.96

[a] Average ± s.d. of 3 determinations. Because of high reproducibility of results, single determinations were made for other moisture sorption profiles.

HXF, respectively, and the moisture uptake by the same polymers at 40 °C/60% RH are 5.56%, 5.60% and 5.52% w/w, respectively, indicating lower moisture sorption at higher temperature. The moisture sorption by all three grades of polymers approximately doubles when the humidity is increased from 60% RH to 80% RH, reaching 12-13% w/w at 25 °C/80% RH and ∼11% w/w at 40 °C/80%RH. At 40 °C/90%RH, Klucel[TM] MXF, EXF, and HXF absorb 17.55%, 16.77%, and 16.96% w/w moisture, respectively. HPC is commonly used as a carrier for ASDs[25,26] and in the melt granulation of drug substances by hot-melt extrusion.[27−30] The moisture sorption results presented here will, therefore, be important in evaluating stability and performance of such products. The results also show that there is a decrease in moisture sorption with the increase in temperature from 25 °C to 40 °C, but the difference becomes prominent only at high humidity (>70% RH). There is lower moisture sorption at a higher temperature because a larger number of water molecules gain sufficient energy at the higher temperature to break hydrogen bonds with polymer and escape into the atmosphere.[31]

Hydroxypropyl Methylcellulose (HPMC)

HPMC is also a water-soluble and amorphous cellulosic polymer suitable as a carrier for ASDs.[32−35] It has methoxy and hydroxypropyl substitutions in the cellulose backbone, where the hydroxypropyl group imparts hydrophilicity to the polymer, while the methoxy group provides hydrophobicity, thus making the polymer somewhat amphiphilic. We have used three viscosity grades of HPMC,

commercially available as Affinisol[TM] 15cP, Affinisol[TM] 100cP, and Affinisol[TM] 4M, in our studies. These polymers are specially designed by the manufacturer for the development of ASDs by melt extrusion, but they may also be used for ASDs prepared by spray drying. The difference in viscosity exerted by the three different grades of HPMC is apparently due to the difference in chain length or molecular weight. Table 3 gives the moisture sorption results of the three grades of Affinisol[TM] at 25 °C and 40 °C as the function of relative humidity, which shows that there is no significant difference in the moisture sorption profiles among them. When the data are plotted graphically in Fig. 3, the profiles are also superimposable. These results demonstrate that the moisture sorption sites in all three grades of HPMC are structurally similar since the only difference among them is their chain length or molecular weight.

Fig. 3 shows that the equilibrium moisture content of HPMC (Affinisol[TM]) increases gradually and rather slowly up to 60% RH but the increase becomes relatively sharper at 70% and higher RH. This is also evident from the data presented in Table 3, where, until 25 °C/60%RH, the different grades of Affinisol[TM] absorbed ∼3.6% w/w moisture. At 25 °C/70%RH, Affinisol[TM] absorbs ∼5.5% w/w moisture (Table 3), which increases even more rapidly at higher RH. At 25 °C/90% RH, Affinisol[TM] 15cP, Affinisol[TM] 100cP and Affinisol[TM] 4M absorb 18.19%, 18.66% and 16.77% w/w moisture, respectively. These results are in general agreement with the moisture sorption by these polymers reported earlier by Gupta et al.[36]

As mentioned earlier, the moisture sorption by the three grades of HPMC was determined without any consideration of their particle
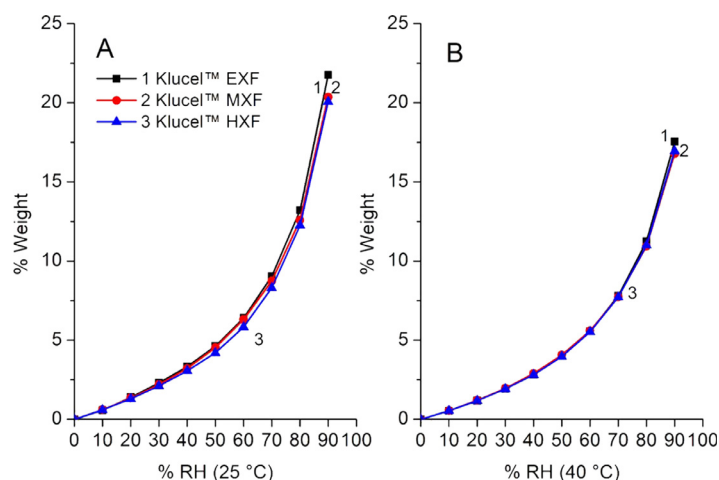

Figure 2. Moisture sorption isotherms of three different grades of hydroxypropyl cellulose (Klucel[TM] EXF, Klucel[TM] MXF and Klucel[TM] HXF) at (A) 25 °C and (B) 40 °C as a function of relative humidity (%RH)

Table 3
Moisture Sorption by Affinisol™ 15cP, Affinisol™ 100cP and Affinisol™ 4M at 25 and 40 °C.

	Affinisol HPMC %weight gain					
	25 °C	25 °C	25 °C	40 °C	40 °C	40 °C
RH	15cp[a]	100cp	4M	15cp	100cp	4M
0	0	0	0	0	0	0
10	0.41±0.00	0.45	0.40	0.39	0.39	0.39
20	0.88±0.03	0.80	0.75	0.80	0.80	0.80
30	1.36±0.11	1.28	1.12	1.24	1.24	1.24
40	1.95±0.13	1.76	1.66	1.74	1.73	1.77
50	2.63±0.17	2.76	2.37	2.41	2.38	2.47
60	3.56±0.18	3.78	3.56	3.32	3.31	3.53
70	5.37±0.22	5.77	5.50	4.77	4.85	5.05
80	9.63±0.44	9.82	9.00	7.89	7.79	7.72
90	18.19±0.38	18.66	16.77	13.51	13.04	12.72

[a] Average ± s.d. of 3 determinations. All other values are from single determinations.

size, specific surface area or any other physical properties. The almost superimposable moisture sorption profiles in Fig. 3 indicates that the similarity in moisture sorption by the three grades of HPMC is due to similarity in their chemical structure and may not depend on their physical properties.

The results of the present investigation also show that the moisture sorption by HPMC decreases with the increase in temperature from 25 to 40 °C, where the decrease is more prominent at 80% and 90% RH. The amount of absorbed moisture is not more than 5% w/w until 40 °C/70% RH is reached, and Affinisol™ absorbs only ~13% w/w moisture at 40 °C/90%RH (Table 3).

A comparison of data presented in Table 3 with those in Table 2 shows that HPMC is apparently less hygroscopic than HPC. This is possibly because HPC is substituted in its chemical structure by hydrophilic hydroxypropyl group with the degree of substitution (DS) of 2.2, while HPMC has less substitution by the hydroxypropyl group (DS=0.23) and more substitution by the hydrophobic methyl groups (DS =1.91).[23] The methyl substitution might have reduced the number of hydrogen bonding sites in HPMC, thus reducing its moisture sorption.

Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)

HPMCAS has complex substitutions on its cellulose backbone. It has similarity with HPMC by having methyl (-CH₃), hydroxypropyl [-CH₂CH(CH₃)OH] and hydroxypropyl methyl [-CH₂CH(CH₃)OCH₃] groups, but it is chemically modified by further substitution with

acetyl (-COCH₃), hydroxypropyl acetyl [-CH₂CH(CH₃)OCOCH₃], succinoyl [-COCH₂CH₂COOH], and hydroxypropyl succinoyl [-CH₂CH(CH₃) OCOCH₂CH₂COOH] groups in the structure. During such chemical changes, much of the hydroxypropyl moiety, which is hydrophilic in nature, is replaced by hydrophobic moieties, and, therefore, HPMCAS becomes water insoluble. It dissolves in water only after ionization of the succinic acid groups at pH>5.5. HPMCAS has been used extensively in the development of ASDs,[12,37−39] and because of its ability to produce supersaturated solutions of drugs by the interaction between ionized succinoyl moieties and weakly basic drugs,[40] 7 out of 20 ASD pharmaceutical products marketed in the USA since 2007 have HPMCAS as the polymeric carrier.[12]

Table 4 gives moisture sorption results at 25 and 40 °C for the three grades of HPMCAS used, which indicate that the moisture sorption by all three grades of HPMCAS is relatively low, although there are certain differences in moisture sorption in the order of LF>MF>HF, which is evident when the data are plotted graphically in Fig. 4 (lines 1, 2 and 3). When moisture sorption profiles at 25 and 40 °C are compared, there is practically no effect of temperature on the moisture sorption up to 70% RH by different grades of HPMCAS; there is a lower moisture sorption 40 °C as compared to 25 °C only at 80 and 90% RH.

When the moisture sorption by HPMCAS in Table 4 is compared with those of HPC and HPMC in Tables 2 and 3, respectively, it is evident that HPMCAS is less hygroscopic than HPC, and its moisture sorption is in general comparable to that of HPMC up to 70% RH, while at 80 and 90% RH, the moisture sorption by HPMCAS is
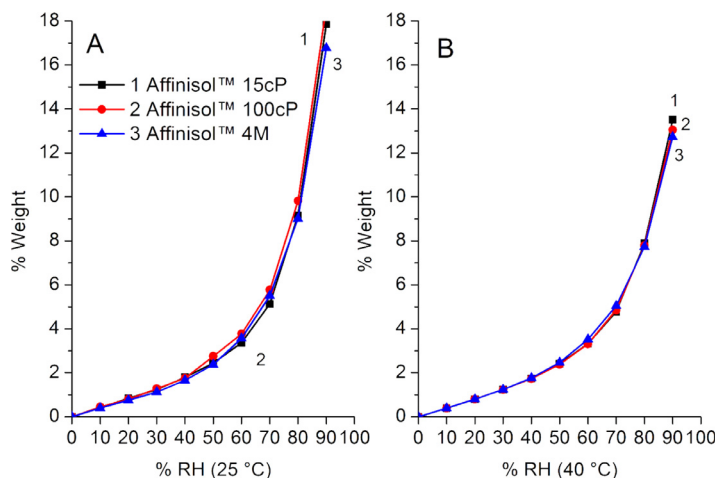

Figure 3. Moisture sorption isotherms of three grades of hydroxypropyl methyl cellulose (Affinisol™ 15cP, Affinisol™ 100 cP and Affinisol™ 4M) at (A) 25 °C and (B) 40 °C as a function of relative humidity (%RH).

Table 4
Moisture Sorption by LF, MF and HF Grades of Hydroxypropyl Methyl Acetate Succinate (HPMCAS) at 25 and 40 °C.

| | HPMCAS % weight gain | | | | | |
| | 25 °C | 25 °C | 25 °C | 40 °C | 40 °C | 40 °C |
RH	LF	MF[a]	HF	LF	MF	HF
0	0	0	0	0	0	0
10	0.62	0.56±0.01	0.46	0.55	0.51	0.46
20	1.14	1.13±0.04	0.96	1.04	0.97	0.88
30	1.67	1.68±0.07	1.44	1.57	1.41	1.30
40	2.33	2.26±0.10	1.96	2.24	1.90	1.77
50	3.25	2.93±0.10	2.56	3.05	2.62	2.37
60	4.34	3.85±0.04	3.36	3.99	3.50	3.21
70	5.62	5.20±0.05	4.66	5.13	4.62	4.28
80	7.31	7.05±0.08	6.39	6.59	5.99	5.64
90	9.86	9.70±0.18	8.90	8.64	7.99	7.55

[a] Average ± s.d. of 3 determinations. Because of high reproducibility of results, single determinations were made for other moisture sorption profiles.

somewhat lower than that by HPMC. The hygroscopicity of HPC is apparently due to hydrogen bonding between moisture and hydroxyl groups associated with hydroxypropyl moieties of HPC, and the substitution of hydroxypropyl groups with relatively more hydrophobic moieties in both HPMC and HPMCAS make them less prone to hydrogen bonding with water and thus less hygroscopic.

As shown in Fig. 4, although the difference is relatively small, the moisture sorption by the three grades of HPMCAS is in the order of L>M>F. This appears to be due to the difference in their chemical structures by having different succinoyl to acetyl ratios. L, M, and F grades of HPMCAS have decreasing succinoyl contents of 14-18, 10-14, and 4-8%, respectively, while their acetyl contents increase to 5-9, 7-11, and 10−14%, respectively. It appears that higher ratios of succinoyl moieties make the polymer more hydrophilic and, therefore, more hygroscopic.

Hydroxypropyl Methyl Phthalate (HPMCP)

HPMCP was originally developed as an enteric coating agent for oral dosage forms,[41] but, like HPMCAS, it has been extensively investigated in recent years as a carrier for ASDs for its ability to improve physical stability of drugs in formulations and exert supersaturation of drugs in aqueous media.[42−44] It comes in primarily two grades, HPMCP HP-50 and HPMCP HP-55, having phthalyl contents of 24% and 31%, respectively, which dissolve above pH 5.0 and 5.5, respectively, due to the ionization of the phthalic acid moiety. Like HPMCAS,

HPMCP exerts its supersaturating effect by the interaction between the ionized acidic group in the polymer with the weakly basic drug.

Moisture sorption profiles of HPMCP as a function of RH are given in Table 5, and they are also plotted in Fig. 4 for comparison between them and with that of HPMCAS. Fig. 4 shows that the moisture sorption profiles of the two grades of HPMCP are similar as the plots are essentially superimposable (lines 4 and 5), and, although slightly higher, the results are also comparable to that of HPMCAS. This is because, in both HPMCAS and HPMCP, most of the hydroxypropyl groups originally present in HPC are substituted by more lipophilic moieties. For this reason, a comparison between Figs. 2 and 4 demonstrates that, like HPMCAS, HPMCP is also much less hygroscopic than HPC.

Ethyl Cellulose (EC)

Ethyl cellulose (EC) is marketed as Ethocel™ by Dow Chemical, which is now part of DowDupont due to the merger between Dow and Dupont. It is a water-insoluble cellulose ether that is generally used as a coating material for controlled release solid dosage forms. However, in recent years, it has also been investigated as the carrier for ASDs either alone or in combination with other polymers,[45,46] especially when the ASDs were intended to be sustained release products.[47−49] EC is commercially available in different grades, which differ in their viscosity depending on molecular weights, but they are chemically similar by having the ethoxyl content of 48−49.5% w/w.[50] The moisture sorption results for three representative grades of EC, namely, Ethocel™ 7P, Ethocel™ 10P, and Ethocel™ 20P, as a
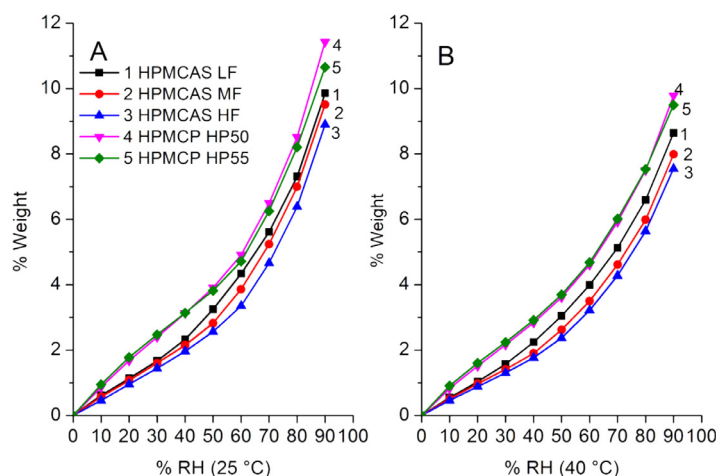

Figure 4. Moisture sorption isotherms of HPMCAS (LF, MF and HF grades) and HPMCP (HP-50 and HPMCP HP-55 grades) at (A) 25 °C and (B) 40 °C as a function of relative humidity (%RH).

Table 5
Moisture Sorption by Different Grades of Hydroxypropyl Methyl Phthalate (HPMCP) at 25 and 40 °C

	HPMCP % weight gain			
	HP 50	HP 55[a]	HP 50	HP 55
RH	25 °C	25 °C	40 °C	40 °C
0	0	0	0	0
10	0.87	0.87±0.07	0.83	0.91
20	1.67	1.62±0.14	1.51	1.61
30	2.39	2.24±0.20	2.16	2.24
40	3.13	2.90±0.21	2.84	2.92
50	3.91	3.72±0.09	3.61	3.70
60	4.92	4.84±0.10	4.61	4.68
70	6.49	6.37±0.13	5.92	6.02
80	8.51	8.19±0.07	7.50	7.53
90	11.43	10.58±0.07	9.78	9.49

[a] Average ± s.d. of 3 determinations. Because of high reproducibility of results, only single determinations were made for other moisture sorption profiles.

function of RH at 25 and 40 °C are given in Table 6, and the data are also plotted in Fig. 5 to show whether any difference in moisture sorption among the three grades exist or not.

EC is very nonhygroscopic as compared to other cellulosic polymers, since even at 90% RH, it absorbs <4% moisture. The moisture sorption by all three grades of EC studied is essentially the same because of the similarity in their chemical structure, the only difference being in their molecular weights. At such a low moisture content, there is no significant effect of temperature on moisture sorption.

Effect of Moisture on Glass Transition Temperature (T_g) of Polymers

T_g of polymers plays a critical role in the physical stability of ASDs.[51,52] This is because the amorphous solid changes from a rigid glassy state below T_g to a soft rubbery state above T_g, where any dispersed drug may phase separate or crystallize out due to higher molecular mobility. Therefore, to prevent crystallization of drugs from ASDs, it is essential that the T_g of the polymer used should be high so that the T_g values of ASDs formed also become high. We have previously reported that moisture sorption may drastically reduce the T_g of PVPs and related polymers, such as Kollidon® VA64 and Soluplus®.[18] It was of interest in the present investigation to determine what impacts moisture sorption may have in reducing T_g of different cellulosic polymers.

Effect of Moisture on T_g of HPC

Complex and rather anomalous thermal properties for HPC (Klucel™) have been reported in the literature, and, therefore, it was difficult to study the effect of moisture on its glass transition temperature (T_g). Rials and Glasser[52] reported that HPC is a semicrystalline material rather than a fully amorphous one by having a T_g of 19 °C and a melting point of 220 °C. Using Klucel™ EXF and Klucel™ HXF, Picker-Freyer and Dürig[53] also reported HPC to be semicrystalline, where they observed T_g values in the range of 0 °C to minus 25 °C in presence of 1 to 10% moisture in the polymer. More detailed analyses of thermal properties of HPC (Klucel™ LF)

Table 6
Moisture Sorption by Three Grades of Ethyl Cellulose (EC) at 25 °C and 40 °C.

	Ethyl cellulose (Ethocel) % weight gain by different grades					
	25 °C	25 °C	25 °C	40 °C	40 °C	40 °C
RH	7P	10P[a]	20P	7P	l0P	20P
0	0	0	0	0	0	0
10	0.25	0.21±0.04	0.24	0.22	0.21	0.20
20	0.48	0.48±0.01	0.45	0.44	0.44	0.43
30	0.73	0.71±0.00	0.68	0.66	0.69	0.65
40	1.04	0.95±0.01	0.93	0.90	0.96	0.91
50	1.35	1.23±0.01	1.20	1.16	1.27	1.20
60	1.65	1.55±0.00	1.51	1.48	1.66	1.55
70	1.94	1.97±0.01	1.92	1.87	2.11	1.99
80	2.10	2.60±0.01	2.56	2.48	2.74	2.57
90	3.34	3.84±0.06	3.72	3.44	3.68	3.42

[a] Average ± s.d. of 3 determinations. Because of high reproducibility of results, single determinations were made for other moisture sorption profiles.
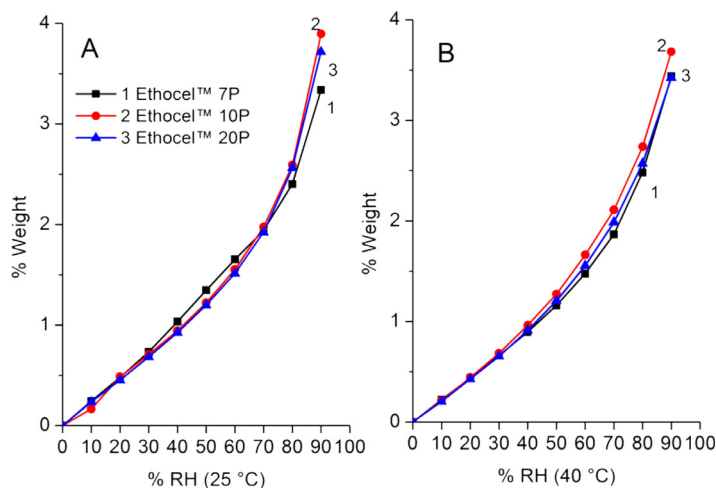

Figure 5. Moisture sorption by different grades of ethyl cellulose (Ethocel™ 7P, Ethocel™ 10P and Ethocel™ 20P) at (A) 25 °C and (B) 40 °C as a function of relative humidity (%RH)

were conducted by Meena al.,[5] where they observed a shallow baseline shift in the DSC scan of the polymer at 111 °C, which they attributed to T_g, and instead of any melting endotherm, they observed degradation of the polymer at 227 °C. Additionally, Meena al.[5] observed that HPC exhibited only an amorphous halo in powder X-ray diffraction (PXRD) analysis like other amorphous cellulosic polymers, and there was no indication of crystalline peaks in PXRD patterns as was observed by other investigators for semicrystalline or microcrystalline celluloses.[54,55]

Because of the above-mentioned discrepancies in reported thermal properties of HPC, we determined DSC scans of Klucel[TM] EXF, Klucel[TM] MXF, and Klucel[TM] HXF with 0, 1, 2.5 and 5 percent moisture contents, and the results are shown in Fig. 6. At T_g, an amorphous material changes from a brittle glassy state at lower temperature to a viscous rubbery state at a higher temperature. Such a change in physical state is usually accompanied by a change in heat capacity of the material and, therefore, a baseline shift occurs in the DSC scan. Although there appear to be some thermal events at different temperatures, all baseline shifts for HPC in Fig. 6 are very shallow. Gómez-Carracedo et al[56] also observed very small baseline shifts in DSC scans of HPC and suggested that the scans must be magnified greatly to observe any T_g. We have identified several thermal events by magnifying DSC scans, and the temperatures where any changes might have happened are also noted in Fig. 6 (detailed magnifications not shown). The difference among Klucel[TM] EXF, Klucel[TM] MXF and Klucel[TM] HXF are in their molecular weights, which are 80,000, 850,000 and 1,150,000, and it is expected that T_g values of polymers will increase with the increase in molecular weight as it was observed earlier for PVP,[18] but there is no such increase in T_g of different HPC grades in Fig. 6 when the dried samples (0 moisture content) are compared. There is also no consistent effect of moisture on the possible thermal events observed in the polymers. Several baseline shifts observed in DSC scans could be due to reorientation of polymeric chains and not due to glass transition.

Because of the absence of any endothermic peaks in DSC scans in the present investigation and the absence of crystalline peaks in PXRD patterns reported by Meena al.,[5] it appears that HPC may not be semicrystalline at all, and the lack of any discernable T_g in DSC scans is possibly because there is no difference in heat capacity of the material between below and above T_g. Therefore, the DSC analysis may not be an appropriate method for determining T_g and thereby molecular mobility of HPC with increasing moisture content. It may also be noted that we did not observe any significant T_g at low temperatures at around or below 0°C, and, therefore, the effects of moisture sorption on glass transition could also not be studied by taking such values into consideration. Nevertheless, it is hoped that the results of the present investigation will address or shed light on some of the discrepancies with thermal properties of HPC reported in the literature.

Since the polymer changes from the glassy state to the rubbery state at T_g, an alternative approach for determining the T_g could be the measurement of complex melt viscosity. In this way, Gómez-Carracedo et al.[56] determined T_g of different grades of HPC to be between 100 and 110 °C. Meena et al.[5] and Batra et al.[30] also observed drastic decrease in complex viscosity of HPC between 100 and 150 °C, but no specific values for T_g were given. These reports indicate that the T_g of HPC could be somewhere around 100°C. The complex viscosity method is, however, not suitable for studying the effect of moisture on T_g since the moisture may not be retained in the samples during the determination of melt viscosity at elevated temperatures.

Effect of Moisture on T_g of HPMC

Fig. 7 shows the effect of moisture on T_g of two grades of HPMC, namely, Affinisol[TM] 15cP and Affinisol[TM] 4M. The results show that the

baseline shift for the glass transition of HPMC is very shallow like that of HPC mentioned above and the plasticizing effect of water is such that any change in T_g due to moisture sorption is difficult to delineate. For Affinisol[TM] 15cP, the moisture-free material has a T_g of 104.7 °C, but any change in T_g in presence of 1, 2.5, and 5.0% w/w moisture may be identified only in the expanded scale as there is very little baseline shift in DSC scans, possibly because there is no significant change in heat capacity during glass transition. For the second polymer, Affinisol[TM] 4M, T_g decreases from 107.6 °C in a moisture-free sample to 89.5 °C in presence of 1% moisture, and any T_g at higher moisture content may be observed only in the expanded scale. Based on the results of the present investigation, it is also not a semicrystalline material; rather, it is an amorphous polymer with very little change in heat capacity at different temperatures. It should also be mentioned here that only high and low viscosity (and molecular weight) grades of HPMC were used in the present investigation for the determination of the effect of moisture on T_g since it was expected that the intermediate grade (Affinisol[TM] 100cP) would behave similarly.

Effect of Moisture on T_g of HPMCAS

Fig. 8 shows DSC scans of different grades of HPMCAS with increasing moisture levels. As given in Table 7, T_g values of dry (moisture-free) HPMCAS LF, HPMCAS MF, and HPMCAS HF are 122 °C, 123 °C, and 122 °C, respectively, which gradually decrease when their moisture contents are increased to 1, 2.5 and then to 5% w/w. At 5% moisture content, T_g of the three grades of HPMCAS are 80, 88 and 87 °C, respectively. According to Table 4, the moisture sorption reaches 5% w/w around the high humidity of 70% RH at 25 and 40 °C, and, therefore, the results of the T_g analysis indicate that HPMCAS could be stored at humidity as high as 70% RH under ambient room temperature and its T_g would still remain about 50 °C above the room temperature of around 25 °C, thus minimizing its molecular mobility and potential stability issues. Such an stabilizing effect could be one of the reasons why HPMCAS has in recent years gained popularity as a carrier for ASDs.

Effect of Moisture on the T_g of HPMCP

The DSC scans of HPMCP (grade HP50) with increasing moisture levels is also shown in Fig. 8, and individual T_g values are tabulated in Table 7, along with those for HPMCAS. The T_g of HPMCP-HP50 decreases from 141 °C in the moisture-free sample to 120 °C after the absorption of 1% moisture, and the T_g further decreases with the increase in moisture content. As shown earlier in Table 5, the polymer absorbs about 6% moisture at 70% RH at 25 and 40 °C. However, since its T_g decreases to only 80 °C even at 7.5% moisture content, it is evident that the T_g of the polymer will remain high and much above the ambient room temperature even when the polymer is stored at a humidity >70% RH. We have used only one of the two grades of HPMCP (HP50) in studying the effect of moisture content on T_g since Table 5 showed that the moisture sorption by both grades is similar.

Effect of Moisture on Tg and other Thermal Properties of EC

The results of DSC analyses of the dry (moisture-free) samples of the three grades of EC used, namely, Ethocel[TM] 7P, Ethocel[TM] 10P, and Ethocel[TM] 20P, and the effect of different moisture contents (0, 1, 2 and 3% w/w) on one of them (Ethocel[TM] 10P) are given in Fig. 9. The effect of moisture sorption on the two other grades of EC was not studied as the results were expected to be similar. It should also be mentioned here that any effect of >3% moisture content could not be studied due to limited moisture sorption by EC.

As shown in Fig. 9A, all three grades of EC showed both glass transition temperatures (T_g) and melting endotherms,
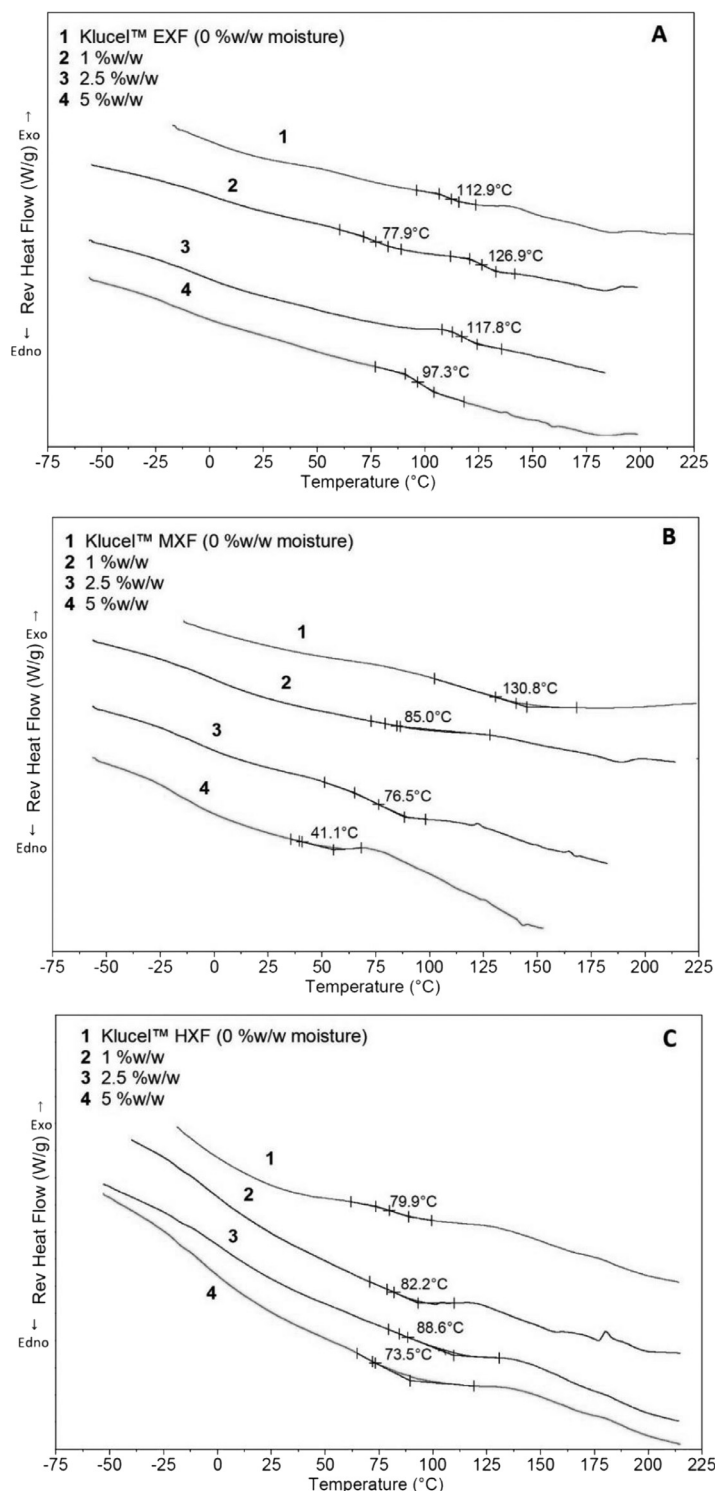
Figure 6. DSC scans of (A) Klucel™ EXF, (B) Klucel™ MXF and (C) Klucel™ HXF (three different grades of polymers differing in chain length) with different moisture contents (0, 1, 2.5 and 5% w/w). The y-axis represents reversing heat flow along with directions of endotherms and exotherms.

demonstrating that, unlike other cellulosic polymers used in the present investigation, they are semicrystalline. T_g values of Ethocel™ 7P and Ethocel™ 10P were around 129°C, while the T_g of Ethocel™ 20P was somewhat broader with the onset at 115°C. All three materials had melting endotherms around 160°C in their dry state. According to Fig. 9B, there was no effect of moisture on the melting endotherm of EC, and while there were some decreases in

T_g due to the presence of moisture, the T_g still remained above 100°C. Although the moisture sorption by EC is relatively low and the effect of any absorbed moisture on its T_g is relatively minor that are favorable to physical stability of any embedded drugs, the semi-crystalline nature of EC observed in the present investigation is pos-sibly the reason why EC is water-insoluble and not much suitable as carriers for ASDs.
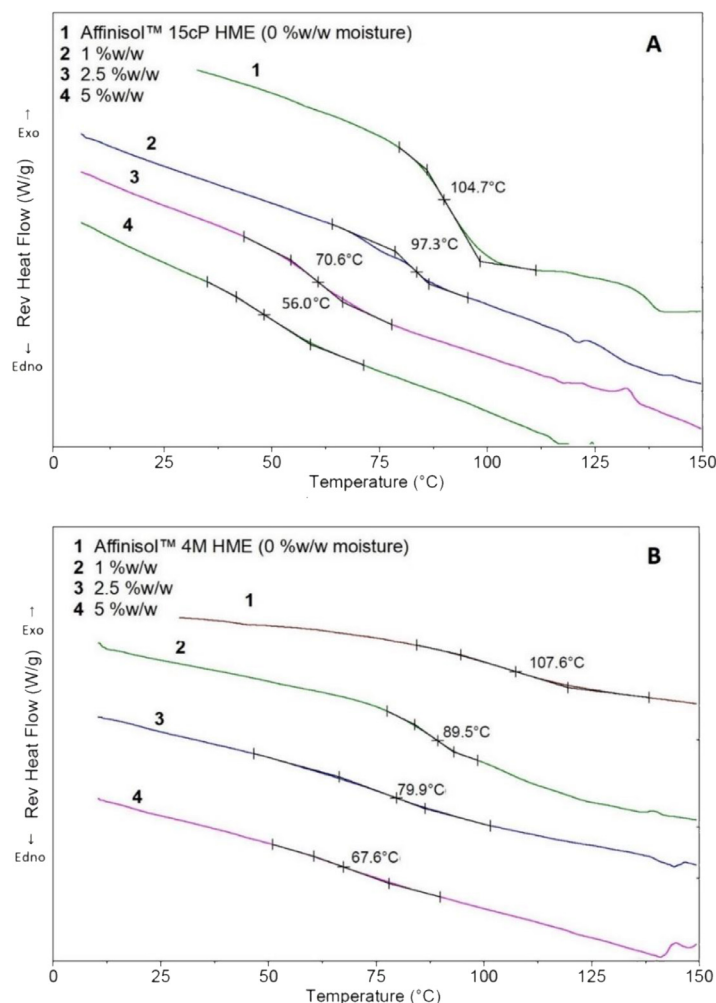
Figure 7. DSC scans (A) Affinisol™ 15cP and (B) Affinisol™ 4M (two grades of HPMC) with different moisture contents (0, 1, 2.5 and 5% w/w). The y-axis represents reversing heat flow along with directions of endotherms and exotherms.

Comparison of experimentally determined glass transition temperatures with theoretically calculated values

Hancock and Zografi [57] calculated the effect of moisture sorption in decreasing T_g of polymers theoretically by using the Gordon-Taylor/Kelley-Bueche equation [58,59] We have previously used the same method to calculate the effects of moisture on T_g of different grades of PVP as well as Kollidon® VA64 and Soluplus®.[18] A similar method has also been used in the present investigation to calculate the effects of moisture on T_g of HPMCAS and HPMCP to determine whether there is a correlation of experimental values with theoretical ones. Such an analysis could not be done for HPC since there was no consistent decrease in T_g with the increase in moisture content, and, for HPMC, T_g values could not be determined reliably when the moisture sorption was >1% w/w. We have also not determined the effect of moisture on T_g of EC as it is a semicrystalline material and there is no consistent effect of moisture on T_g.

The Gordon-Taylor/Kelley-Bueche equation applicable to the binary polymer-water system for the calculation of T_g is given below:

$$T_{g\ mix} = [(w_1 \cdot T_{g1}) + (K \cdot w_2 \cdot T_{g2})]/[w_1 + (K \cdot w_2)]$$

$$where\ K = (\rho_1 \cdot T_{g1})/(\rho_2 \cdot T_{g2})$$

where w_1 is mass fraction of water, w_2 is mass fraction of polymer, T_{g1} is glass transition temperature of water, T_{g2} is glass transition temperature of polymer in absence of water, ρ_1 is true density of water, and ρ_2 is true density of polymer. As per the manufacturers' technical literature, the density of 1.27 g/cm^3 for HPMCAS LF, MF, and HF was used for theoretical calculation of the change in T_g values in presence of moisture, and a density value of 1.28 g/cm^3 was used for HPMCP.

Although there is a general agreement between experimental and calculated T_g values in Fig. 10, it appears that, at low moisture contents (2.5% and less), the Gordon-Taylor/Kelley-Bueche equation underestimated the decrease in T_g of water-polymer system as the calculated T_g values are higher than the experimental ones. On the other hand, at higher moisture content, it appears that the equation overestimates the decrease in T_g, i.e., the calculated T_g values are lower than the experimental ones, which is evident in two of the polymers in Fig. 10. A similar phenomenon was also observed earlier for PVPs and related polymers.[18] As explained earlier,[18] the discrepancy between experimental and theoretical values could be because the Gordon-Taylor/Kelley-Bueche equation was originally developed for fitting the glass transition temperature of random copolymers. It may also be applicable to mixtures with relatively weak specific intermolecular interactions. However, it does not consider the strength and degree of hydrogen bonding between water and polymer during moisture sorption. The water may be present in polymers as tightly bound water, loosely bound water, or bulk water, and such a difference may influence the plasticizing effect of water. Thus, the
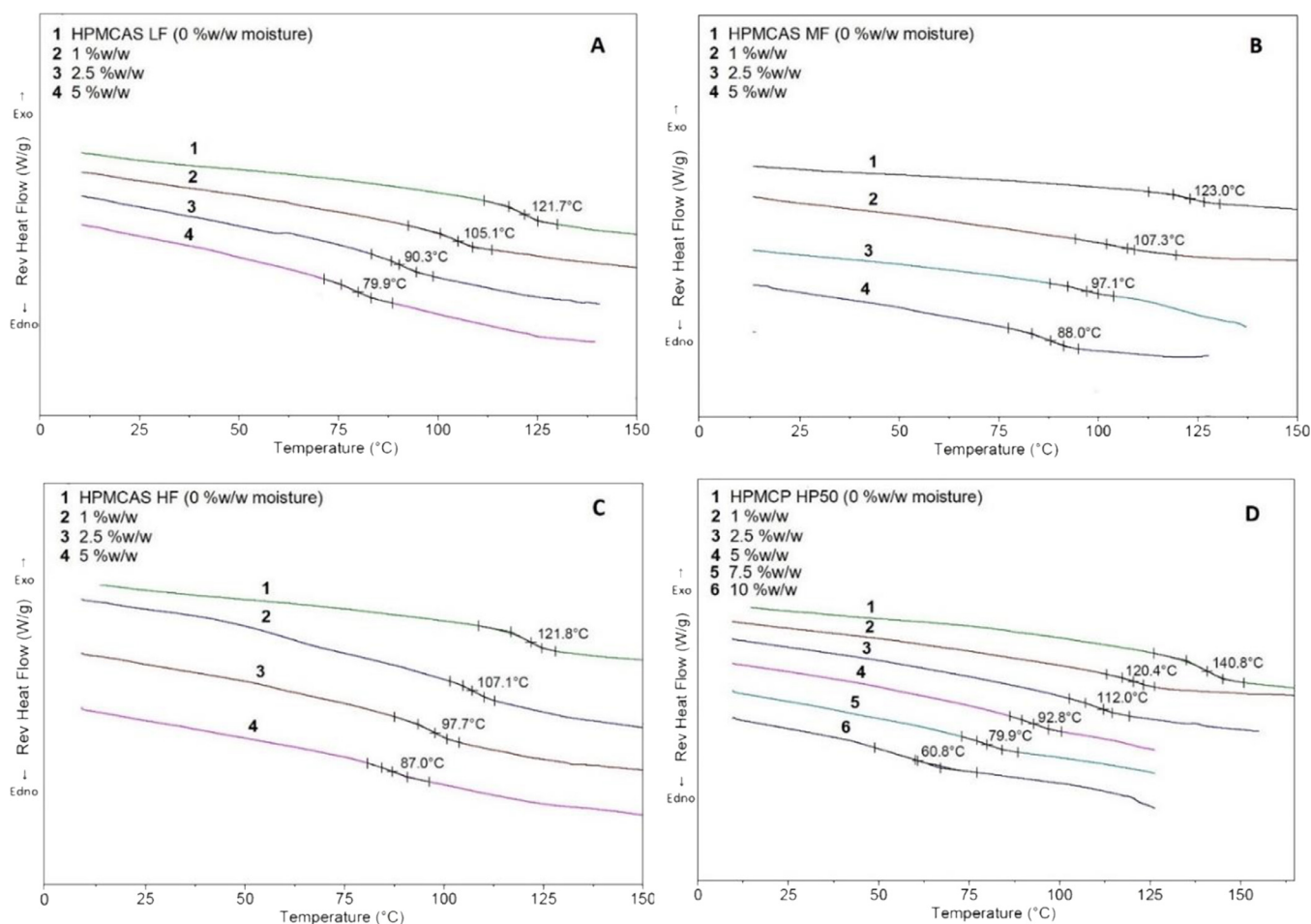
Figure 8. Effects of moisture contents on glass transition temperatures of (A) HPMCAS LF, (B) HPMCAS MF, (C) HPMCAS HF and (D) HMCP HP50. The y-axis represents reversing heat flow along with directions of endotherms and exotherms.

interaction between the polymer and 'bound' water may result in higher plasticization of polymer, while the bulk water may have less plasticization effect. Nevertheless, these results show that the Gordon-Taylor/Kelley-Bueche equation provides a rough estimate of the moisture effect on T_g of polymers and may be used in certain cases in absence of experimental values.

Conclusions

The moisture sorption by the polymeric carrier used in an ASD may reduce the T_g of the system and increase molecular mobility of both drug and polymer, thus leading to physical instability of ASD and crystallization of drug. It is, therefore, essential that the polymeric carrier for an ASD is carefully selected such that it is not much hygroscopic and has limited contribution to moisture sorption and

physical instability of the product. For the judicious selection of carriers for ASDs, we have undertaken a systematic investigation of moisture sorption by different polymers commonly used in ASDs, such as HPC, HPMC, HPMCAS, HPMCP and EC, as a function of relative humidity (RH) in the range of 10 to 90% RH. Since each of these polymers is available from manufacturers in multiple grades, several different grades of each polymer were also used. The moisture sorption studies were conducted at two different temperatures of 25 and 40 °C by using a VTI dynamic moisture sorption analyzer from TA Instruments; two temperatures were used since the drug products are generally stored at the ambient room temperature around 25 °C and their accelerated stability testing is usually conducted at 40 °C.

Among the polymers used, HPMC and HPC are water-soluble throughout the gastrointestinal pH range of 1 to 7.5, HPMCAS and

Table 7
Glass Transition Temperatures of Different Grades of HPMCAS and of HPMCP-HP50 as a Function of Moisture Content.

Moisture content (%w/w)	HPMCAS LF	HPMCAS MF	HPMCAS HF	HPMCP HP50
0	121.8	123.0	121.8	140.8
1	105.1	107.3	107.1	120.4
2.5	90.3	97.1	97.4	112.0
5	79.9	88.0	87.0	92.8
7.5	ND	ND	ND	79.9
10	ND	ND	ND	60.8

ND = Not determined since the highest moisture sorption by the polymers is around or below these moisture levels.
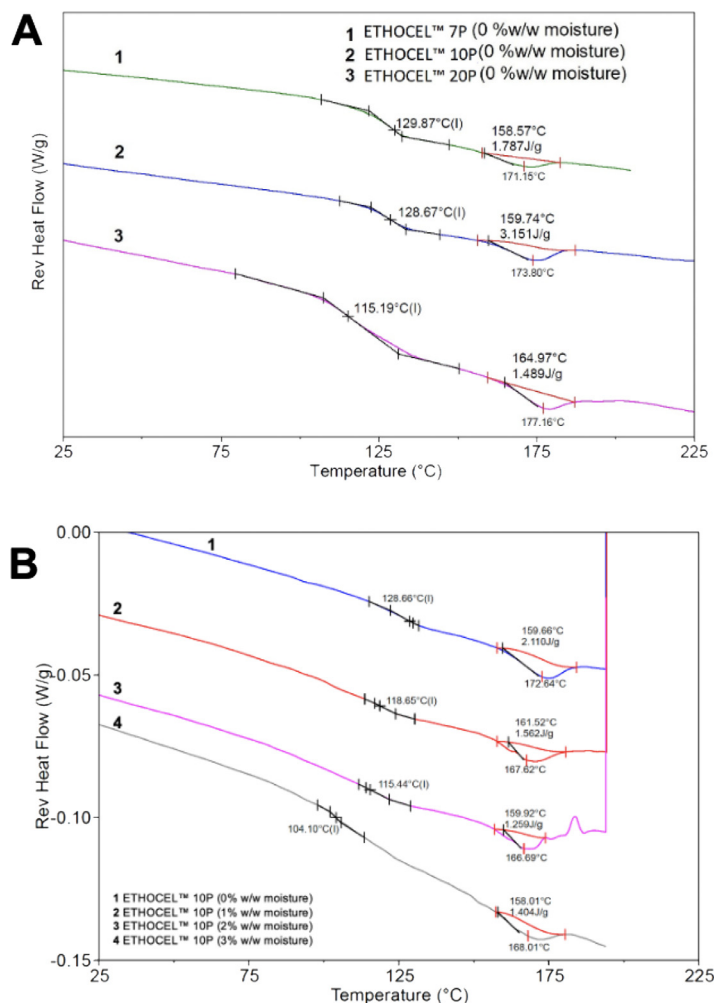
Figure 9. (A) DSC scans of dry (moisture-free) samples of three different grades of ethyl cellulose (Ethocel™ 7P, Ethocel™ 10P, Ethocel™ 20P) and (B) effects of 0, 1, 2 and 3% w/w moisture on DSC scans of Ethocel™ 10P.

HPMCP are enteric polymers that are soluble at different intestinal pH conditions higher than 5.5, 6.0 or 6.5 depending on their grades, and EC is a water-insoluble polymer that is usually used in combination with water-soluble polymers. It was observed that HPC absorbed most moisture, followed in decreasing order by HPMC, HPMCP, HPMCAS, and EC. Between 25 and 40 °C, there was less moisture sorption at higher temperature than that at the lower temperature.

Since moisture sorption may increase molecular mobility of polymers by reducing their T_g, effects of different amounts of moisture on T_g of the polymers were also determined by DSC. In DSC scans of HPC, there were no distinctive shifts in baselines for Tg, and, therefore, the effect of moisture on T_g of HPC could not be determined by DSC analysis. HPMC, however, gave a relatively shallow baseline shift in its DSC scan corresponding to its T_g, but the T_g practically disappeared when the moisture content increased from 1 to 2.5% w/w due to the plasticization of the material. Unlike HPC and HPMC, there was a gradual decrease in T_g of HMPMCAS and HPMCP with the increase in moisture content, which is in general agreement with the Gordon-Taylor/Kelley-Bueche equation. EC was found to be a semicrystalline polymer having both T_g and melting endotherm, and while there was some decrease in its T_g due to moisture sorption, there was no effect of moisture on its melting point. Among the different cellulosic polymers used in the present investigation, the hygroscopicity of HPMCAS and HPMCP are such that their T_g would remain at least 50 °C higher than the ambient room temperature of 25 °C even after exposure to 70% RH. It is hoped that the results of the present investigation will provide basic guidance for the selection of polymers for ASDs.

Declaration of Competing Interest

This work has not been supported by funding from any external sources. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
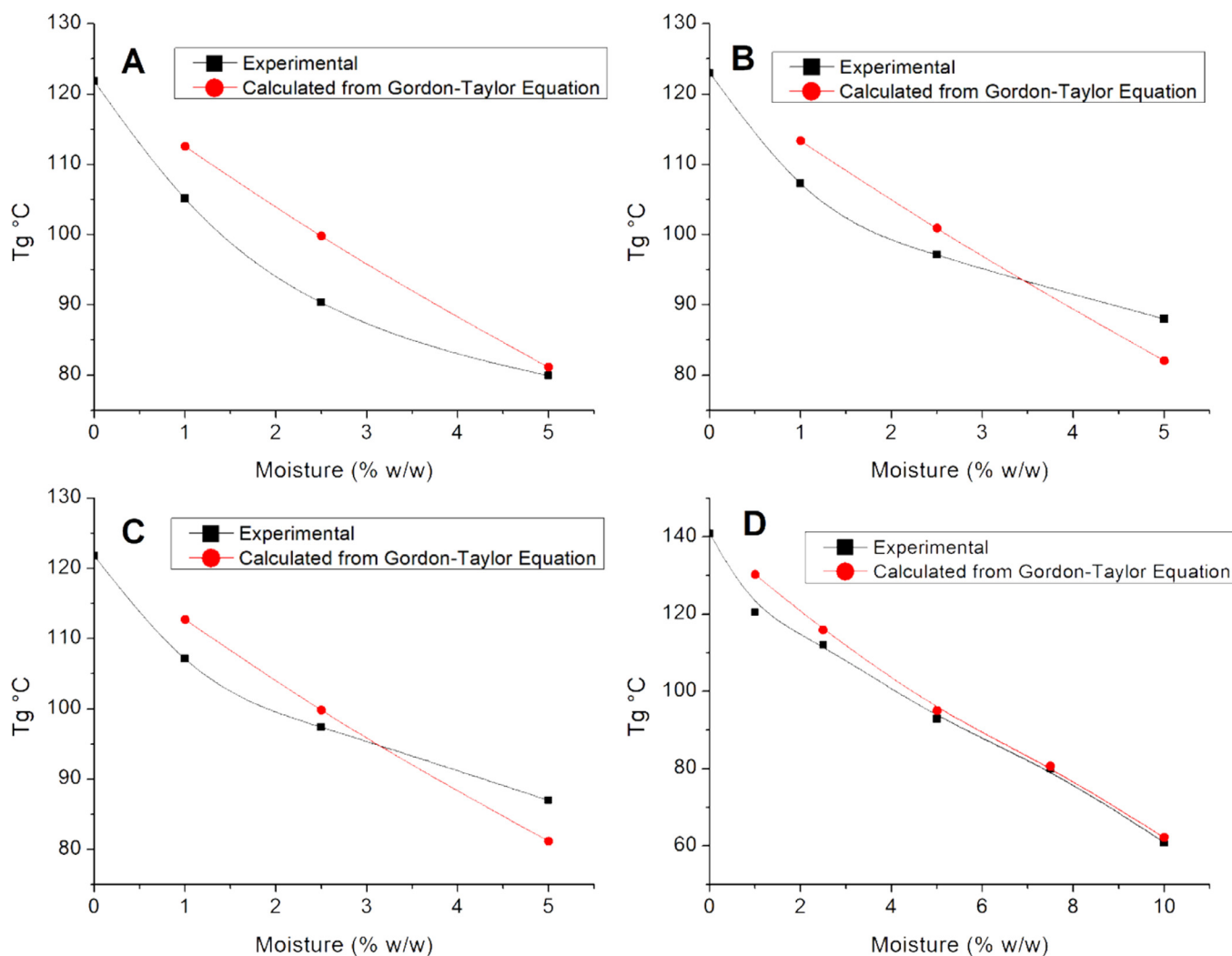
Figure 10. The comparison of the effect of moisture content on experimental and calculated T_g values of (A) HPMCAS LF, (B) HPMCAS MF, (C) HPMCAS HF and (D) HPMCP HP50.

References

1. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. *J Pharm Sci*. 2016;105(9):2527–2544. https://doi.org/10.1016/j.xphs.2015.10.008.
2. Vasanthavada M, Tong W-Q, Serajuddin ATM. Development of solid dispersion for poorly water-soluble drugs. *Water-Insoluble Drug Formul Second Ed*. 2008:499–529. https://doi.org/10.1201/9781420009552.ch18.
3. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci*. 1999;88(10):1058–1066. https://doi.org/10.1021/js980403l.
4. Gupta SS, Meena A, Parikh T, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - I: Polyvinylpyrrolidone and related polymers. *J Excipients Food Chem*. 2014;5(1):32–45. https://doi.org/10.1208/s12249-015-0426-6.
5. Meena A, Parikh T, Gupta SS, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - II: Cellulosic polymers. *J Excipients Food Chem*. 2014;5(1):46–55.
6. Parikh T, Gupta SS, Meena A, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - III: Polymethacrylates and polymethacrylic acid based polymers. *J Excipients Food Chem*. 2014;5:56–64.
7. Newman AW, Reutzel-edens SM, Zografi G. Characterization of the 'hygroscopic' properties of active pharmaceutical ingredients. *J Pharm Sci*. 2008;97(3):1047–1059. https://doi.org/10.1002/jps.
8. Marsac PJ, Rumondor ACF, Nivens DE, Kestur US, Lia S, Taylor LS. Effect of temperature and moisture on the miscibility of amorphous dispersions of felodipine and poly(vinyl pyrrolidone). *J Pharm Sci*. 2010;99(1):169–185. https://doi.org/10.1002/jps.21809.
9. Rumondor ACF, Marsac PJ, Stanford LA, Taylor LS. Phase behavior of poly(vinylpyrrolidone) containing amorphous solid dispersions in the presence of moisture. *Mol Pharm*. 2009;6(5):1492–1505. https://doi.org/10.1021/mp900050c.
10. Rumondor ACF, Taylor LS. *Effect of polymer hygroscopicity on the phase behavior of amorphous solid dispersions in the presence of moisture*. 2009;7(2):477–490.
11. Rumondor ACF, Taylor LS. Effect of polymer hygroscopicity on the phase behavior of amorphous solid dispersions in the presence of moisture. *Mol Pharm*. 2010;7(2):477–490. https://doi.org/10.1021/mp9002283.
12. Solanki NG, Gumaste SG, Shah AV, Serajuddin ATM. Effects of surfactants on itraconazole-hydroxypropyl methylcellulose acetate succinate solid dispersion prepared by hot melt extrusion. ii: rheological analysis and extrudability testing. *J Pharm Sci*. 2019;108(9):3063–3073. https://doi.org/10.1016/j.xphs.2019.05.010.
13. Janssens S, De Zeure A, Paudel A, Van Humbeeck J, Rombaut P, Van Den Mooter G. Influence of preparation methods on solid state supersaturation of amorphous solid dispersions: a case study with itraconazole and eudragit E100. *Pharm Res*. 2010;27(5):775–785. https://doi.org/10.1007/s11095-010-0069-y.
14. Kojima T, Higashi K, Suzuki T, Tomono K, Moribe K, Yamamoto K. Stabilization of a supersaturated solution of mefenamic acid from a solid dispersion with Eudragit® EPO. *Pharm Res*. 2012;29(10):2777–2791. https://doi.org/10.1007/s11095-011-0655-7.
15. Callahan JC, Cleary GW, Elefant M, Kaplan G, Kensler T, Nash RA. Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm*. 1982;8(3):355–369. https://doi.org/10.3109/03639048209022105.
16. Sadek HM, Olsen JL. Determination of water-adsorption isotherms of hydrophilic polymers. *Pharm Technol*. 1981;5(2):42–48.
17. Bühler V. *Kollidon® Polyvinylpyrrolidone Excipients for the Pharmaceutical Industry. Vol 9th*. BASF; 2008. http://www.pharma-solutions.basf.com/pdf/G-EMPMD256_-Kollidon_Polyvinylpyrrolidone_excipients_for_the_pharmaceutical_industry.pdf.
18. Patel NG, Serajuddin ATM. Moisture sorption by polymeric excipients commonly used in amorphous solid dispersion and its effect on glass transition temperature:

I. Polyvinylpyrrolidone and related copolymers. *Int J Pharm.* 2022:616. https://doi.org/10.1016/j.ijpharm.2022.121532.

19. Zografi G, Kontny MJ, Yang AYS, Brenner GS. Surface area and water vapor sorption of macrocrystalline cellulose. *Int J Pharm.* 1984;18(1-2):99–116. https://doi.org/10.1016/0378-5173(84)90111-X.

20. Ocieczek A, Kostek R. The effect of micronization on sorptive properties wheat cellulose. *Inżynieria I Apar Chem.* 2009;48(40):108–109.

21. Bruno L, Kasapis S, Heng PWS. Effect of polymer molecular weight on the structural properties of non aqueous ethyl cellulose gels intended for topical drug delivery. *Carbohydr Polym.* 2012;88(1):382–388. https://doi.org/10.1016/j.carbpol.2011.12.031.

22. Fukasawa M, Obara S. Molecular weight determination of hypromellose phthalate (HPMCP) using size exclusion chromatography with a multi-angle laser light scattering detector. *Chem Pharm Bull.* 2003;51(11):1304–1306. https://doi.org/10.1248/cpb.51.1304.

23. Arca HC, Mosquera-Giraldo LI, Bi V, Xu D, Taylor LS, Edgar KJ. Pharmaceutical applications of cellulose ethers and cellulose ether esters. *Biomacromolecules.* 2018;19(7):2351–2376. https://doi.org/10.1021/acs.biomac.8b00517.

24. Brady J, Drig T, Lee PI, Li JX. *Polymer Properties and Characterization.* 2017. https://doi.org/10.1016/B978-0-12-802447-8.00007-8.

25. Onoue S, Sato H, Ogawa K, et al. Improved dissolution and pharmacokinetic behavior of cyclosporine A using high-energy amorphous solid dispersion approach. *Int J Pharm.* 2010;399(1-2):94–101. https://doi.org/10.1016/j.ijpharm.2010.08.007.

26. Ozeki T, Yuasa H, Kanaya Y. Application of the solid dispersion method to the controlled release of medicine. IX. Difference in the release of flurbiprofen from solid dispersions with poly(ethylene oxide) and hydroxypropylcellulose and the interaction between medicine and polymers. *Int J Pharm.* 1997;155(2):209–217. https://doi.org/10.1016/S0378-5173(97)00167-1.

27. Lakshman JP, Kowalski J, Vasanthavada M, Tong W-Q, Joshi YM, Serajuddin ATM. Application of melt granulation technology to enhance tabletting properties of poorly compactible high-dose drugs. *J Pharm Sci.* 2011;100(4):1553–1565. https://doi.org/10.1002/jps.22369.

28. Batra A, Desai D, Serajuddin ATM. Investigating the use of polymeric binders in twin screw melt granulation process for improving compactibility of drugs. *J Pharm Sci.* 2017;106(1):140–150. https://doi.org/10.1016/j.xphs.2016.07.014.

29. Batra A, Thongsukmak A, Desai D, Serajuddin ATM. The Effect of process variables and binder concentration on tabletability of metformin hydrochloride and acetaminophen granules produced by twin screw melt granulation with different polymeric binders. *AAPS PharmSciTech.* 2021;22(4). https://doi.org/10.1208/s12249-021-02018-6.

30. Batra A, Yang F, Kogan M, et al. Comparison of hydroxypropylcellulose and hot-melt extrudable hypromellose in twin-screw melt granulation of metformin hydrochloride: effect of rheological properties of polymer on melt granulation and granule properties. *Macromol.* 2021;2(1):1–19. https://doi.org/10.3390/macromol2010001.

31. Oksanen CA, Zografi G. Molecular mobility in mixtures of absorbed water and solid poly(vinylpyrrolidone). *Pharm Res.* 1993;10(6):791–799. https://doi.org/10.1023/A:1018988506336.

32. Adibkia K, Barzegar-Jalali M, Maheri-Esfanjani H, et al. Physicochemical characterization of naproxen solid dispersions prepared via spray drying technology. *Powder Technol.* 2013;246:448–455. https://doi.org/10.1016/j.powtec.2013.05.044.

33. Verreck G, Six K, Van Den Mooter G, Peeters J, Brewster ME. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion- Part I. *Int J Pharm.* 2003;251:165–174. 10.1016/s0378-5173(02)00591-4.

34. Six K, Berghmans H, Leuner C, et al. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion, Part II. *Pharm Res.* 2003;20(7):1047–1054. https://doi.org/10.1023/A:1024414423779.

35. Zhao M, Barker SA, Belton PS, McGregor C, Craig DQM. Development of fully amorphous dispersions of a low Tg drug via co-spray drying with hydrophilic polymers. *Eur J Pharm Biopharm.* 2012;82(3):572–579. https://doi.org/10.1016/j.ejpb.2012.07.012.

36. Gupta SS, Solanki N, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion, IV: Affinisol™ HPMC HME polymers. *AAPS PharmSciTech.* 2016;17(1):148–157. https://doi.org/10.1208/s12249-015-0426-6.

37. Solanki NG, Lam K, Tahsin M, Gumaste SG, Shah AV, Serajuddin ATM. Effects of surfactants on itraconazole-hpmcas solid dispersion prepared by hot-melt extrusion I: miscibility and drug release. *J Pharm Sci.* 2019;108(4):1453–1465. https://doi.org/10.1016/j.xphs.2018.10.058.

38. Solanki NG, Kathawala M, Serajuddin ATM. Effects of surfactants on itraconazole-hydroxypropyl methylcellulose acetate succinate solid dispersion prepared by hot melt extrusion III: tableting of extrudates and drug release from tablets. *J Pharm Sci.* 2019;108(12):3859–3869. https://doi.org/10.1016/j.xphs.2019.09.014.

39. Adhikari A, Polli JE. Characterization of grades of HPMCAS spray dried dispersions of itraconazole based on supersaturation kinetics and molecular interactions impacting formulation performance. *Pharm Res.* 2020;37(10):4–7. https://doi.org/10.1007/s11095-020-02909-6.

40. Curatolo W, Nightingale JA, Herbig SM. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. *Pharm Res.* 2009;26(6):1419–1431. https://doi.org/10.1007/s11095-009-9852-z.

41. Hypromellose Phthalate HPMCP HP50. *Shin-Etsu Chem Co,* Ltd Cellul.:1-9.

42. Albadarin AB, Potter CB, Davis MT, et al. Development of stability-enhanced ternary solid dispersions via combinations of HPMCP and Soluplus® processed by hot melt extrusion. *Int J Pharm.* 2017;532(1):603–611. https://doi.org/10.1016/j.ijpharm.2017.09.035.

43. Li N, Taylor LS. Tailoring supersaturation from amorphous solid dispersions. *J Control Release.* 2018;10:114–125. https://doi.org/10.1016/j.jconrel.2018.04.014.Tailoring.

44. Song Y, Yang X, Chen X, Nie H, Byrn S, Lubach JW. Investigation of drug-excipient interactions in lapatinib amorphous solid dispersions using solid-state NMR spectroscopy. *Mol Pharm.* 2015;12(3):857–866. https://doi.org/10.1021/mp500692a.

45. Sadia M, Arafat B, Ahmed W, Forbes RT, Alhnan MA. Channelled tablets: an innovative approach to accelerating drug release from 3D printed tablets. *J Control Release.* 2018;269:355–363. https://doi.org/10.1016/j.jconrel.2017.11.022.

46. Feng X, Vo A, Patil H, et al. The effects of polymer carrier, hot melt extrusion process and downstream processing parameters on the moisture sorption properties of amorphous solid dispersions. *J Pharm Pharmacol.* 2016;68(5):692–704. doi:10.1111%2Fjphp.12488.

47. Maincent J, Williams RO. Sustained-release amorphous solid dispersions. *Drug Deliv Transl Res.* 2018;8(6):1714–1725. https://doi.org/10.1007/s13346-018-0494-8.

48. De Brabander C, van den Mooter G, Vervaet C, Remon JP. Characterization of ibuprofen as a nontraditional plasticizer of ethyl cellulose. *J Pharm Sci.* 2002;91(7):1678–1685. https://doi.org/10.1002/jps.10159.

49. De Brabander C, Vervaet C, Remon JP. Development and evaluation of sustained release mini-matrices prepared via hot melt extrusion. *J Control Release.* 2003;89(2):235–247. https://doi.org/10.1016/S0168-3659(03)00075-0.

50. Cellulosics Dow. *Ethocel, Ethylcellulose Polymers.* 20052005:1–27. *Techinical Handbook.*

51. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J Pharm Sci.* 1997;86(1):1. https://doi.org/10.1021/js9601896.

52. Rials TG, Glasser WG. Thermal and dynamic mechanical properties of hydroxypropyl cellulose films. *J Appl Polym Sci.* 1988;36(4):749–758. https://doi.org/10.1002/app.1988.070360402.

53. Picker-Freyer KM, Dürig T. Physical mechanical and tablet formation properties of hydroxypropylcellulose: in pure form and in mixtures. *AAPS PharmSciTech.* 2007;8(4):82. https://doi.org/10.1208/pt0804092.

54. Stubberud L, Arwidsson HG, Larsson A, Graffner C. Water solid interactions II. Effect of moisture sorption and glass transition temperature on compactibility of microcrystalline cellulose alone or in binary mixtures with polyvinyl pyrrolidone. *Int J Pharm.* 1996;134(1-2):79–88. https://doi.org/10.1016/0378-5173(95)04439-6.

55. Mihranyan A, Llagostera AP, Karmhag R, Strømme M, Ek R. Moisture sorption by cellulose powders of varying crystallinity. *Int J Pharm.* 2004;269(2):433–442. https://doi.org/10.1016/j.ijpharm.2003.09.030.

56. Gómez-Carracedo a, Alvarez-Lorenzo C, Gómez-Amoza J, Concheiro A. Chemical structure and glass transition temperature of non-ionic cellulose ethers. *J Therm Anal Calorim.* 2003;73(2):587–596. 10.1023/A:1025434314396.

57. Hancock BC, Zografi G. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm Res.* 1994;11(4):471–477. https://doi.org/10.1023/A:1018941810744.

58. Gordon M, Taylor JS. Ideal copolymers and the second-order transitions of synthetic rubbers. I. Noncrystalline copolymers. *Rubber Chem Technol.* 1952;26(2):323–335. https://doi.org/10.5254/1.3539818.

59. Kelley FN, Bueche F. Viscosity and glass temperature relations for polymer-diluent systems. *J Polym Sci.* 1961;50(154):549–556. https://doi.org/10.1002/pol.1961.1205015421.