



Moisture sorption by polymeric excipients commonly used in amorphous solid dispersions and its effect on glass transition temperature: III. Methacrylic acid-methyl methacrylate and related copolymers (Eudragit®)

Nirali G. Patel, Sabrina Banella¹, Abu T.M. Serajuddin^{*}

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY 11439, USA

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ABSTRACT

Moisture sorption by polymeric carriers used in amorphous solid dispersion (ASD) plays a critical role in the physical stability of the dispersed drug as it can increase molecular mobility of drug in ASD by decreasing the glass transition temperatures (T_g) of the drug-polymer system, leading to drug crystallization. The present report describes Part III of a systematic investigation of moisture sorption by different polymers used in ASDs, where the results for four chemically different methacrylic acid-methyl methacrylate and related copolymers, namely, Eudragit® EPO, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100, as the function of relative humidity (RH) are presented. Effects of moisture sorption on T_g of the polymers were also determined. Among the polymers, Eudragit® EPO is the least hygroscopic, having absorbed, for example, 1.3% w/w moisture at 25 °C/60% RH, while the three other polymers absorbed 4.7–7.5% w/w moisture at the same condition. The moisture sorption was relatively lower at 40 °C than that at 25 °C. The apparent T_g of polymers decreased with the increase in moisture content; however, T_g values remained higher than the usual storage temperature of ASD (25 °C) even at high RH, indicating that the effect of moisture sorption on the physical stability of ASD could be minimal when these polymers are used in ASDs.

1. Introduction

Amorphous solid dispersion (ASD) has emerged as one of the most viable options among different formulation technologies applied to improve the dissolution rate and bioavailability of poorly water-soluble drugs. In an ASD, the drug is dispersed either molecularly or in the amorphous state in polymeric carriers that are also amorphous by spray drying, melt extrusion, etc. (Serajuddin, 1999; Baghel et al., 2016; Vasanthavada et al., 2018). Fractions of drug substances in ASDs are often less than 25% w/w, while the remaining parts of the formulations are usually polymers and, in some cases, other excipients like surfactants are included (Solanki et al., 2019a; Solanki et al., 2019b). It is, therefore, critically important that polymers used for ASDs are selected by careful evaluation of their physicochemical properties and performance. However, most of the reports on polymeric excipients in the literature are related to their application in solid dosage forms as binders, disintegrants, coating agents, matrices, membranes for controlled release, and so forth, and there is only a very limited number of reports in the

literature on physicochemical properties of polymers relevant to the development of amorphous solid dispersion. For these reasons, we have systematically investigated some of these properties in our laboratory. Previously, we reported on the thermal and viscoelastic properties of several PVP and related polymers (Gupta et al., 2014), celluloses (Meena et al., 2014; Gupta et al., 2016), and methacrylic acid-methyl acrylate copolymers (Parikh et al., 2014) used in ASDs. Hygroscopicity is another physicochemical property influencing the performance of polymers and the stability of ASDs. Therefore, in Part I and Part II of the present series of papers, we reported moisture sorption as a function of relative humidity (RH) and its effect on glass transition temperature (T_g) of, respectively, different PVPs and related polymers (Patel and Serajuddin, 2022) and celluloses (Patel et al., 2022). In the present Part III of the series, we are reporting the moisture sorption and its effect on T_g of methacrylic acid-methacrylate copolymers. Moisture sorption by ASDs containing drug-polymer mixtures and its effects on T_g of the systems will be reported in the future.

Copolymers of methacrylic acid and methyl methacrylate are

^{*} Corresponding author.

E-mail address: serajuda@stjohns.edu (A.T.M. Serajuddin).

¹ Current address: Department of Life Sciences and Biotechnology, University of Ferrara, 44121 Ferrara, Italy.

commercially available with the trade name of Eudragit® from Evonik Corporation, Parsippany, NJ, USA. Eudragit® is prepared synthetically by polymerization of acrylic and methacrylic acids or their esters like methyl ester, butyl ester, dimethyl aminoethyl ester, etc. They all exist in the amorphous state (Parikh et al., 2014). According to Thakral et al. (2013), Eudragit® is available in four general chemical grades, namely, Eudragit® E, Eudragit® L and S, Eudragit® RL and RS, and Eudragit® NE and NM. Another polymer, Eudragit® L100-55, has certain similarities with Eudragit® L but may be considered as a distinctly different grade because of the difference in its chemical structure and physico-chemical properties. Structures of the different grades of Eudragit® with brief descriptions of their chemical nature are shown in Table 1.

Because of the differences in their chemical structures, the pharmaceutical attributes of different grades of Eudragit® differ greatly. Since the tertiary amine group of Eudragit® E undergoes protonation at a relatively low pH, it is water soluble under gastric pH conditions of less than 5. But, it is practically non-protonated at pH > 5 and, therefore, insoluble under intestinal pH conditions. In contrast to Eudragit® E, Eudragit® L, and Eudragit® S dissolve at higher intestinal pH conditions by the ionization of their acidic groups; while the L grade dissolves at pH > 6, the S grade dissolves only at pH > 7 since a lesser number of the carboxyl group (-COOH) is present in its structure due to the lower MA to MM ratio. To lower the dissolving pH, another polymer, Eudragit® L100-55, has also been marketed by the manufacturer, which is chemically similar to Eudragit® L, except that it is produced by 1:1 copolymerization of methacrylic acid with ethyl acrylate (EA) rather than methyl methacrylate. As a result, it starts dissolving at a lower pH (pH > 5.5) than that of the L grade (pH > 6.0), thus enabling drug release under the lower duodenal pH condition. Eudragit® L, Eudragit® S, and Eudragit® L100-55 are generally called enteric polymers as they are water-insoluble at lower gastric pH conditions and water-soluble only under intestinal pH conditions. Unlike all the above-mentioned polymers, Eudragit® RL and RS are water-insoluble under all pH conditions, and they undergo only some swelling at both gastric and intestinal pH conditions. For these reasons, they are usually used as tablet matrices or tablet coating films in sustained-release drug products. Eudragit® NE and NM are also water-insoluble polymers that are generally used for sustained-release drug delivery. The Eudragit® polymers may again be categorized into different sub-grades for specific applications in the formulation. For example, Eudragit® EPO belongs to the E grade, and it is marketed as a powder for oral use (*per oral* or PO). Often, numbers like 100, 30, 40, etc., are also attached to the names of the polymers, where 100 refers to dry, neat polymer, and 30 or 40 refer, respectively, to 30% or 40% w/v aqueous dispersions.

Different Eudragit® grades have extensively been investigated as carriers for ASDs. For example, there are many reports on the use of Eudragit® E as polymeric carriers to increase dissolution rates of poorly water-soluble drugs and to exert supersaturation effects on drugs in aqueous media (Chokshi et al., 2005; Janssens et al., 2010; Kojima et al., 2012; Xie et al., 2017; Fan et al., 2021). It has also found its use in 3D-printed tablets produced by fused diffusion modeling (FDM) where filaments containing amorphous solid dispersions of drugs in Eudragit® E are produced by hot melt extrusion and then printed into tablets (Serajuddin, 2023). Other polymers like Eudragit® S (Higashi et al., 2015; Metre et al., 2018) and Eudragit® L (Hasegawa et al., 1985; Nazzal et al., 2002) have also been used for the development of ASDs. Since Eudragit® RL and RS are water-insoluble polymers, Otsuka et al. (1993) reported that using these polymers to prepare ASDs leads to slow and erratic drug release rates, and, therefore, these polymers have not been much used in ASDs. There are also no significant reports on the use of Eudragit® NE and NM in ASDs as they are water-insoluble. Despite the interest in using several Eudragit® polymers to develop ASDs, there are no reports on their moisture sorption under different RH conditions and how moisture sorption may influence their glass transition temperatures (T_g) and the physical stability of ASDs produced. Most of the reports on the interaction between Eudragit® and water in the literature are on the

moisture barrier properties of the polymers when they are used as coating agents for solid dosage forms (Mwesigwa and Basit, 2016).

We have studied moisture sorption by four Eudragit® polymers, namely, Eudragit® EPO, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100, in the present investigation. The polymers were selected by considering their chemical structures and potential application in developing ASDs. Among them, Eudragit® EPO is highly soluble at low gastric pH conditions (pH < 5), and it is commonly used in ASDs to provide immediate drug release in gastric pH environments after oral administration. However, there could be incomplete or variable drug release from ASDs containing Eudragit® EPO if the drug is not fully released at low pH or there is an increase in gastric pH to above 5 in the fed state. The other polymers, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100, are all enteric polymers that dissolve at pH higher than 5.5, 6, and 7, respectively. We have studied all three enteric Eudragit® polymers primarily because a different enteric polymer, hydroxypropyl methylcellulose acetate succinate (HPMCAS) is available in 3 different grades that dissolve at pH higher than 5.5, 6.0 and 7. HPMCAS has in recent years been extensively investigated for its ability to provide supersaturation of drugs in aqueous media. Seven ASDs using HPMCAS as the polymeric carrier have already been marketed in the US (Solanki et al., 2019a). We recently reported moisture sorption properties and their effect on T_g of the three grades of HPMCAS (Patel et al., 2022), and, therefore, it was important to also investigate how the moisture sorption behavior of the three grades of Eudragit® compared with that of the three grades of HPMCAS reported earlier. Eudragit® RL/RS and Eudragit® NE/NM were not selected for the present investigation since they are water-insoluble and may not have much application in the development of ASDs for increasing dissolution rates of drugs.

In the present investigation, we have also conducted moisture sorption experiments for each polymer at two temperatures of 25 and 40 °C. Although solid dosage forms are generally stored at room temperature of ~ 25 °C, they are subjected to 40 °C during accelerated stability testing. It was, therefore, of interest to determine whether there is any difference in moisture sorption at the two temperatures.

2. Materials and methods

2.1. Materials

Eudragit® EPO, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100 were supplied by Evonik Corporation, Parsippany, NJ, USA.

2.2. Methods

The detailed methods for studying moisture sorption and thermal properties of polymers were reported in Part I and Part II of the present series of papers (Patel and Serajuddin, 2022; Patel et al., 2022). Therefore, only brief descriptions of the methods are given below:

2.2.1. Moisture sorption study

An automated dynamic vapor sorption analyzer (VTI SA, TA Instruments, Wilmington, DE, USA) was used for moisture sorption analysis at 25 and 40 °C. Different relative humidity (RH) conditions in the range of 10% RH to 90% RH within the instrument chamber were generated at 10% RH intervals by combining different ratios of dry nitrogen and water-saturated nitrogen passed through a water reservoir. Each sample was first subjected to a drying step to remove residual moisture. For this purpose, a sample of 25 ± 5 mg of the polymer was placed on a quartz pan, which was then mounted on a microbalance in the VTI moisture sorption analyzer for drying at 40 °C for 1 h using the dry nitrogen flow. The RH of the chamber was then increased from 10 to 90% at 10% intervals. The weight change threshold at each moisture sorption step was set at 0.004% w/w in 5 min, and a maximum period of 1440 min was given for the isotherm to reach the threshold at each step.

Table 1
Chemical structures of different Eudragit® grades.

Trade name	Structure	Molecular weight	Description
Eudragit® E		~47,000	It is a cationic polymer chemically comprised of dimethyl aminoethyl methacrylate, butyl methacrylate, and methyl methacrylate at a ratio of 2:1:1 in the polymeric chain
Eudragit® L and Eudragit® S		~125,000	They are anionic polymers with L and S having, respectively, 1:1 and 1:2 ratios of methacrylic acid (MA) and methyl methacrylate (MM) in polymeric chains.
Eudragit® L100-55		~320,000	It is chemically similar to Eudragit® L, except that it is produced by 1:1 copolymerization of methacrylic acid with ethyl acrylate (EA) rather than methyl methacrylate.
Eudragit® RL and Eudragit® RS	<p>Eudragit RL: m=0.2, n=2, o= 1 Eudragit RS: m=0.1, n=2, o= 1</p>	~32,000	They are copolymers of methyl methacrylate and ethyl methacrylate at 2:1 ratio, where RL and RS additionally contain, respectively, 8.8–12.0% and 4.5–6.8% quaternary ammonium groups with methyl methacrylic acid.

(continued on next page)

Table 1 (continued)

Trade name	Structure	Molecular weight	Description
Eudragit® NE and Eudragit® NM		NE: ~750,000 NM: ~600,000	Both NE and NM grades are neutral copolymers based on ethyl acrylate and methyl methacrylate at 2:1 ratio with certain differences in their molecular weights and manufacturing methods. They are available as aqueous, milky dispersions containing 30 and 40% polymers, respectively.

2.2.2. Thermal analysis of polymer with different moisture contents

A novel method was developed to absorb an accurate amount of moisture into a polymer sample and then retain the moisture during DSC scanning of the sample. For this purpose, ~5 mg of the sample was weighed on a Tzero aluminum DSC pan, and the DSC pan was then placed on the flat-bottomed aluminum pan used to hold the moisture analysis sample in the VTI instrument. The sample was dried at 50 °C for 15 min under dry nitrogen flow, which was then followed by the continuation of purging of dry nitrogen for another 60 min while the sample cooled down to 25 °C. It was confirmed by the thermogravimetric (TG) analysis that the sample was completely moisture-free after such drying. To absorb moisture, the dried sample was subjected to 25 °C/90% RH until the sample gained pre-defined weight (1%, 2.5%, 5%, etc.). The DSC pan containing the absorbed moisture was then removed from the moisture sorption apparatus, and a Tzero aluminum lid was

placed on the top and sealed immediately so that all the absorbed moisture was retained within the pan. The whole process of removing the sample from VTI and sealing took < 10 s. Modulated DSC analysis of the sealed sample was conducted using Q200 modulated DSC analyzer (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 considered as T_g . Although this technique allows the incorporation of predetermined amounts of moisture in a sample inside a sealed DSC pan, there is a potential, as reported earlier by Patel et al. (2022), that the moisture might partially escape the sample during heating and be trapped in the headspace of the sample pan. Consequently, the effect of moisture in lowering T_g of polymers may be underestimated. Nonetheless, as shown earlier (Patel et al., 2022; Patel and Serajuddin, 2022), the method reasonably estimates the changes in T_g due to moisture sorption.

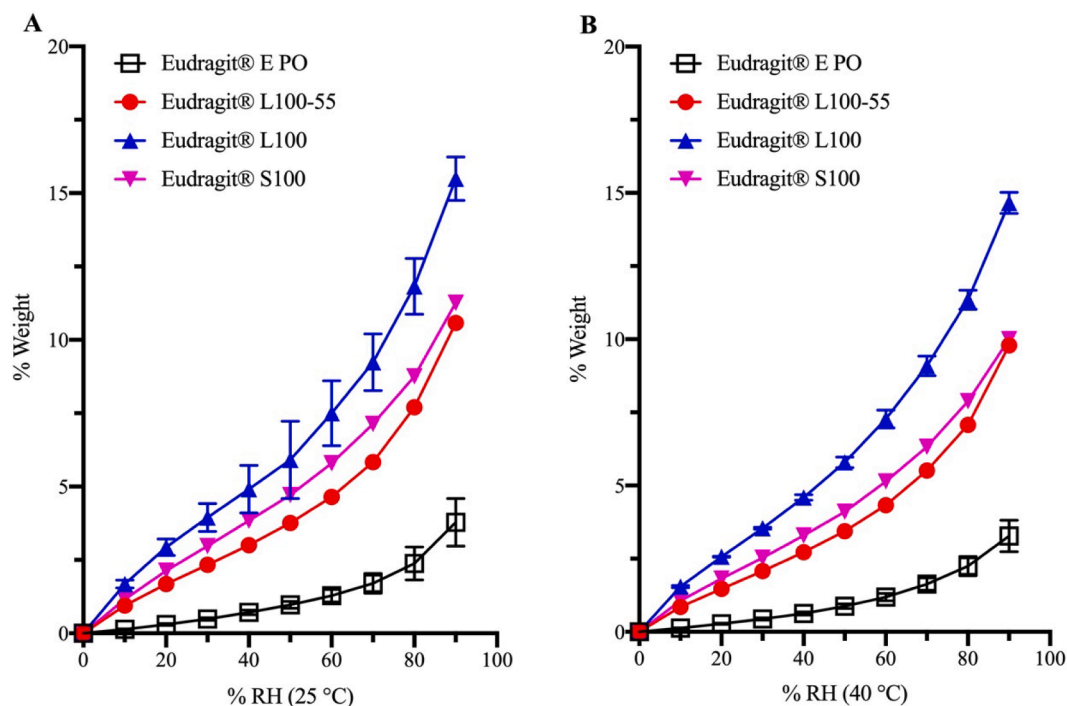


Fig. 1. Moisture sorption (weight gain) as a function of relative humidity (RH) by Eudragit® EPO, Eudragit® L100, Eudragit® S100, and Eudragit® L100-55 at (A) 25 °C and (B) 40 °C. Average values \pm s.d. are plotted when moisture sorption was determined in triplicate, and in other cases, average values of duplicate determinations are plotted.

3. Results and discussion

3.1. Moisture sorption by methacrylic acid-methyl methacrylate and related copolymers (Eudragit®)

The results of the moisture sorption analysis of different Eudragit® grades are given in Table 1, and, to demonstrate differences in moisture sorption among them, the results are also plotted in Fig. 1. It may be observed in Table 2 that the results of moisture sorption experiments are highly reproducible. When there is practically no difference in moisture sorption in duplicate experiments, the average of duplicate values is given in the table, and individual values are noted in parentheses under the average values. Moisture sorption in several experiments was also determined in triplicate, where average values \pm s.d. are given in the table. All materials were used as received from the manufacturers, and no considerations were made for their particle sizes or surface areas. This is because, although no data on the effect of particle size on the moisture sorption by Eudragit® polymers are available, Zografí et al. (1984) reported that, in the case of celluloses, it depends on the interaction between moisture and polymer like hydrogen bonding, and, therefore, the moisture sorption depends on the number of binding sites in the polymeric chains and not on the specific surface area of polymer used. This was confirmed by Ociecek and Kostek (2009), who observed that three widely different particle sizes of a cellulose gave essentially similar moisture sorption profiles. It is possible that the moisture sorption by Eudragit® also occurs similarly due to certain chemical interactions between moisture and polymer. It may also be mentioned here that different batches of each Eudragit® grade were used in the present investigation for duplicate or triplicate experiments, which could have different particle sizes due to any batch-to-batch variability. However, the lack of any such batch-to-batch variability in the moisture sorption indicates that if there were any difference in particle size of different batches, its effect was minimal and negligible.

As shown in Table 2, Eudragit® EPO has very low hygroscopicity as it absorbs only about 1 and 1.7 percent moisture at 50 and 70% RH, respectively, at 25 °C, and the moisture sorption was only 3.8% w/w at 25 °C/90% RH. By comparison, moisture sorption by Eudragit® L100-55, Eudragit® L100, and Eudragit® S100 is much higher. Among the three later polymers, the moisture sorption was in the order of Eudragit® L100 > Eudragit® S100 > Eudragit® L100-55. For example, at 25 °C/70% RH, the three polymers absorbed 9.24, 7.13, and 5.83% moisture, respectively, and at 25 °C/90% RH, there was the moisture sorption of 15.49, 11.26, and 10.58%, respectively.

Structural differences among different grades of Eudragit® (Table 1) may explain differences in their moisture sorption. It has been reported in the literature that the adsorption of water on the surface of solids generally occurs with the oxygen in water acting as the Lewis base and the solid site as the Lewis acid, leading to the formation of hydrogen

bonds (Zografí 1988). The only hydrophilic site available in Eudragit® EPO is the tertiary amine that may not form any hydrogen bond with the adsorbed moisture in the microenvironment of the solid surface. As shown in Table 1, there are no other potential hydrogen bonding sites in Eudragit® EPO. This could be the reason why Eudragit® EPO is relatively non-hygroscopic compared to the other grades of polymers. In contrast, the three other polymers used in the present investigation have -COOH groups in their structures capable of hydrogen bonding with moisture and, as a result, they are hygroscopic. As mentioned earlier, between Eudragit® L and Eudragit® S, the L grade has twice the fraction of methacrylic acid in the structure (and, therefore, more carboxyl groups) than the S grade, and, consequently, it is more hygroscopic. Between Eudragit® L100 and Eudragit® L100-55, there are specific structural differences in polymer chains as the former is a 1:1-copolymer of methacrylic acid and methyl methacrylate, while the latter is a 1:1 copolymer of methacrylic acid and ethyl acrylate. It is possible that the presence of less hydrophobic methyl group rather than the ethyl group makes Eudragit® L100 more hygroscopic than Eudragit® L100-55.

3.1.1. Effect of temperature on moisture sorption

Table 2 and Fig. 1 also show the effect of temperature on moisture sorption by different grades of Eudragit®, where, in general, the moisture contents were lower at 40 °C than that at 25 °C, which agrees with observations made earlier with PVPs and related polymers (Patel and Serajuddin, 2022) and cellulosic polymers (Patel et al., 2022). Oksanen and Zografí (1993) suggested that the adsorbed water gains higher energy at a higher temperature that can break hydrogen bonding between water and polymer, and, as a consequence, there is the potential for lower moisture sorption with increasing temperature. In the present investigation, the difference between moisture contents of Eudragit® EPO at 25 °C and 40 °C is small possibly because, as mentioned earlier, the potential for hydrogen bonding between the polymer and water is very low.

As mentioned earlier, Eudragit® L100-55, Eudragit® L, and Eudragit® S are enteric polymers that dissolve under intestinal pH conditions above pH 5.5, 6, and 7, respectively. Since three cellulosic polymers, HPMCAS L, M, and H, also dissolve under similar conditions above pH 5.5, 6, and 7, respectively, it is of interest to compare moisture sorption by the Eudragit® grades with that of the HPMCAS grades (Patel et al., 2022). Although both Eudragit® and HPMCAS absorb relatively low levels of moisture, the Eudragit® grades of polymers are somewhat more hygroscopic than the HPMCAS grades. For example, Table 2 shows that, at 25 °C/60% RH, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100 absorb, respectively, 4.65, 7.50, and 5.79 w/w moisture, while HPMCAS L, M, and H absorb, respectively, 4.34, 3.86 and 3.36% w/w moisture at the same condition.

Table 2

Moisture sorption by different grades of Eudragit® as a function of relative humidity (RH) at 25 and 40 °C.

RH	%Weight Gain ^a							
	25 °C	25 °C	25 °C	25 °C	40 °C	40 °C	40 °C	40 °C
0	0	0	0	0	0	0	0	0
10	0.14 \pm 0.02	0.95 (0.97,0.92)	1.68 \pm 0.13	1.16 (1.22,1.09)	0.13 \pm 0.01	0.85 (0.86,0.84)	1.55 \pm 0.04	1.06 (1.03,1.08)
20	0.30 \pm 0.03	1.68 (1.67,1.69)	2.93 \pm 0.28	2.13 (2.18,2.07)	0.28 \pm 0.03	1.47 (1.48,1.46)	2.57 \pm 0.02	1.82 (1.79,1.85)
30	0.49 \pm 0.05	2.33 (2.29,2.36)	3.95 \pm 0.48	2.97 (3.02,2.92)	0.44 \pm 0.04	2.08 (2.09,2.07)	3.54 \pm 0.03	2.53 (2.49,2.57)
40	0.71 \pm 0.08	3.00 (2.96,3.04)	4.91 \pm 0.81	3.84 (3.83,3.84)	0.63 \pm 0.06	2.72 (2.73,2.70)	4.59 \pm 0.10	3.29 (3.24,3.33)
50	0.97 \pm 0.12	3.76 (3.76,3.75)	5.91 \pm 1.32	4.71 (4.63,4.79)	0.88 \pm 0.08	3.44 (3.43,3.45)	5.79 \pm 0.18	4.10 (4.05,4.15)
60	1.28 \pm 0.21	4.65 (4.65,4.64)	7.50 \pm 1.11	5.79 (5.70,5.87)	1.19 \pm 0.13	4.33 (4.34,4.31)	7.27 \pm 0.31	5.14 (5.07,5.20)
70	1.70 \pm 0.34	5.83 (5.86,5.79)	9.24 \pm 0.97	7.13 (7.15,7.10)	1.63 \pm 0.21	5.51 (5.51,5.50)	9.09 \pm 0.34	6.32 (6.25,6.38)
80	2.38 \pm 0.56	7.70 (7.73,7.66)	11.82 \pm 0.95	8.75 (8.97,8.52)	2.25 \pm 0.33	7.07 (7.06,7.07)	11.35 \pm 0.33	7.88 (7.86,7.89)
90	3.78 \pm 0.81	10.58 (10.65,10.50)	15.49 \pm 0.74	11.26 (11.84,10.67)	3.28 \pm 0.54	9.79 (9.77,9.80)	14.66 \pm 0.36	10.00 (9.94,10.06)

^a Average values \pm s.d is given in case of triplicate determinations, and average values with individual values under parentheses are given when the experiments were conducted in duplicate.

3.2. Effect of moisture sorption on the glass transition temperature of polymers

Since the moisture sorption by polymers lowers glass transition temperatures (T_g), which may, in turn, adversely influence the physical stability of any dispersed drugs (e.g., crystallization), we studied DSC scans of Eudragit® EPO, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100 as functions of moisture contents to determine effects of moisture sorption on T_g of the polymers. The DSC scans of the polymers are shown in Fig. 2, and the changes in T_g values are tabulated in Table 3. The following is a brief description of the experimental data. In addition, the decreases in T_g with the increase in moisture content have been calculated theoretically by using the Gordon-Taylor/Kelley-Bueche equation and the results are also presented in Table 3, which will be discussed in the next section.

3.2.1. Eudragit® EPO

DSC scans of Eudragit® EPO with different moisture contents are given in Fig. 2A, and the change in T_g is tabulated in Table 3 along with that of other polymers used. As shown in Table 2, the polymer absorbs 2.38% w/w moisture at 25 °C/80% RH and a maximum of 3.78% w/w moisture at 25 °C/90% RH. Therefore, we studied the effects of 0, 1, and 2.5% moisture content on T_g of Eudragit® EPO. It is apparent that there is only a very small decrease in T_g even when the polymer is exposed to high humidity. For example, the T_g of Eudragit® EPO decreases from 52 °C in a moisture-free sample to 48 °C at 1% moisture content, which is the approximate extent of moisture sorption at 25 °C/60% RH, and a moisture content of 2.5% w/w ($T_g \sim 44$ °C) does not reach even at 25 °C/80% RH.

3.2.2. Eudragit® L100-55

Since Eudragit® L100-55 is more hygroscopic than Eudragit® EPO, we could study the effects of up to 10% moisture sorption on its T_g . As

shown in Fig. 2B and Table 3, the T_g of Eudragit® L100-55 is above 40 °C even after the moisture sorption of 10% w/w, which is comparable to the exposure to 25 °C/90% RH. At 5% moisture content, which is comparable to the exposure to 60 to 70% RH at 25 °C, the T_g is 58.7 °C. Such relatively high glass transition temperatures after exposure to high humidity indicates that there may not be major effects of moisture sorption on the physical stability of ASDs prepared with Eudragit® L100-55.

3.2.3. Eudragit® L100

DSC scans of Eudragit® L 100 at 0, 1, 2.5, 5, and 10% w/w moisture contents are given in Fig. 2C, and the individual T_g values are listed in Table 3. These results show that there is a decrease in T_g of Eudragit® L100 from 192 °C in the moisture-free sample to 187 °C at 1% moisture content and, ultimately, 118 °C at 10% moisture content. The 10% w/w moisture sorption by the polymer is essentially comparable to its exposure to 70–80% RH. Thus, even after exposure to very high humidity, the T_g of Eudragit® L100 remains much higher than the ambient storage temperature of solid dosage forms, which is usually around 25 °C, and, therefore, there is the possibility that the moisture sorption by Eudragit® L100 may also not have much adverse effect on the physical stability of ASDs prepared by using it as a carrier. It should, however, be mentioned here that because of its high T_g , Eudragit® L100 may not be suitable for the preparation of ASDs by hot melt extrusion, especially if the drugs degrade at high temperatures, and any ASDs under such circumstances will possibly have to be prepared by spray drying or other solvent evaporation methods.

3.2.4. Eudragit® S100

As shown in Fig. 2D and Table 3, the T_g of Eudragit® S100 decreases from 173 °C in the moisture-free sample to 149 °C at 1% moisture content and ultimately 105 °C at 10% moisture content. Therefore, like Eudragit® L100 described above, any ASD prepared by using Eudragit®

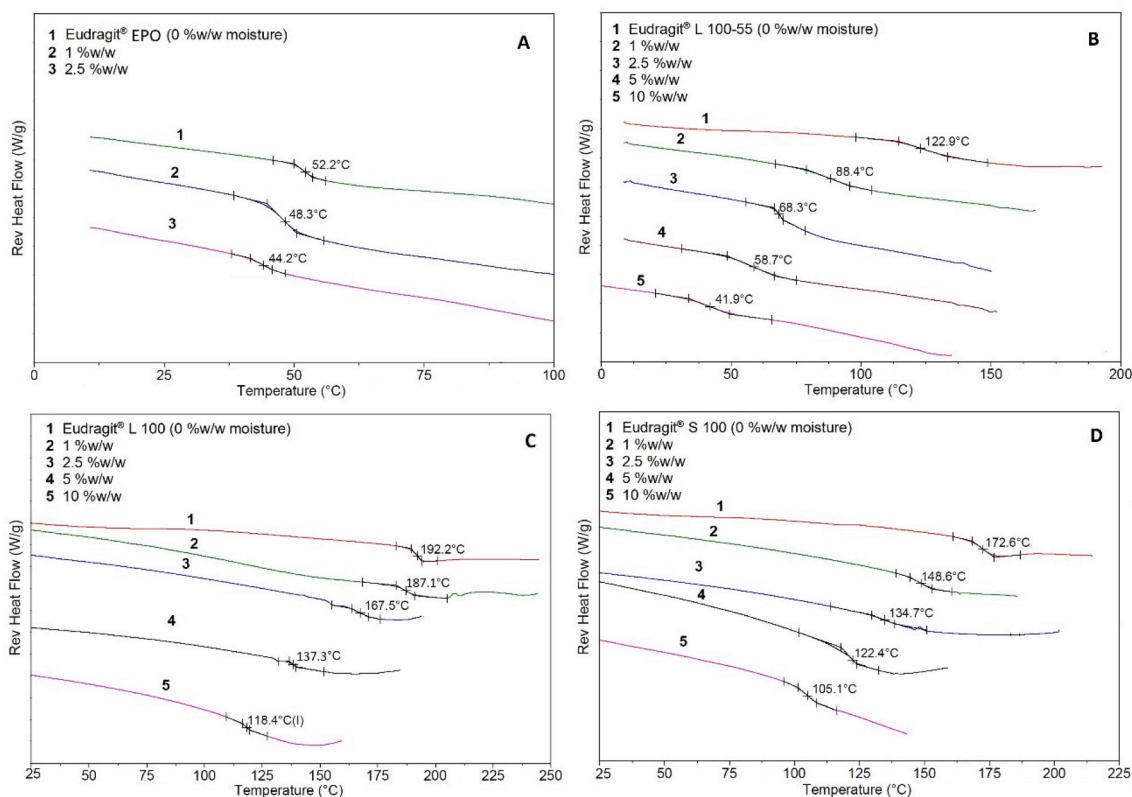


Fig. 2. DSC scans of (A) Eudragit® EPO, (B) Eudragit® L100-55, (C) Eudragit® L100, and (D) Eudragit® S100 show effects of increasing water content in decreasing glass transition temperature.

Table 3

Glass transition temperatures of different grades of Eudragit® as a function of moisture content.

Moisture Content (% w/w)	Eudragit® EPO		Eudragit® L100-55		Eudragit® L100		Eudragit® S100	
	Experi-mental T _g -exp	Calculated T _g . calc	Experi-mental T _g -exp	Calculated T _g . calc	Experi-mental T _g -exp	Calculated T _g . calc	Experi-mental T _g -exp	Calculated T _g . calc
0	52.2	–	122.9	–	192.2	–	172.6	–
1	48.3	44.2	88.4	113.9	187.1	178.9	148.6	160.8
2.5	44.2	36.8	68.3	101.3	167.5	160.5	134.7	143.7
5	^a		58.7	82.1	137.3	135.5	122.4	118.7
10	^a		41.9	50.1	118.4	88.9	105.1	84.4

^a Not determined since the moisture sorption by the polymer is less than 5% w/w.

S100 will not be much adversely affected by moisture sorption.

3.3. Comparison of experimentally determined glass transition temperatures with theoretical calculations

Hancock and Zografi (1994) showed that the effect of moisture sorption on the T_g of polymers may also be calculated theoretically by applying the Gordon-Taylor/Kelley-Bueche equation (Kelley and Bueche, 1961; Gordon and Taylor, 1952) given below:

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

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

In the above equation, w₁ is the mass fraction of water, w₂ is the mass fraction of polymer, T_{g1} is the glass transition temperature of the water, T_{g2} is the glass transition temperature of the polymer in the absence of water, ρ₁ is the true density of water, and ρ₂ is the true density of the polymer. A comparison of theoretically calculated T_g values with experimental values as a function of moisture content may provide a mechanistic understanding of the interaction between water and polymers.

The theoretically calculated T_g values of different Eudragit® grades are given in Table 3 next to the experimental values, where the calculations were made by using the T_g values of Eudragit® experimentally determined in the present investigation at 0% RH (Table 3), the T_g value of 135°K for amorphous water determined by Sugisaki et al. (1968), and a true density 1.12 for different Eudragit® grades. Although there are certain similarities between experimentally determined and theoretically calculated T_g values (T_g-exp vs T_g-calc), as shown in Table 3, differences also exist between the two sets of values for each polymer. This is because, while the Gordon-Taylor/Kelley-Bueche equation was developed to calculate T_g values of the amorphous blends of compatible polymers and copolymers, the effect of water on a polymer is much more complex. According to Zografi and associates (Zografi 1988; Oksanen and Zografi, 1993; Hancock and Zografi, 1994), a certain proportion of small water molecules may be tightly bound with polymers by such chemical interaction as hydrogen bonding, thus exerting strong plasticizing effects, and the amounts adsorbed in excess of this amount may be 'solvent-like', approaching the property of bulk water that may not have as much plasticizing effects on polymers as that of the tightly bound water. As shown in Table 3, the experimental T_g values of Eudragit® EPO at the two moisture levels studied (1 and 2.5% w/w) were higher than the theoretically calculated values, which is possibly because the polymer is relatively nonhygroscopic and the adsorbed water may only be in a loosely bound or solvent-like state at the surface of the solid. In contrast, the experimental T_g values of Eudragit® L100-55 are much lower than the theoretically calculated values, indicating a strong interaction between water and the polymer resulting in higher plasticizing effects. There is, however, relatively good agreement between experimental and theoretically calculated T_g values of Eudragit® L and Eudragit® S, except at the high 10% moisture levels where the experimental values are higher than the theoretically calculated values, possibly because the adsorbed water was partially solvent-like and did not have as much plasticizing effect as the bound water.

The results presented in Table 3 and Fig. 2 give general trends in the decrease in glass transition temperatures with the increase in moisture contents of different grades of Eudragit® polymers. Since no systematic studies on moisture sorption by polymers commonly used in ASDs have been reported in the literature, the results of the present investigation, along with the results published previously in the present series of papers (Patel and Serajuddin, 2022; Patel et al., 2022) may serve as the basis for selecting polymers for ASDs based on moisture sorption and its effect on T_g. However, it should be noted that the results presented in these papers are for neat polymers only, and the moisture sorption by ASDs could be more complex. In an ASD, the drug is dispersed in polymers either molecularly or in the amorphous state, where the drug may also lower the glass transition temperature of the polymer used (Gupta et al., 2015). Plasticization due to drug, in addition to moisture sorption, may further destabilize an ASD. Another complicating factor with ASD is that the presence of a drug may also lower moisture sorption by ASDs since the drugs are often more hydrophobic and less hygroscopic than the polymers (Wei et al., 2020). In addition, a possible interaction between the hydrophobic drug and the hydrophilic polymer may decrease the moisture sorption by the polymers. Further studies on moisture sorption by drug-polymer mixtures and its effect on the physical stability of ASDs are currently in progress in our laboratory, and the results will be published in the near future.

4. Summary and conclusions

Moisture sorption by polymeric carriers used in the development of amorphous solid dispersions (ASD) and its effect on glass transition temperatures (T_g) of polymers play critical roles in the physical stability of dispersed drugs in the drug products developed. As part of our continuing investigation on moisture sorption by polymers used in ASDs, we have determined moisture sorption by several methacrylic acid-methyl methacrylate and related copolymers, namely, Eudragit® EPO, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100, as a function of relative humidity at two different temperatures of 25 and 40 °C by using a VTI dynamic moisture sorption analyzer from TA Instruments. The effect of moisture sorption on the T_g of the polymers was then determined. The polymers were selected based on their current or potential use in ASDs. Among them, Eudragit® EPO is a cationic polymer with dimethyl aminoethyl methacrylate, butyl methacrylate, and methyl methacrylate ratio of 2:1:1 that is soluble at pH below 5 due to the protonation of tertiary amine groups present in the structure. Eudragit® L and Eudragit® S, on the other hand, are anionic polymers having, respectively, 1:1 and 1:2 ratios of methacrylic acid (MA) and methyl methacrylate (MM) in the polymeric chain. Eudragit® L100-55 is structurally similar to Eudragit® L, except that it is a 1:1 copolymer between methacrylic acid (MA) and ethyl acrylate (EA), where MMA present in Eudragit® L is replaced by EA. All three polymers, Eudragit® L100-55, Eudragit® L, and Eudragit® S, are enteric polymers that dissolve at pH > 5.5, pH > 6, and pH > 7, respectively, by the ionization of the carboxyl group (–COOH) present in their structures. Among the polymers, Eudragit® EPO is the least hygroscopic with 1.28% and 3.78% w/w moisture sorption at 25 °C/60% RH and 25 °C/90% RH, respectively. In contrast, the extents of moisture sorption by Eudragit®

L100-55, Eudragit® L, and Eudragit® S at 25 °C/60% RH and 25 °C/90% RH are in the ranges of 4.65–7.50 and 10.58–15.49, respectively. The difference in moisture sorption by the polymers appears to be due to the difference in hydrogen bonding sites in their structures. Between the two temperatures used for moisture sorption, the polymers absorbed less moisture at 40 °C than that at 25 °C; since the moisture is at a higher energy state at 40 °C, it escapes the materials more easily due to the breakage of hydrogen bonds between polymers and water.

The T_g values of the moisture-free samples of Eudragit® EPO, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100 are 52.2, 122.9, 192.2, and 172.6, respectively. They decrease with the increase in moisture content, and the experimentally determined decrease in T_g values roughly agree with theoretical calculations based on the Gordon-Taylor/Kelley-Bueche equation. There are, however, certain deviations between experimentally determined T_g values with those calculated theoretically, possibly because the moisture sorption by polymers is a complex process as a certain proportion of water may be tightly bound with polymers by hydrogen bonding having a strong plasticizing effect and the excess water may exist in the solvent-like state with a lower plasticizing effect. Although the T_g values of Eudragit® polymers decrease with the increase in moisture sorption, they remain higher than that at the normal storage temperature of ASDs (25 °C) even after exposure to high humidity. Therefore, it is expected that the moisture sorption by Eudragit® polymers during storage may not have much negative impact on the physical stability of ASDs produced by using them.

Among the polymers used, Eudragit® L100-55, Eudragit® L100, and Eudragit® S100 are enteric polymers that dissolve under intestinal pH conditions, and they do not have much difference in their moisture sorption profiles as the function of relative humidity. Although all of them may be used for the preparation of ASDs by spray drying, the results of the present investigation indicate that Eudragit® L100-55 may be more suitable for the preparation of ASD by hot melt extrusion because of its lower T_g (122.9 °C) as compared to Eudragit® L100 and Eudragit® S100, which have much higher T_g values of 192.2 °C and 172.6 °C, respectively, that may necessitate very high melt extrusion temperatures. It is hoped that the results of the present investigation will help 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.

Data availability

Data will be made available on request.

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Data sources

The raw data used for the preparation of this paper have been saved at St. John's University by the corresponding author.

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