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Influence of commonly used excipients on the chemical degradation of enalapril maleate in its solid state: The role of condensed water

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ABSTRACT

The physicochemical stability of enalapril maleate was investigated in the presence of fourteen different excipients divided into four different classes. The extent of a drug-excipient interaction was investigated by following the chemical stability using HPLC. It was found that there is a certain order in the stability of enalapril maleate. Enalapril maleate remained most stable in the presence of: disaccharides > celluloses > starches > superdisintegrants. The amount of degradation can be related to the excipient characteristics. A material with a higher water sorption capacity and lower crystallinity presents a more reactive particle surface. It was revealed that the condensation layer deposited on the surface of the excipient is responsible for the degradation of enalapril maleate. A confirmation was found by changing the surface of the excipient and influencing the environmental humidity that allowed a variable build-up of the condensation layer. For this particle-particle interaction, the microenvironmental pH only presents a minor effect as it was found to not be a determining factor for degradation. Moreover, there appears to be a firm relationship between the degradation of enalapril maleate and the water sorption-activity of excipients.

1. Introduction

The active pharmaceutical ingredient enalapril is applied in pharmaceutical oral formulations as a salt (1:1) with maleate to ensure its physicochemical stability. The structural formula of enalapril maleate is shown in Fig. 1. This substance presents itself as a very stable crystalline solid which can be stored for 4 years at room temperature without degradation and is able to withstand relatively high temperature and humidity (Verbeeck et al., 2017) (Fig. 3).

However, when mixed with excipients in a tablet formulation it may become very unstable (Ip and Brenner, 1987; Verbeeck et al., 2017). The factors that play a major role are the humidity (Al-Omari et al., 2001; Eyjolfsson, 2003; Simončič et al., 2007) and the influence of the microenvironmental pH which have both been extensively researched (Bout and Vromans, 2021; Chen et al., 2014; Cunha et al., 2013). Remarkably, the degradation of enalapril maleate does not show the same profile in solution as in a dry physical mixture. In aqueous solution, the degradation pathway to the hydrolysis product enalaprilat is most dominant. As seen in Fig. 1, enalapril maleate contains an ester bond making the substance prone to hydrolysis. Only in acidic solutions (pH < 5), another degradation pathway becomes apparent which results in a cyclisation product enalapril diketopiperazine. In the solid state, the diketopiperazine formation is the prevailing degradation route and hydrolysis hardly occurs (Al-Omari et al., 2001; Ip and Brenner, 1987).

In our previous study, we demonstrated that in the presence of sodium starch glycolate, a well-used pharmaceutical excipient, degradation of enalapril maleate predominantly led to diketopiperazine formation. The interaction between the two substances was found to be particle surface related. This conclusion is based upon the existence of a dependency on the mixing ratio and particle size of enalapril maleate. Using differential scanning calorimetry (DSC), we also showed that enalapril maleate rapidly loses its crystalline structure once mixed with sodium starch glycolate. This physical transition appeared to be highly dependent on the ambient humidity level illustrated by microscopic images. As a result of the loss of crystallinity, chemical degradation follows subsequently. We have argued that dependent on the amount of water present, a certain amount of enalapril maleate is able to temporarily dissolve. Depending upon the microenvironmental pH, four different protonated forms of enalapril can emerge. As this involves in the most cases a change in the charge of the molecule, recrystallisation into the original crystal lattice is not possible anymore. Because of a change in the charged state of enalapril, the free form presents a lowered

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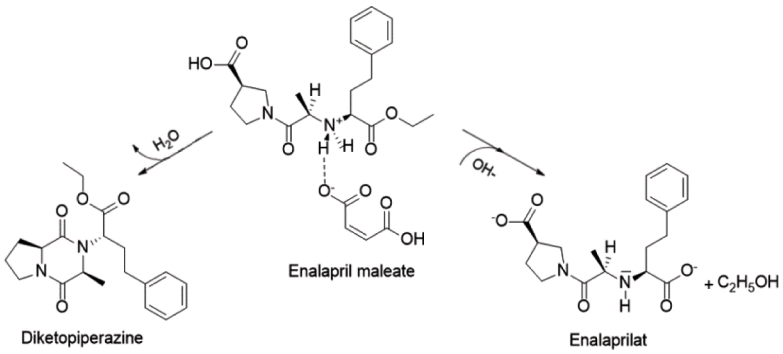

Fig. 1. Molecular structure of enalapril maleate and the degradation products diketopiperazine and enalaprilat. Enalapril is bound to maleate through hydrogen bonding.

Table 1
A: Overview of all used materials for experiments.

Divided class	Materials	Brand name, supplier, country
	Enalapril maleate	Enalapril maleate, Zhejiang Huahai Pharmaceutical Co. Ltd., China
Disacc-harides	Lactose monohydrate	Pharmatose 200 M, DFE Pharma, Germany
	Spray-dried lactose	Supertab® 11SD, DFE Pharma, Germany
	Anhydrous lactose	Supertab® 21AN, DFE Pharma, Germany
Cellu-loses	Microcrystalline cellulose	Vivapur® 101, JRS Pharma, Germany
	Silicified microcrystalline cellulose	PROSOLV® SMCC 90, JRS Pharma, Germany
Starches	Potato starch	Native starch - potato based, Roquette, France
	Corn starch	Meritena® Pharma 141, Tereos, France
	Pregelatinized starch	C*Gel-Instant® 12,018, Cargill, United States
	Partially pregelatinized starch	Starch 1500®, Colorcon, United States
	Amylopectin	Amylopectin from maize, Sigma-Aldrich, The Netherlands
Super-disinte-grants	Sodium starch glycolate	Primojel® type A, DFE Pharma, Germany
	Sodium starch glycolate	Glycolys® type A, Roquette, France
	Croscarmellose sodium	Ac-di-sol® SD-711, DuPont, United States
	Crospovidone	Kollidon® CL, BASF, Germany
	Silicon dioxide	ZEOFREE® 5162, Evonik Silica, Finland
Table I.B: Overview of all used materials for analysis		
	Reagents	Brand name, supplier, country
	Acetonitrile	Acetonitril, Lach-ner, Czech Republic
	Sodium dihydrogen phosphate	EMSURE®ACS, MilliporeSigma, Germany
	2 M hydrochloric acid	Hydrochloric acid, dilute, RS, Actu-All, The Netherlands
	Magnesium chloride	Magnesium chloride hexahydrate, EMD Millipore Corp, Germany
	Glycerol 99%	Glycerol (602,005), Gustav Heess, Germany
	Potassium iodide	Potassium chloride, Sigma-Aldrich, Germany
	Sodium chloride	Sodium chloride, Sigma-Aldrich, Germany

solubility in comparison to the salt form (Williams et al., 2013). The subsequent precipitation of enalapril therefore leads to a gradual loss of crystallinity. One of the formed molecular conformations is the zwitterion. This presents both a positive and a negative group which makes it react relatively easily to form diketopiperazine through an intramolecular cyclisation. Thus the instability of enalapril maleate in the presence of sodium starch glycolate is ascribed to the degree to which enalapril maleate can dissolve and the pH at which this process occurs. (Bout and Vromans, 2021)

Although the solid state instability of enalapril maleate in the presence of sodium starch glycolate and its relation with moisture has been demonstrated, the precise mechanism that causes this instability still remains unclear. It is not known which attributes of the excipient are responsible for the degradation and what role sorbed water plays in this respect.

In this article, a comprehensive study was undertaken relating the properties of excipients to the instability of enalapril maleate. The focus is on investigating the location of moisture sorbed by excipients through application of the Brunauer-Emmet-Teller (BET), the Guggenheim-Andersen-de Boer (GAB) and Young-Nelson models to sorption isotherms. For this, we investigated a range of excipients with diverse affinities towards moisture uptake. In addition, we explored the nature of the interaction by relating properties of the excipients to the instability of enalapril maleate.

2. Materials and methods

2.1. Materials

The different materials and chemicals employed are listed in table 1. All were of pharmaceutical grade.

2.2. Binary mixtures

Physical blends were produced in a mixing ratio of 1:100 (enalapril maleate:excipient). The chemical stability of enalapril maleate was studied by placing the samples for 720 h at 60 °C in vials in three different conditions: 1) 'dry' (13%RH), 2) 'contained' (vial of 1.5 mL with 200 mg of sample closed with cap, where samples previously were stored at 25 °C/50%RH) and 3) 'humid' condition (58%RH), where conditions were maintained in a desiccator containing a mixture of glycerol and water (Glycerine Producers' Association, 1963). The humidity was monitored using a Thermo-hygrometer Testo 605i. Samples were taken in duplicate at time points $t = 0$, $t = 24$, $t = 48$, $t = 72$, $t = 96$, $t = 168$, $t = 288$, $t = 480$ and $t = 720$ h. The degradation of enalapril maleate was measured with the use of a validated HPLC-method (Bout and Vromans, 2021). The degradation rate constant k was calculated through linear regression with the assumption of first order kinetics.

2.3. Water vapor sorption study

For each powder, a moisture sorption isotherm was measured in duplicate with the Dynamic Vapor Sorption (DVS Q5000 SA) equipment from TA Instruments (USA) with complementary software of TA

instruments Universal analysis 2000 (v4.5A). Samples were placed in an aluminum pan and measured at 25 °C ± 0.1. After equilibration at 0% RH for 60 min, a sorption/desorption profile from 0%RH to 90%RH was ran with 10%RH steps which proceeded only if the weight change was stable (<0.002%) for 10 min with a maximum dwell time of 120 min. To further evaluate the water sorption of the excipients, two models were applied:

2.3.1. Guggenheim, Anderson, Deboer (GAB)-model

The GAB-model fits the sorption and desorption data to describe the behavior of physical adsorbed layers of molecules. The GAB-model was fitted with the use of the Universal analysis software of TA instruments in order to determine the corresponding monolayer moisture content (*Wm*), BET-constant (*c*) and GAB-constant (*K*) (Quirijns et al., 2005). Outcomes of the parameters are given in Appendix B.

2.3.2. Young-Nelson (Y&N)-model

The Y&N-model also fits the experimental isotherm data and divides the total water sorption *(m)* into three locations, according to equations Eq. (1) and Eq. (2).

$$m = m_m + m_c + m_i \quad (1)$$

$$m = A(\theta + \beta) + B\Psi \quad (2)$$

where m_m, m_c and m_i correspond to a tightly bound monolayer, condensed external water and internally absorbed water. Θ, Ψ and β describe the fraction of molecules covered by a monolayer, the fraction covered in a multilayer and the amount of water in the multilayer, respectively. A and B represent constant values that are related to either the fraction of adsorbed and absorbed moisture. Following the mathematical equations related to the Young-Nelson model, the determined BET-constant (*c*) was fitted to determine the amount of moisture present as a monolayer *(AΘ)*, as condensed external moisture (Aβ) and as internal absorbed moisture (BΨ) (Young and Nelson, 1967). The values of Θ, β and constant values of A and B were obtained for each material using a multiple regression technique (Bravo-Osuna et al., 2005; Faroongsarng and Peck, 1994; Nokhodchi et al., 1997). Outcomes of the parameters are given in Appendix C.

2.4. Moisture content determination

All powders were stored at 25 °C/50%RH prior to measurement of the moisture content. One gram of powder was placed in the infrared moisture analyzer (Sartorius MA160, Germany) for 3 h at 130 °C. Any weight change was attributed to the amount of evaporated moisture.

2.5. Surface contact experiments

The surface properties of the excipient sodium starch glycolate were studied using two experimental set ups. Firstly, the hydration state of the of excipient sodium starch glycolate was influenced. Prior to mixing with enalapril maleate, the powder of sodium starch glycolate was placed in the moisture analyser at 105 °C for 3 h to remove its sorbed moisture. The moisture content of the powder before was 5.66% and after drying was measured to be 0.17%. Thereafter the dried powder was mixed with enalapril maleate in a ratio of 1:3 (enalapril maleate: excipient) and 500 mg of this mixture was put in vials. These vials were then placed in seven humid conditions ranging from 13%RH (stove with desiccant), 30%RH (saturated with magnesium chloride), 50%RH (mixture of glycerol:water), 66%RH (saturated with potassium iodide), 75%RH (saturated with sodium chloride), 97%RH (mixture of glycerol: water) and 100%RH (water) (Glycerine Producers' Association, 1963). Samples were taken at $t = 0$, 3.5, 5.5,18 and 24 h and the content of enalapril maleate was measured.

Secondly, the particle surface of sodium starch glycolate was altered through granulation. About 400 g of powder was placed in a laboratory mixer (Diosna P1–6, Germany) with 10% of silicon dioxide and mixed for 5 min. An amount of 200 g of water was added to this mixture for 20 min. The granulate was sieved down in a mixer (Bohle Menger LM20, Germany). The resulting sieved granules were positioned in a stove at 70 °C for 24 h to dry. The same procedure was executed again but this time without silica to create granules of solely sodium starch glycolate powder. The granulate was sieved through a sieve of 150–300 μm. The particle size distribution of the dried granulates and pure sodium starch glycolate powder was determined with the use of Laser diffraction (Helos/BR, Germany). The median particle size (D_{50}) of regular sodium starch glycolate showed to be 43 μm. The distribution of both granules with and without deposited silica were similar to each other with an D_{50} of 167 μm and 174 μm, respectively. The three types of SSG powders were mixed with enalapril maleate in a ratio of 1:100 (enalapril maleate: sodium starch glycolate) and stored at 60 °C/58%RH. Samples were analysed over time to follow the content of enalapril maleate.

Table 2
. A: Preparation of saturated solutions using distilled water as solvent in order to measure the microenvironmental pH.

Pure substances	Concentration of the excipient in solution(g/ml)
Superdisintegrants	0.1
Starches	0.25
Celluloses	0.25
Disaccharides	0.50
Pure enalapril maleate	0.50
Table IIB: Preparation of saturated solutions using a solution of enalapril maleate (concentration: 25 g/L) as solvent in order to measure the microenvironmental pH.	
Binary mixtures in ratio 1:100 of enalapril maleate with:	Concentration of the mixture in solution (g/ml)
Superdisintegrants	0.05–0.15
Starches	Ranging from 0.15 to 0.25
Celluloses	0.25
Disaccharides	0.50

2.6. Amount of zwitterion

Based on the molecular structure of enalapril, the charge distribution of the molecule was plotted by using the Plugin of Marvin JS (V19.23.0; 2019). The plugin is able to estimate the theoretical amount (%) of zwitterion at a pH range of 1 to 14 with an acidic pKa of 3.7 and a basic pKa of 5.2 for enalapril. The amount of zwitterion was used as a measurement for the maximum reactivity that would be able to degrade in a binary mixture. The microenvironmental pH of the pure excipients and mixtures with enalapril maleate (ratio of 1:100) was measured with a pH meter (Metrohm 913, Singapore). To obtain saturated solutions needed for pH measurement, 5 g of substance was dissolved resulting in different concentrations for each material (see table 2). The pure substances were dissolved in either distilled water (table 2A) or in a saturated solution of enalapril maleate with a concentration of 25 g/L (table IIB). The measured result was taken as the microenvironmental pH.

3. Results and discussion

3.1. Chemical stability of enalapril maleate in powder mixtures

The stability of enalapril maleate mixed with excipients was investigated at three different storage conditions: Dry (60 °C/13%RH), contained (closed vials at 60 °C) or at humid conditions (60 °C/58%RH) for a total of 720 h. The results are presented in Figs. 2 and 3. Here, the excipients are classified into four categories: disaccharides, celluloses, starches and superdisintegrants. In Fig. 2, the degree of degradation of enalapril maleate is expressed as the first-order degradation rate constant (*k*). The results show that *k* is influenced once mixed with the excipients. This is dependent on the type of excipient; enalapril maleate

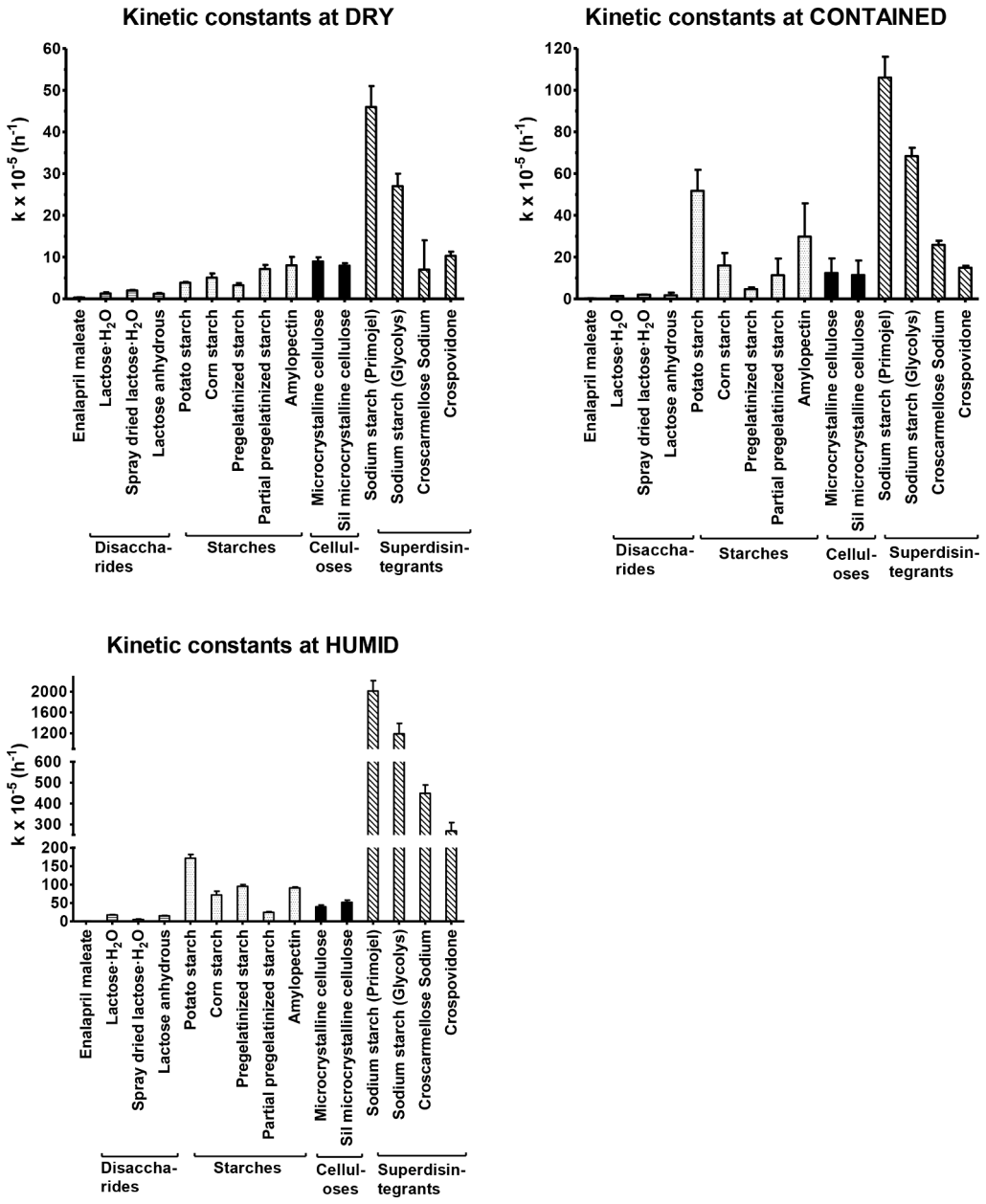

Fig. 2. Solid-state stability data of enalapril maleate in a binary mixture of enalapril maleate:excipient at a 1:100 ratio. Mixtures were stored at three different conditions: dry (60 °C/13%RH), contained (closed vials at 60 °C) and humid (60 °C/58%RH). Data is presented as mean ± SD ($n = 2$). Please print this figure in color in print . .

remained most stable in the presence of the disaccharides and most unstable with the superdisintegrants. Moreover, the humidity has a noticeable effect on the extent of degradation.

3.2. Stability in relation to properties of excipients

Fig. 4A illustrates that the degradation of enalapril maleate increases with the sorption capacity of an excipient. This capacity represents the maximum amount of moisture a material has taken up at 90%RH as measured by the DVS. One particular aspect that differs considerably between the excipients lies in their ability to sorb moisture. That difference can also be traced back to their use in a formulation. For example, superdisintegrants present a great affinity to moisture sorption while they are meant to enhance the disintegration of an oral solid dosage form. On the contrary, disaccharides present a very low affinity for moisture. They are mostly used for their application as binders to maintain a stable solid dosage form.

A direct relation between the amount of amorphous domains of cellulose and amount of sorbed water has been well documented (Ioelovich, 2009; Ioelovich and Leykin, 2011; Mihranyan et al., 2004). Now, it is also evident that degradation is more pronounced in a mixture with excipients that present the following: a higher sorption capacity and a lower degree of crystallinity (Fig. 4). Accordingly, the former is dependent upon the environmental humidity, since this determines the amount of water that is actually sorbed.

The numbers that are depicted in Fig. 4B originate from literature (see Appendix A). In fact, instead of the crystallinity, the amorphous content could also have been used. In view of the solid state, crystalline and amorphous compounds bind differently to water. Overall, a more amorphous compound is known to be more able to absorb moisture than a more ordered crystalline compound (Hancock and Zografi, 1993). Disordered structures of an amorphous state allow more space for

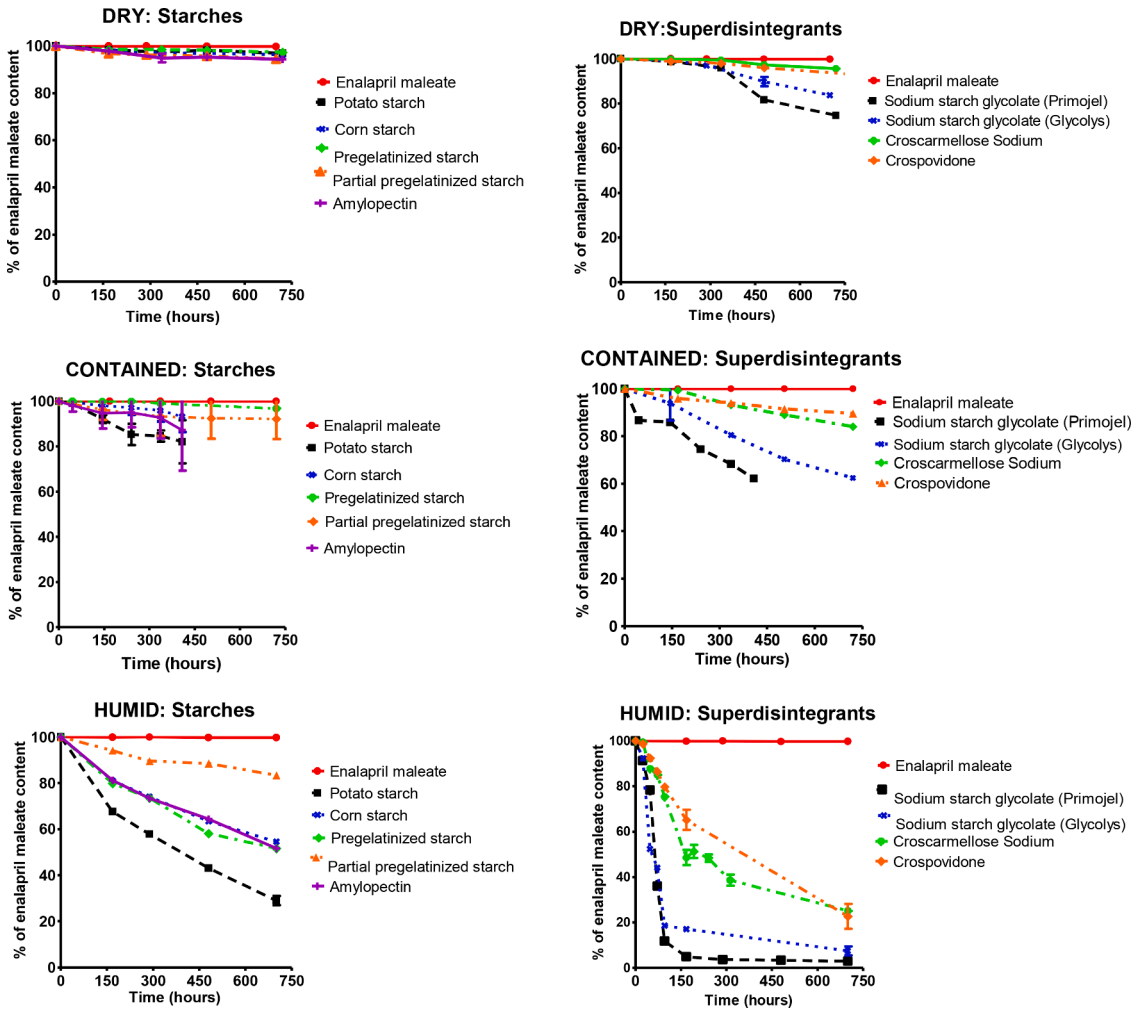

Fig. 3. Content of enalapril maleate (%) over time in presence of starches and superdisintegrants (ratio 1:100) after storage at three different conditions: dry (60 °C/13%RH), contained (closed vials at 60 °C) and humid (60 °C/58%RH). Data is presented as mean ± SD ($n = 2$).

moisture to come in and fill the voids which also can explain their higher amount of sorption capacity (Mihranyan et al., 2006). Basically, this water uptake can be regarded as bulk absorption. As mentioned earlier, we have concluded that the degradation of enalapril maleate is a surface-related phenomenon. This seems to contradict with the foregoing discussion which points to internal moisture sorption. This means that bulk sorption does not directly explain in which manner this influences the degradation of enalapril maleate at the particle-particle interface.

3.3. Particle surface

In a previous study we have shown that the mixing ratio between enalapril maleate and sodium starch glycolate is of dominant importance for the degree of degradation occurring. It was argued that this has to do with the fact that the interaction between the compounds takes place in the microenvironment of the particle-particle interface. A way to study the interaction between particles and a possible moisture-effect, is to influence their surface. As shown in Fig. 5, the stability of enalapril maleate was followed over time in presence of three different kind of powders, referred to as regular sodium starch glycolate, granulated sodium starch glycolate and silicified granulated sodium starch glycolate. Sorption isotherms showed that the sorption capacity of regular sodium starch glycolate is 43%±1.0, for granulated powder 52%±0.8 and for silicified granules 46%±1.9. In a mixture of enalapril maleate and regular sodium starch glycolate, enalapril maleate is vulnerable to degradation. When enalapril maleate is exposed to an increased particle size of sodium starch glycolate through granulation, this led to a slightly slower decrease of degradation. However, at the end of the time period of 700 h enalapril maleate still is fully degraded. If the granules of sodium starch glycolate were also coated with silica particles, there is a slower degradation and enalapril maleate remained more stable. Obviously, direct surface contact between the two substances is necessary to promote the degradation.

Previously, we have demonstrated that the degradation of enalapril maleate is preceded by a change in physical state from crystalline state to amorphous which has been attributed to temporary dissolution of the compound (Bout and Vromans, 2021). For this phenomenon, dissolution is an essential step. Clearly, this requires an adequate amount of liquid water. Therefore, the question remains if the moisture that is responsible for the degradation of enalapril maleate is located at the surface. Using the model of Young-Nelson, the sorption of moisture is distinguished into three locations of deposition. At a low humidity, adsorption of moisture exhibits first the formation of a monolayer (single atom deposition) on the surface and within pores of the particle. At a higher humidity, moisture is built up at a second location as absorbed in the material and/or at the third location as a multilayer. Upon increase of the number of layers, there is a certain threshold after which the physical state of this adsorbed moisture can be considered as a liquid. This is also referred to as condensed water. The consequence of this is that it exhibits the properties of liquid water such as the expression of solubility towards substances (Alvarez-Lorenzo et al., 2000; Faroongsarng and

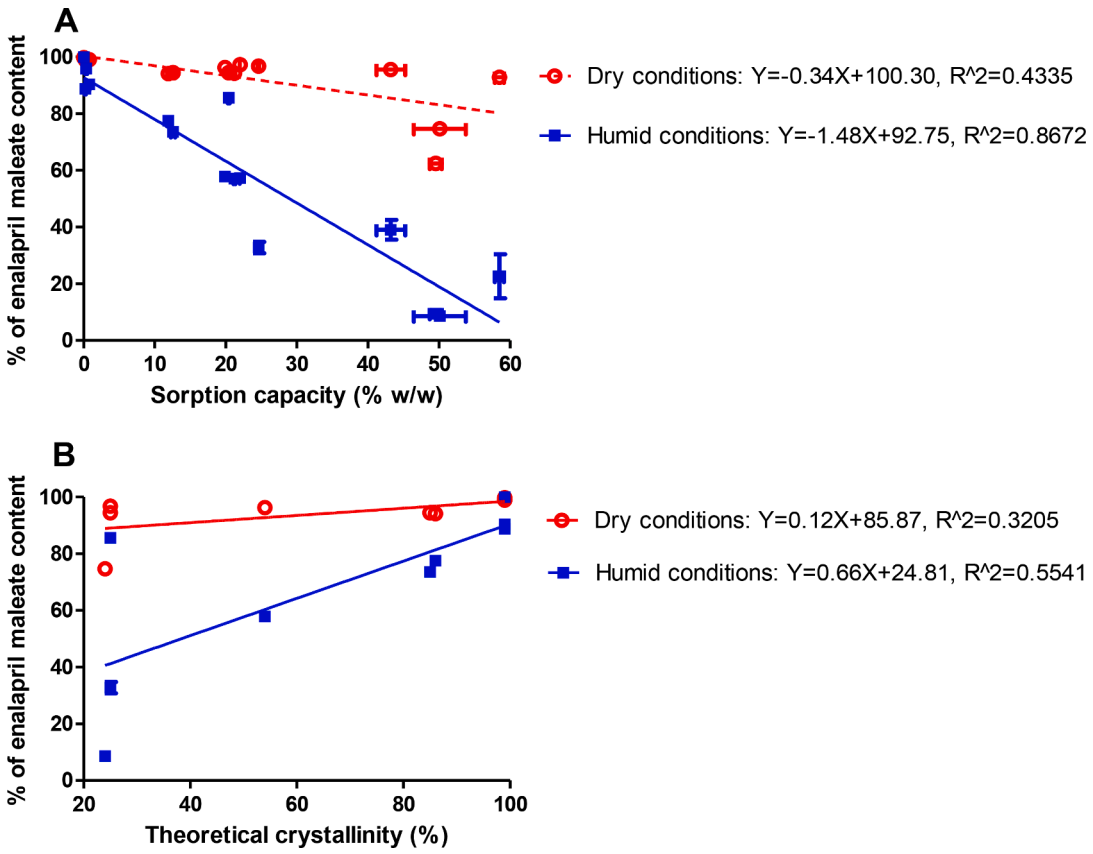

Fig. 4. Amount of degradation of enalapril maleate in mixture (1:100) after storage at 720 h at either a dry environment (60 °C/13%RH) or a humid environment (60 °C/58%RH) in relation to: a) the water sorption capacity (% w/w) of the excipients (n = 15) and to: b) known amount of crystalline content (%) for certain excipients (n = 9). Data is presented as mean ± SD (n = 2).

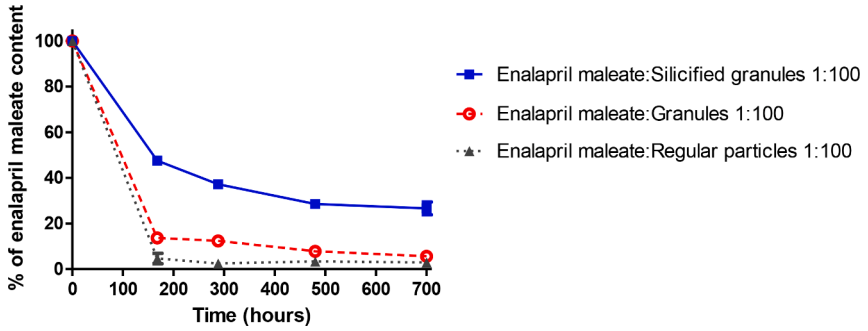

Fig. 5. Stability profile of enalapril maleate in binary mixtures of three kinds of sodium starch glycolate particles: regular, granules and silicified granules of sodium starch glycolate which were stored at 60 °C/58%RH. Data is presented as mean ± SD (n = 2). Please print this figure in color in print.

Peck, 1994; Young and Nelson, 1967). Fig. 6 shows the amount of degradation of enalapril maleate in mixture with pre-dried sodium starch glycolate powder in a ratio of 1:3 after storage at varying humidities for 24 h. Considering that enalapril maleate presents no affinity to moisture, any observed sorption would thus be attributed to the pre-dried sodium starch glycolate powder. The amount of sorption of pre-dried sodium starch glycolate at these humidities is also portrayed in Fig. 6. As can be seen, pre-dried sodium starch glycolate starts to sorb moisture at a RH% as low as 10%. However, as can be deduced from Fig. 6, only above 50%RH degradation of enalapril maleate is apparent within 24 h. These results seem to confirm earlier findings of that sufficient build-up of moisture is necessary for degradation to occur.

The role of water onto the surface of a solid is thus divided into adsorption as a monolayer or as a build up of multilayers (defined as condensation of water). According to Fig. 7, the degradation of enalapril maleate is proportional to the amount of liquid ("condensed") water on the surface of the excipients (see Appendix B and C for the corresponding parameters). Faroongsarng and Peck previously found that the superdisintegrants exhibit more condensation of moisture on their surface than cellulose and starch (Faroongsarng and Peck, 1994). This difference in moisture sorption is also consistent with our studied materials (see Appendix C).

Heidarian et al., show that lactose with a higher amorphous content bind water more strongly making water less able to induce reactions (Heidarian et al., 2006). Mihranyan et al. also found that the instability of acetylsalicylic acid was increased in the presence of celluloses with a higher crystallinity. They also concluded that the location and availability of sorbed moisture was crucial (Mihranyan et al., 2006). The reason for the improved stability of acetylsalicylic acid is mostly attributed to the explanation that more amorphous and more

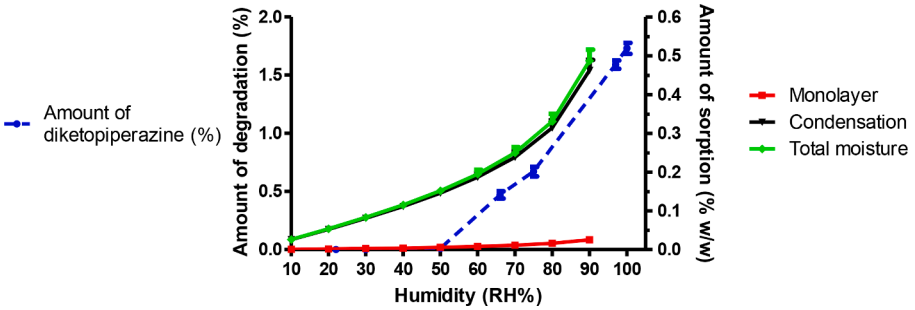

Fig. 6. Amount of degradation product diketopiperazine after storage at 40 °C at various humidities for 24 h in mixtures of enalapril maleate with pre-dried sodium starch glycolate in a ratio of 1:3 (left y-axis). The amount of moisture sorption of pre-dried sodium starch glycolate dependent on the humidity (RH%) is divided into two layers (right y-axis). Data is presented as mean ± SD (n = 2).

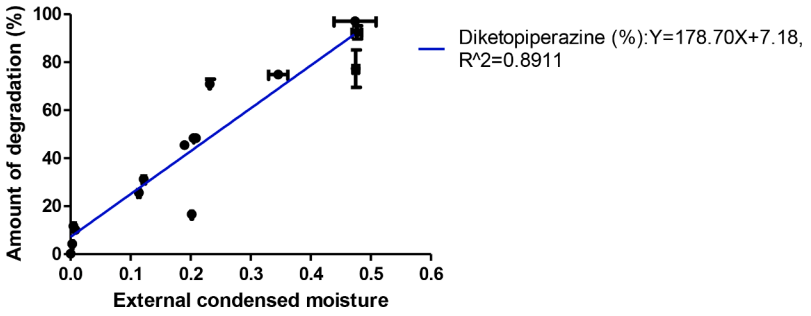

Fig. 7. Plot of the amount of degradation of enalapril maleate in binary mixtures (ratio 1:100) in the presence of excipients with their calculated Y&N-parameter external condensed moisture. Data is presented as mean ± SD (n = 2). Please print this figure in color in print.

Table 4
Microenvironmental pH of enalapril maleate and the studied excipients.

Excipient	pH of pure substance	pH of mixture in ratio 1:100 (enalapril maleate: excipient)	pH of excipient with saturated enalapril maleate-solution
Disaccharides			
Lactose•1H_2O	4.42	2.74 (0.01)	2.58 (0.01)
Spray dried Lactose•1H_2O	3.94	2.75 (0.01)	2.57 (0.01)
Lactose anhydrous	4.26	2.81 (0.04)	2.58 (0.00)
Starches			
Corn starch	5.11	3.09 (0.03)	2.69 (0.01)
Potato starch	6.46	3.15 (0.03)	2.88 (0.01)
Pregelatinized starch	5.92	3.15 (0.03)	2.61 (0.01)
Partially pregelatinized Starch	4.92	2.97 (0.01)	2.61 (0.01)
Amylopectin	4.56	3.06 (0.02)	2.68 (0.01)
Celluloses			
Microcrystalline cellulose	6.09	3.12 (0.00)	2.63 (0.01)
Silicified microcrystalline cellulose	5.09	3.10 (0.00)	2.64 (0.01)
Superdisintegrants			
Sodium starch glycolate (Primojel)	6.32	5.81 (0.02)	4.24 (0.01)
Sodium starch glycolate (Glycolys)	6.36	5.84 (0.01)	4.11 (0.01)
Croscarmellose sodium	4.87	5.15 (0.04)	4.43 (0.01)
Crospovidone	3.81	3.28 (0.02)	2.70 (0.01)
Active substance			
Enalapril maleate	2.59[a]	n.a.[b]	2.58 (0.02)

[a]of the enalapril maleate-solution (25 g/L).

hygroscopic materials are able to absorb moisture making it unavailable to acetylsalicylic acid (Mwesigwa and Basit, 2015; Veronica et al., 2021). By way of contrast, we found the exact opposite by examining multiple classes of excipients with a greater amount of amorphous domains. A relationship was found between the declining theoretical known crystallinity of various materials and more degradation of enalapril maleate occurring (Fig. 4B). Our study demonstrates that materials that are able to absorb relatively large quantities of water such as starches apparently also deposit significant amounts of condensed water at the surface of the particles. I.e. the water is not only molecularly dispersed in the material, but present as a condensed layer on the surface. This implies that the explanation given for the stability of acetylsalicylic acid might be achieved due to another mechanism than through absorption.

3.4. Microenvironmental pH

As stated, we argued that degradation of enalapril maleate is preceded by the conversion of the crystalline to the amorphous state of the compound (Bout and Vromans, 2021). This is thought to find place in the condensed water that is present on the surface of excipient particles. A small quantity of enalapril maleate is able to dissolve in this moisture layer that causes the gradual change from crystalline to amorphous form. We have previously discussed that especially the zwitterion is vulnerable to cyclisation. This points to the significance of the microenvironmental pH that exists at the excipient particle surface. The idea is that there is a maximum tendency to degradation through cyclisation at the pH where the maximum amount of zwitterion exists, i.e. a pH of 4.5. Table 4 summarizes the differences between the measured pH for pure excipients and the pH for a mixture of enalapril maleate with an excipient. The mixture of 1:100 ratio displays the result of the overall pH of the system. On the contrary, the mixture of an excipient with saturated enalapril maleate-solution displays the effect of the excipient on a solution in which enalapril maleate is already dissolved. The excipients all show a range of pH's but once it is combined with enalapril maleate it

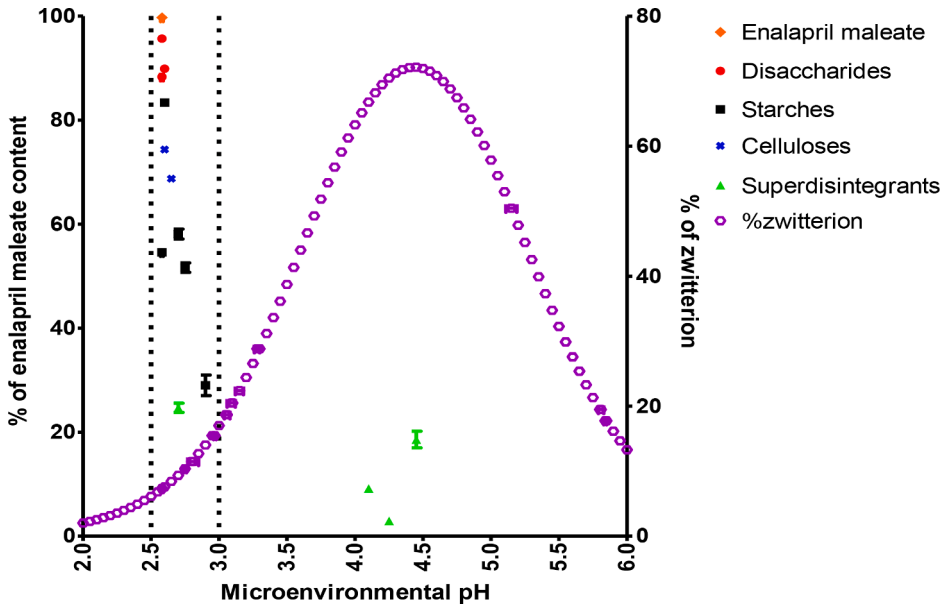

Fig. 8. The stability of enalapril maleate after $t = 700$ h at humid conditions (60 °C/58%RH) as presented by the microenvironmental of enalapril maleate in a mixture with excipient in a ratio 1:100 with on the right y-axis the amount of zwitterion theoretically present at that particular pH. The area between the dotted lines shows a small variation in% of zwitterion but a great variety in stability of enalapril maleate (%).

shifts mostly to the pH presented by enalapril maleate. The only three excipients that do show some buffering capabilities are the three superdisintegrants sodium starch glycolate (two grades) and croscarmellose sodium where the pH does not fall to a lower range of pH.

In order to simulate the condition at particle interface level, we realized that in the amount of water present there would always be a saturation of dissolved enalapril maleate. Addition of a saturated solution of enalapril maleate to an excipient allowed us to measure the anticipated microenvironmental pH. Fig. 8 shows the amount of degradation of enalapril maleate in relation to the microenvironmental pH that is presumed to exist at the surface of the excipient particles. Fig. 8 also depicts the occurrence of the zwitterion. Obviously, there does not exist a clear relationship between the degradation of enalapril maleate and the percentage of the compound that exists as a zwitterion. It can be seen that most excipients do not alter the microenvironmental pH as presented by pure enalapril maleate. However, their ability to cause degradation of enalapril maleate does vary greatly. Vehovec et al. related the degradation of enalapril maleate to the microenvironmental pH of various grades of cellulose. They found that enalapril maleate was more stable in presence of a more acidic cellulose of a pH-range between 6.2 and 6.8. It should be mentioned that the microenvironmental pH was determined using only cellulose in a water suspension (Vehovec et al., 2012). As shown in table IV, the microenvironmental pH is lowered if enalapril maleate is present in the water suspension. This indicates that, as the celluloses present no buffering capabilities, a difference in moisture sorption capability of the studied grades of cellulose seems to be a more explanatory factor. This statement was confirmed as they also related the total amount of moisture content to the degradation and found that more unbound water affected the stability (Vehovec et al., 2012). Apparently, differences in structure and ability of the excipients to present a condensed layer is more relevant in this respect than the microenvironmental pH.

4. Conclusion

The stability of enalapril maleate in the solid state is greatly affected by the excipient it is being exposed to. Excipients with a higher moisture sorption capacity and more amorphous domains cause more degradation of enalapril maleate. These excipients present an adsorptive layer of liquid water. Apparently, this moisture does not fully diffuse into the bulk. It is revealed that with increasing humidity, the amount of condensed water increases. This study shows that the dominating factor on degradation of enalapril is the available amount of condensed water rather than the molecular structure of the excipient. It is found that the rate and extent of degradation is primarily dependent on the amount of condensed water present at the surface.

Data references

The data that supports the findings of this study are openly available in the repository Mendeley Data which can be accessed through: doi:10.17632/m2gy86fc2s.2.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2022.106121.

References

Alvarez-Lorenzo, C., Gómez-Amoza, J., Martínez-Pacheco, R., Souto, C., Concheiro, A., 2000. Interactions between hydroxypropylcelluloses and vapor/liquid water. Eur. J. Pharm. Biopharm. 50, 307–318.

Bout, M.R., Vromans, H., 2021. Study on the mechanism responsible for the incompatibility of enalapril maleate with sodium starch glycolate. J. Pharm. Sci. 110, 2074–2082.

Bravo-Osuna, I., Ferrero, C., Jiménez-Castellanos, M., 2005. Water sorption-desorption behaviour of methyl methacrylate-starch copolymers: effect of hydrophobic graft and drying method. Eur. J. Pharm. Biopharm. 59, 537–548.

Faroongsarng, D., Peck, G., 1994. The swelling & water uptake of tablets III: moisture sorption behavior of tablet disintegrants. Drug Dev. Ind. Pharm. 20, 779–798.

Glycerine Producers' Association, 1963. Physical Properties of Glycerine and Its Solutions. New York.
Hancock, B., Zografi, G., 1993. The use of solution theories for predicting water vapor absorption by amorphous pharmaceutical solids: a test of the Flory-Huggins and Vrentas models. Pharm. Res. 10, 1262–1267.
Heidarian, M., Mihranyana, A., Strømmeb, M., Ragnar, E., 2006. Influence of water-cellulose binding energy on stability of acetylsalicylic acid. Int. J. Pharm. 323, 139–145.
Ioelovich, M., 2009. Accessibility and crystallinity of cellulose. Bioresources 4, 1168–1177.
Ioelovich, M., Leykin, A., 2011. Study of sorption properties of cellulose and its derivatives. BioRes 6, 178–195.
Mihranyan, A., Piñas Llagostera, A., Karmhag, R., Strømme, M., Ek, R., 2004. Moisture sorption by cellulose powders of varying crystallinity. Int. J. Pharm. 269, 433–442.
Mihranyan, A., Strömme, M., Ek, R., 2006. Influence of cellulose powder structure on moisture-induced degradation of acetylsalicylic acid. Eur. J. Pharm. Sci. 27, 220–225.
Mwesigwa, E., Basit, A., 2015. An investigation into moisture barrier film coating efficacy and its relevance to drug stability in solid dosage forms. Int. J. Pharm. 497, 70–77.
Nokhodchi, A., Ford, J.L., Rubinstein, M.H., 1997. Studies on the interaction between water and (hydroxypropyl)methylcellulose. J. Pharm. Sci. 86, 608–614.
Quirijns, E., Van Boxtel, A., Van Loon, W., Van Straten, G., 2005. Sorption isotherms, GAB parameters and isosteric heat of sorption. J. Sci. Food Agric. 85, 1805–1814.
Vehovec, T., Gartner, A., Planinšek, O., Obreza, A., 2012. Influence of different types of commercially available microcrystalline cellulose on degradation of perindopril erbumine and enalapril maleate in binary mixtures. Acta Pharm. 62, 515–528. https://doi.org/10.2478/v10007-012-0039-5.
Veronica, N., Liew, C., Heng, P., 2021. Investigation on the impact of different proportions of components in formulations on stability of a moisture sensitive drug. Int. J. Pharm. 603, 1–11.
Williams, H.D., Trevaskis, N.L., Charman, S.A., Shanker, R.M., Charman, W.N., Pouton, C.W., Porter, C.J.H., 2013. Strategies to address low drug solubility in discovery and development. Pharmacol. Rev. 65, 334–345.
Young, J., Nelson, G., 1967. Research of hysteresis between sorption and desorption isotherms of wheat. Trans. ASAE 10, 756–761.