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FORCED DEGRADATION STUDY OF ENALAPRIL MALEATE AND ITS COMPATIBILITY STUDY WITH THE SELECTED EXCIPIENTS

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ABSTRACT

Enalapril maleate's physicochemical stability was examined in the presence of fourteen distinct excipients categorized into four groups. The degree of a drug-excipient interaction was examined by using HPLC to monitor the chemical stability. It was discovered that enalapril maleate's stability follows a certain sequence. The following combinations kept enalapril maleate the most stable: disaccharides, celluloses, starches, and superdisintegrants. The properties of the excipient may have an impact on the rate of deterioration. A material's particle surface is more reactive when it has a lower crystallinity and a greater water sorption capacity. The breakdown of enalapril maleate was shown to be caused by the condensation layer that formed on the excipient's surface. By altering the excipient's surface and the humidity of the surrounding air, a mechanism was discovered that permitted a changeable accumulation of the condensation layer. The microenvironmental pH for this particle-particle interaction only has a little impact since it wasn't determined to be a deciding factor for degradation. Furthermore, there seems to be a strong correlation between the excipients' water sorption activity and the breakdown of enalapril maleate.

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; Simonˇciˇc 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

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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

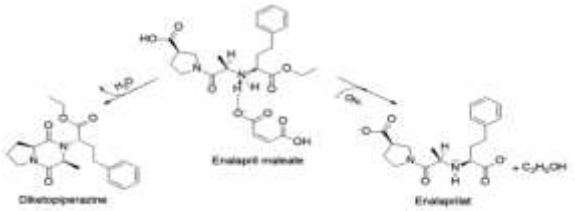

Fig. 1. Molecular structure of enalapril maleate and the degradation products diketopiperazine and enalaprilat. Enalapril is bound to maleate through hydrogen bonding.

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

	Materials	Brand name, supplier, country
Divided class	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 1.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.

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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 GuggenheimAndersen-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 mm, mc and mi correspond to a tightly bound monolayer, condensed external water and internally absorbed water. Θ, Ψ and β describe

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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 (D50) 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 D50 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.

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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

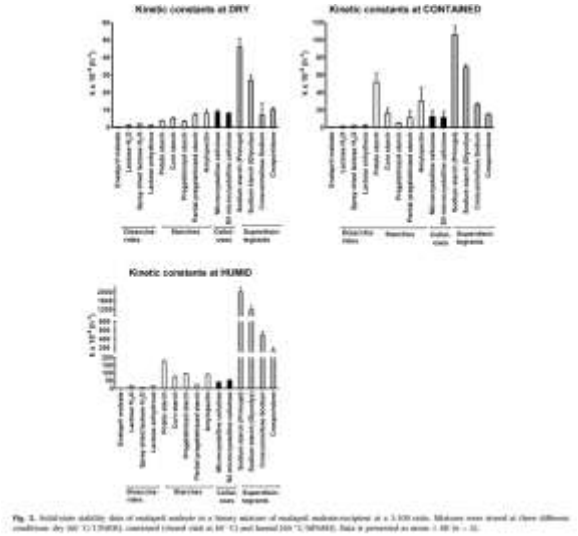
2.6. Amount of zwitterion

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 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

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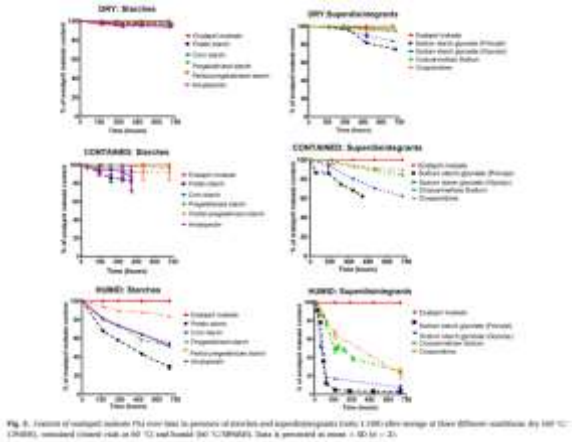
example, superdisintegrants present a great affinity to moisture sorption while they are meant to enhance the disintegration of an oral solid dosage form. On the contrary, disaccharides present a very low affinity for moisture. They are mostly used for their application as binders to maintain a stable 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 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

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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 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.

4. CONCLUSION

The excipient that enalapril maleate is exposed to has a significant impact on its stability in the solid form. Enalapril maleate is more readily broken down by excipients with more amorphous domains and a greater potential for moisture sorption. These excipients have a liquid water adsorptive layer. It seems that the wetness does not completely permeate the surrounding area. It is discovered that the quantity of condensed water rises with increasing humidity. This research demonstrates that the quantity of condensed water available, not the excipient's

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molecular makeup, is the primary factor influencing enalapril breakdown. It is discovered that the quantity of condensed water at the surface largely determines the pace and degree of deterioration.

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