History of Medicine:Vol.08 No. 2 (2022):740-747

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

STABILITY AND EXCIPIENT COMPATIBILITY ASSESSMENT OF ENALAPRIL MALEATE THROUGH FORCED DEGRADATION STUDIES

[1] Anil Kumar G, [2] Wajidali Mohammad

[1]Associate Professor,[2]Assistant Professor

[12]Department of Pharmaceutical Chemistry

Jayamukhi Institute of Pharmaceutical Sciences, Narsampet, Warangal, Telangana

ABSTRACT

The stability of Enalapril Maleate, an angiotensin-converting enzyme (ACE) inhibitor used for hypertension and heart failure management, is crucial for ensuring efficacy and safety in pharmaceutical formulations. This study aims to evaluate the stability and excipient compatibility of Enalapril Maleate through forced degradation studies, assessing its degradation profile under various stress conditions and potential interactions with commonly used pharmaceutical excipients.

The forced degradation study was conducted under acidic, basic, oxidative, thermal, and photolytic conditions, in accordance with ICH guidelines. The degraded samples were analyzed using stability-indicating analytical techniques to identify major degradation products and assess the extent of degradation. Additionally, binary mixture studies of Enalapril Maleate with selected excipients were performed to evaluate potential incompatibilities that could affect the formulation's stability, potency, and shelf life.

The results demonstrated that Enalapril Maleate is susceptible to hydrolytic and oxidative degradation, with significant changes observed under acidic and basic conditions. The compatibility study revealed that certain excipients influenced the degradation rate, indicating the need for careful selection of formulation components.

This study provides valuable insights into the stability profile of Enalapril Maleate, assisting in the design of stable formulations and the selection of appropriate excipients to ensure optimal drug performance and regulatory compliance. Further research is recommended for the structural elucidation of degradation products and formulation optimization.

I. INTRODUCTION

Enalapril Maleate is a widely used angiotensin-converting enzyme (ACE) inhibitor prescribed for the treatment of hypertension and heart failure. Its therapeutic efficacy depends on its stability, as degradation can lead to reduced potency, altered pharmacokinetics, and potential toxicity. Therefore, a comprehensive stability and excipient compatibility assessment is crucial for developing stable and effective pharmaceutical formulations.

Forced degradation studies, also known as stress testing, are performed to evaluate the degradation profile of a drug under extreme conditions such as acidic, basic, oxidative, thermal, and photolytic stress. These studies help identify the intrinsic stability of the drug and assist in the development of stability-indicating analytical methods. Additionally, excipient compatibility studies are essential to determine whether interactions between the drug and excipients could accelerate degradation or compromise formulation integrity.

History of Medicine:Vol.08 No. 2 (2022):740-747

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

This study aims to investigate the stability of Enalapril Maleate by subjecting it to forced degradation conditions in accordance with ICH guidelines. It also evaluates the compatibility of Enalapril Maleate with selected excipients commonly used in pharmaceutical formulations. The findings will provide critical insights into formulation design, excipient selection, and quality control strategies, ensuring optimal drug stability and regulatory compliance.

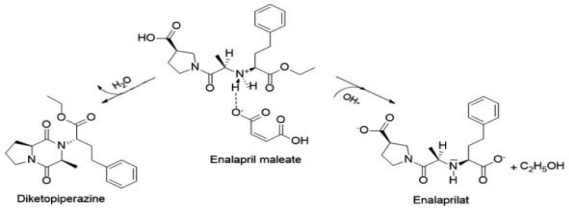

Fig. 1. Molecular structure of enalapril maleate and the degradation products diketopiperazine and enalaprilat. Enalapril is bound to maleate through hydrogen bonding.

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

dissolves more easily than the salt version (Williams et al., 2013). A progressive decrease in crystallinity is therefore caused by the following precipitation of enalapril. The zwitterion is one of the molecular configurations that are created. With its two sets of positively charged and negatively charged groups, it undergoes an intramolecular cyclisation to produce diketopiperazine with little effort. Therefore, the solubility and pH at which enalapril maleate dissolves are the factors that cause its instability when combined with sodium starch glycolate. In a study conducted by Bout and Vromans in 2021,

While it has been shown that enalapril maleate becomes insoluble in water when exposed to sodium starch glycolate, the exact process by which this happens is not yet known. How much of a function sorbed water plays in deterioration or which excipient properties are to blame is unknown.

In this paper, we provide the results of a thorough investigation into the correlation between enalapril maleate instability and the characteristics of excipients. Applying the Brunauer-Emmet-Teller (BET), GuggenheimAndersen-de Boer (GAB), and Young-Nelson models to sorption isotherms allows us to study the location of moisture sorbed by excipients. To achieve this, we tested many excipients with different water-absorbing preferences. Also, we connected excipient characteristics to enalapril maleate instability in order to probe the interaction's nature.

II. 2. MATERIALS AND METHODS

2.1. Materials

Table 1 lists the various materials and compounds that were used. The quality was that of pharmaceuticals.

2.2. Binary mixtures

The enalapril maleate to excipient ratio used to create the physical blends was 1:100. For the purpose of studying the chemical stability of enalapril maleate, three different conditions were used to place the samples in vials for 720 hours at 60 ◦C. The first condition was 'dry,'

History of Medicine:Vol.08 No. 2 (2022):740-747

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

with a relative humidity of 13%. The second condition was 'contained,' with a 1.5 mL vial containing 200 mg of sample and a cap. The samples had previously been stored at 25 ◦C with 50% relative humidity. The third condition was 'humid,' with a relative humidity of 58%. The desiccator was used to maintain the conditions of the third condition. (Glycerine Producers' Association, 1963). A Thermo-hygrometer Testo 605i was used to measure the relative humidity. At time intervals of 0, 24, 48, 72, 96, 168, 288, 480, and 720 h, duplicate samples were collected. A validated HPLC-method was used to assess the degradation of enalapril maleate (Bout and Vromans, 2021). Using linear regression and the first-order kinetics assumption, we were able to determine the degradation rate constant k.

2.3. Water vapor sorption study

The Dynamic Vapour Sorption (DVS Q5000 SA) apparatus from TA Instruments (USA) and its supplementary software, Universal analysis 2000 (v4.5A), were used to measure the moisture sorption isotherm twice for every powder. The samples were tested at 25 ◦C ± 0.1 after being put in an aluminium pan. A sorption/desorption profile was run with 10%RH increments from 0%RH to 90%RH after 60 minutes of equilibration at 0% RH. The profile continued only if the weight change remained steady (<0.002%) for 10 minutes, with a maximum dwell length of 120 minutes. Two models were used to assess the excipients' water sorption capabilities in further detail.

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

Physically adsorbed molecular layers may be described by fitting the sorption and desorption data into the GAB-model. To get the associated monolayer moisture content (Wm), BET-constant (c), and GAB-constant (K), the GAB-model was fitted using the Universal analysis program of TA instruments (Quirijns et al., 2005). Appendix B provides the parameter outcomes.

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

In addition to fitting the actual isotherm data, the Y&N-model uses equations (1) and (2) to split the total water sorption (m) into three regions.

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

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

where mm, mc, and mi stand for an internally absorbed water, condensed external water, and a securely bonded monolayer. The fractions of molecules covered by a monolayer, a multilayer, and the quantity of water in the multilayer are denoted by , Ψ, and β, respectively. Constant values shown by A and B are associated with the percentage of absorbed and adsorbed moisture, respectively. The quantity of moisture present as a monolayer (Ạ), as condensed exterior moisture (Aβ), and as internal absorbed moisture (BΨ) was calculated by fitting the determined BET-constant (c) using the mathematical formulae associated with the Young-Nelson model (Young and Nelson, 1967). A multiple regression approach was used to determine the values of , β, and constant values of A and B for each material (Bravo-Osuna et al., 2005; Faroongsarng and Peck, 1994; Nokhodchi et al., 1997). Appendix C provides the parameters' results.

2.4. Moisture content determination

Before the moisture content was measured, all powders were kept at 25 °C and 50% relative humidity. For three hours at 130 °C, one gramme of powder was subjected to the Sartorius MA160 infrared moisture analyser (Germany). Any variation in weight was ascribed to the quantity of moisture that evaporated.

2.5. Surface contact experiments

Two experimental setups were used to investigate the surface characteristics of the

History of Medicine:Vol.08 No. 2 (2022):740-747

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

excipient sodium starch glycolate. First, the excipient sodium starch glycolate's hydration state was affected. Before being combined with enalapril maleate, the sodium starch glycolate powder was dried in a moisture analyser set at 105 °C for three hours. Prior to drying, the powder's moisture content was 5.66%; upon drying, it was found to be 0.17%. After that, 500 mg of the dry powder and enalapril maleate were combined in a 1:3 ratio (enalapril maleate: excipient) and placed in vials. According to the Glycerine Producers' Association (1963), these vials were then subjected to seven different humid conditions: 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). At t = 0, 3.5, 5.5, 18, and 24 hours, samples were collected, and the amount of enalapril maleate was assessed.

Second, granulation changed the sodium starch glycolate particle surface. A laboratory mixer (Diosna P1–6, Germany) was filled with 400 g of powder and 10% silicon dioxide. The mixture was stirred for five minutes. This combination was mixed with 200 g of water for 20 minutes, and the granulate was sieved in a mixer (Bohle Menger LM20, Germany). The resultant sieved granules were left to dry for 24 hours at 70 °C in a stove. To make granules with just sodium starch glycolate powder, the same process was repeated, but this time without silica. A 150–300 µm sieve was used to filter the granulate. Using laser diffraction (Helos/BR, Germany), the particle size distribution of the dried granulates and pure sodium starch glycolate powder was determined. Regular sodium starch glycolate had a median particle size (D50) of 43 µm. With D50 values of 167 µm and 174 µm, respectively, the dispersion of the granules with and without deposited silica was comparable. Enalapril maleate was combined with the three varieties of SSG powders in a 1:100 ratio (enalapril maleate: sodium starch glycolate), and the mixture was kept at 60 °C/58% relative humidity. Over time, samples were examined to determine the amount of enalapril maleate present.

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

The charge distribution of enalapril was plotted using the Marvin JS Plugin (V19.23.0; 2019) based on its chemical structure. With an acidic pKa of 3.7 and a basic pKa of 5.2 for enalapril, the plugin can calculate the theoretical quantity (%) of zwitterion for pH values between 1 and 14. The greatest reactivity that may break down in a binary combination was measured by the quantity of zwitterion. A pH meter (Metrohm 913, Singapore) was used to test the microenvironmental pH of the pure excipients and combinations containing enalapril maleate (ratio of 1:100). Each material had a varied concentration after 5 g of the item was dissolved to provide the saturated solutions required for the pH measurement (see table 2). Both distilled water (table 2A) and a saturated solution of enalapril maleate at a concentration of 25 g/L (table IIB) were used to dissolve the pure compounds. The measured value was interpreted as the pH of the microenvironment.

III. RESULTS AND DISCUSSION

History of Medicine:Vol.08 No. 2 (2022):740-747

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

3.1. Chemical stability of enalapril maleate in powder mixtures

For a total of 720 hours, the stability of enalapril maleate combined with excipients was examined under three distinct storage conditions: dry (60 ◦C/13%RH), confined (closed vials at 60 ◦C), or humid (60 ◦C/58%RH). Figs. 2 and 3 show the findings. The excipients in this case are divided into four groups: superdisintegrants, celluloses, starches, and disaccharides. The first-order degradation rate constant (k) in Figure 2 represents the extent of enalapril maleate degradation. The findings indicate that after being combined with the excipients, k is affected. Depending on the kind of excipient, enalapril maleate remained most stable when disaccharides were present and most unstable when superdisintegrants were present. Furthermore, the degree of deterioration is significantly impacted by humidity.

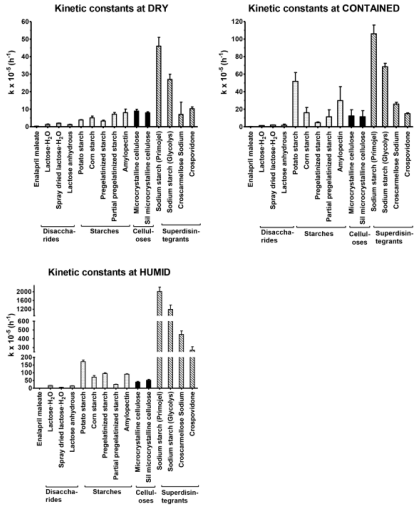

Fig. 2. Solid-state stability data of enalapril maleate in a binary mixture of enalapril maleate:excipient at a 1:100 ratio. Mixtures were stored at three different conditions: dry (60 °C/13%RH), contained (closed vials at 60 °C) and humid (60 °C/58%RH). Data is presented as mean ± SD ($n = 2$).

3.2. Stability in relation to properties of excipients

The degradation of enalapril maleate rises with an excipient's sorption capability, as shown in Fig. 4A. According to the DVS, this capacity is the most moisture that a material can absorb at 90% relative humidity. The excipients' capacity to absorb moisture is one specific feature where they vary significantly from one another. Their use in a formulation is also responsible for this discrepancy. For instance, superdisintegrants, which are designed to improve the disintegration of an oral solid dosage form, have a strong affinity for moisture sorption. Disaccharides, on the other hand, have a very low affinity for moisture. They are mostly used as binders to preserve a solid, stable dose form.

It is well known that the quantity of sorbed water and the number of amorphous domains of cellulose are directly correlated (Ioelovich, 2009; Ioelovich and Leykin, 2011; Mihranyan et al., 2004). It is now clearly clear that degradation is more noticeable in a combination including excipients that exhibit a lower degree of crystallinity and a greater sorption capacity (Fig. 4). Since the quantity of water that is really sorbed depends on the ambient humidity, the former is thus reliant on it.

The figures in Fig. 4B are taken from the literature (see to Appendix A). In actuality, the amorphous component may have been used in place of the crystallinity. Crystalline and amorphous chemicals bond to water in various ways due to the solid state. In general, it is recognised that amorphous compounds are better at absorbing moisture than ordered crystalline ones (Hancock and Zografi, 1993).

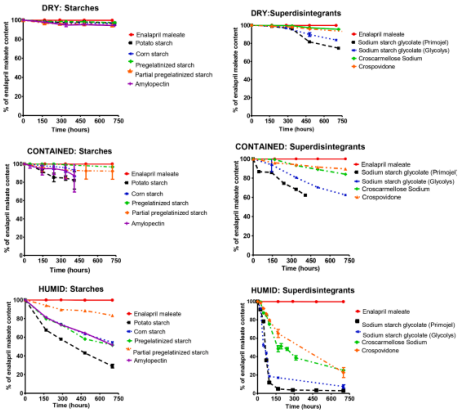

Fig. 3. Content of enalapril maleate (%) over time in presence of starches and superdisintegrants (ratio 1:100) after storage at three different conditions: dry (60 °C/13%RH), contained (closed vials at 60 °C) and humid (60 °C/58%RH). Data is presented as mean ± SD ($n = 2$).

History of Medicine:Vol.08 No. 2 (2022):740-747
DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

Their enhanced sorption capacity may also be explained by the fact that disordered structures in an amorphous form provide more room for moisture to enter and fill the gaps (Mihranyan et al., 2006). In essence, bulk absorption is what this water intake is. As previously stated, we have determined that enalapril maleate degradation is a surface-related event. This seems to go counter to the explanation above, which suggests internal moisture sorption. This indicates that the way that bulk sorption affects the breakdown of enalapril maleate at the particle-particle contact cannot be clearly explained.

3.3. Particle surface

In a prior investigation, we demonstrated that the degree of degradation is mostly determined by the mixing ratio between sodium starch glycolate and enalapril maleate. This was said to be related to the fact that the substances interact inside the particle-particle interface's microenvironment. By altering their surface, one may investigate the interaction between particles and a potential moisture effect. Enalapril maleate's stability was monitored over time in the presence of three distinct types of powders—regular sodium starch glycolate, granulated sodium starch glycolate, and silicified granulated sodium starch glycolate—as seen in Fig. 5. According to sorption isotherms, the sorption capacity of silicified granules is 46%±1.9, that of ordinary sodium starch glycolate is 43%±1.0, and that of granulated powder is 52%±0.8. Enalapril maleate is susceptible to breakdown when combined with ordinary sodium starch glycolate. A somewhat slower rate of degradation was observed when enalapril maleate was exposed to sodium starch glycolate with a larger particle size by granulation. Nevertheless, enalapril maleate is still completely broken down after 700 hours. Enalapril maleate remained more stable and degradation was slowed down if silica particles were additionally coated on the sodium starch glycolate granules. It goes without saying that for the degradation to occur, the two chemicals must come into direct surface contact.

We have previously shown that the physical state of enalapril maleate changes from crystalline to amorphous prior to degradation, which has been ascribed to the compound's transient dissolution (Bout and Vromans, 2021). Dissolution is an important phase for this occurrence. This obviously calls for a sufficient volume of liquid water. As a result, it is still unclear if the moisture causing enalapril maleate to degrade is at the surface. The sorption of moisture is separated into three deposition sites using the Young-Nelson model. The first sign of moisture adsorption at low humidity is the development of a monolayer (single atom deposition) on the particle's surface and within its pores. When the humidity is greater, moisture is absorbed by the substance at the second position and/or accumulated as a multilayer at the third place. The physical condition of this adsorbed moisture may be regarded as a liquid when a specific threshold is reached as the number of layers increases. Another name for this is condensed water. As a result, it displays characteristics of liquid water, including the manifestation of solubility towards compounds (Alvarez-Lorenzo et al., 2000; Faroongsarng and Peck, 1994; Young and Nelson, 1967). After being stored at different humidities for 24 hours, Fig. 6 illustrates the degree of degradation of enalapril maleate in a combination containing pre-dried sodium starch glycolate powder in a ratio of 1:3. Since enalapril maleate has no affinity for moisture, the pre-dried sodium starch glycolate powder would be responsible for any sorption that is seen. Fig. 6 also shows the quantity of sorption of pre-dried sodium starch glycolate at different humidities. It is evident

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

that even at a relative humidity of 10%, pre-dried sodium starch glycolate begins to absorb moisture. However, as shown in Fig. 6, enalapril maleate only degrades over 50%RH in less than 24 hours. These findings seem to support previous research showing that enough moisture accumulation is required for deterioration to take place.

IV. CONCLUSION

The present study successfully evaluated the stability and excipient compatibility of Enalapril Maleate through forced degradation studies. The findings revealed that Enalapril Maleate is highly susceptible to hydrolytic and oxidative degradation, with significant degradation observed under acidic, basic, and oxidative conditions. These results emphasize the need for controlled storage conditions and protective formulation strategies to ensure drug stability.

The excipient compatibility study demonstrated that certain excipients influenced the degradation rate, highlighting the importance of careful excipient selection to maintain the stability, potency, and shelf life of the formulation. The insights gained from this study contribute to the development of stable pharmaceutical formulations, ensuring regulatory compliance and therapeutic efficacy.

Further studies, including identification of degradation products and long-term stability testing, are recommended to enhance the formulation robustness and commercial viability of Enalapril Maleate-based pharmaceutical products.

REFERENCES

1. Alvarez-Lorenzo, C., Gomez-Amoza, ´ J., Martínez-Pacheco, R., Souto, C., Concheiro, A.,2000. Interactions between hydroxypropylcelluloses and vapor/liquid water. Eur. J.Pharm. Biopharm. 50, 307–318.
2. 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.
3. Bravo-Osuna, I., Ferrero, C., Jim´enez-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.
4. 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.
5. Glycerine Producers' Association, 1963. Physical Properties of Glycerine and It Solutions. New York.
6. 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.
7. Heidarian, M., Mihranyana, A., Strømmeb, M., Ragnar, E., 2006. Influence of watercellulose binding energy on stability of acetylsalicylic acid. Int. J. Pharm. 323,139–145.
8. Ioelovich, M., 2009. Accessibility and crystallinity of cellulose. Bioresources 4,1168–1177.
9. Ioelovich, M., Leykin, A., 2011. Study of sorption properties of cellulose and its derivatives. BioRes 6, 178–195.
10. Mihranyan, A., Pinas ˜ Llagostera, A., Karmhag, R., Strømme, M., Ek, R., 2004. Moisture sorption by cellulose

DOI: https://doi.org/10.48047/HM.08.2.2022.740-747

powders of varying crystallinity. Int. J. Pharm. 269, 433–442.

11. Mihranyan, A., Stromme, ¨ M., Ek, R., 2006. Influence of cellulose powder structure on moisture-induced degradation of acetylsalicylic acid. Eur. J. Pharm. Sci. 27,220–225.
12. 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.
13. Nokhodchi, A., Ford, J.L., Rubinstein, M.H., 1997. Studies on the interaction between water and (hydroxypropyl)methylcellulose. J. Pharm. Sci. 86, 608–614.
14. 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.
15. Vehovec, T., Gartner, A., Planinˇsek, 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.