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Original research paper

Influence of different types of commercially available microcrystalline cellulose on degradation of perindopril erbumine and enalapril maleate in binary mixtures

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Influence of some commercially available types of microcrystalline cellulose (MCC) on the stability of certain active pharmaceutical ingredients (APIs), when in contact, has been investigated. Two structurally similar APIs, perindopril erbumine (PER) and enalapril maleate (EM), both well-known angiotensin-converting enzyme inhibitors were used. The main properties of an MCC that could determine the stability for each API were measured and correlated to the stability of these two APIs in binary mixtures. The stability of these APIs differed when in contact with different types of MCC. The dominant properties of MCC from one manufacturer were surface features that influenced the stability of PER and acidity that influenced the stability of EM. In the case of MCC from other manufacturers, unbound water was stability determining for both substances.

Keywords: microcrystalline cellulose, perindopril erbumine, enalapril maleate, stability study, drug-excipient binary mixtures

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Numerous types of microcrystalline cellulose (MCC) are available on the market for a variety of uses in pharmaceutical industry. They can be used as adsorbents, anti-adherents, binders/diluents and tablet disintegrants (1). On the industrial scale, MCC is obtained by hydrolysis of wood and cotton cellulose using dilute mineral acids. The treated pulp is then rinsed and spray-dried with or without an additional process step such as milling. Cellulose from different sources differs in the properties such as crystallinity, moisture content, surface area, porous structure, molecular mass. These properties can be also affected by the conditions of hydrolysis. Preparations of MCC from materials other than wood and cotton (*e.g.*, water hyacinth, coconut shells, wheat and rice straws, *etc.*) have also been reported (2).

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MCC (Fig. 1) is a partially depolymerized cellulose and is composed of crystalline and amorphous domains. The relatively large surface to volume ratio of micro fibrils, due to their small size, and the presence of abundant hydroxyl groups makes MMC hygroscopic (3). An important property of MCC as an excipient is its moisture content, which should not exceed 7.0 % (*m*/*m*) according to the European Pharmacopoeia (4). Hygroscopicity is one of the main limitations to using MCC in pharmaceutical formulations, since it may induce instability of moisture-sensitive drugs (5). MCC has been referred to as a »molecular sponge«, because most of the water held by MCC is present as free water that may be readily lost by evaporation (6). It should be noted that moisture content itself says little about an excipient's propensity to promote hydrolysis. It has been shown that while cellulose powders with a lower degree of crystallinity contain more water than their counterparts with a higher degree (7, 8), the former exhibit lower rates of degradation of acetylsalicylic acid than the latter (9). The study of the influence of water-binding energy of cellulose on the stability of acetylsalicylic acid revealed that each water molecule formed on average more hydrogen bonds in low-crystallinity cellulose (LCC) than in ordinary MCC and in high-crystallinity cellulose (HCC). Therefore, the stability of acetylsalicylic acid was greater in a binary mixture with LCC, since despite a larger amount of total water content, fewer water molecules were available to induce hydrolysis (10).

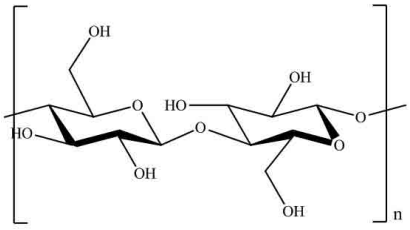

Fig. 1. Structular formula of cellulose.

Perindopril erbumin (PER, Fig. 2a) and enalapril maleate (EM, Fig. 2b) are angiotensin-converting enzyme inhibitors (ACE inhibitors), used in the treatment of hypertension. According to the European Pharmacopoeia and published papers (4, 11–13), the main degradation pathways of PER and EM in solution and in solid state are ester hydrolysis and intramolecular cyclization, respectively, with first-order kinetics with respect to substrate concentration (13–15). While, for hydrolysis, increased relative humidity of the environment plays a major role, the formation of the cyclic product diketopiperazine (DKP) is accelerated at elevated temperature and in an acidic environment. EM is very stable when stored at room temperature (amber glass) for 4 years it showed no evidence of degradation as determined by HPLC analysis (16). PER is less stable. The mechanisms and rates of degradation of both ACE-inhibitors are highly pH dependent, both substances being quite stable in neutral and acidic environments (13).

The different types of MCC, according to manufacturers and also in a monograph of MCC with functionality-related characteristics (FRC) in European Pharmacopoeia (4),

are characterized mainly from the technological and not from the stability point of view. The aim of this study was to investigate the influence of different commercially available types of MCC on the stability of an API when the two are in contact, since the choice of suitable excipients is one of the most important steps in drug formulation and influences the stability of the final product. Therefore, also those physicochemical properties of MCCs which are most important in correlating to stability of these two APIs in binary mixtures were identified and evaluated.

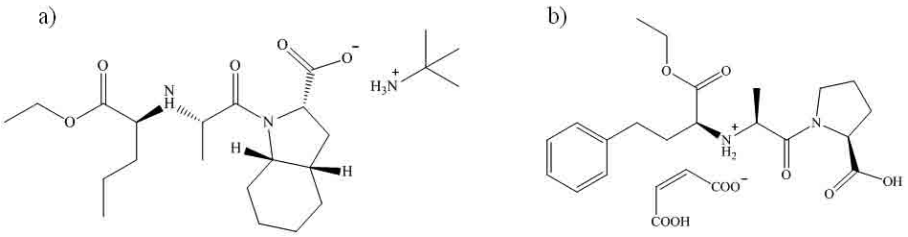

Fig. 2. Molecular structures of: a) perindopril erbumine and b) enalapril maleate.

EXPERIMENTAL

Materials

The different types of microcrystalline cellulose used in binary mixtures with APIs were obtained from three different manufacturers. They are compiled in Table I with important physicochemical properties according to the manufacturers.

For particle size and specific surface area determination of MCCs, ethanol, obtained from J. T. Baker (The Netherlands), was used as dispersion medium.

Probes used for the inverse gas chromatography (IGC) measurements of MCCs were non-polar alkanes, from hexane to decane (Fluka, Switzerland), and polar tetrahydrofuran, acetone, trichloromethane and ethyl acetate obtained from Sigma-Aldrich Chemie (Switzerland). Methane (Messer, Slovenia) was used as a non-adsorbing probe.

Perindopril erbumin and enalapril maleate, produced by Krka, d.d. (Slovenia) were used as APIs.

The following reagents were used for HPLC analysis of PER and its degradation products: acetonitrile (HPLC grade), $HClO_4$ (*p.a.*), obtained from J. T. Baker, sodium heptanesulphonate ($C_7H_{15}NaO_3S$) (*p.a.*) from Merck (Germany), triethylamine (*p.a.*) from Sigma-Aldrich Chemie. The buffer solution of sodium heptanesulphonate with triethylamine was prepared in a concentration of 0.92 mg mL^{-1}, which was adjusted with perchloric acid to pH 2.0.

For HPLC analysis of EM and its degradation products, the following reagents were used: acetonitrile (HPLC grade), H_3PO_4 (*p.a.*) obtained from J. T. Baker, KH_2PO_4 (*p.a.*)

Table I. Physicochemical properties of MCC powders according to the manufacturer

Type of MCC	Particle size (μm)	Moisture content (%)	Loose bulk density (g cm^{-3})	Manufacturer
Avicel PH-101[a]	50	3.0 to 5.0	0.26–0.31	FMC, Ireland
Avicel PH-101[b]	50	3.0 to 5.0	0.26–0.31	
Avicel PH-101[c]	50	3.0 to 5.0	0.26–0.31	
Avicel PH-102	100	3.0 to 5.0	0.28–0.33	
Avicel PH-105	20	≤ 5.0	0.20–0.30	
Avicel PH-112	100	≤ 1.5	0.28–0.34	
Avicel PH-200	180	2.0 to 5.0	0.29–0.36	
Avicel PH-200 LM	180	≤ 1.5	0.30–0.38	
Microcel MC-102	100	max. 7 %	0.28–0.33	Blanver, Brazil
Microcel MC-250	230	max. 7 %	0.33–0.40	
Microcel MC-200	180	max. 7 %	0.33–0.40	
Vivapur 102	100	NI	0.28–0.33	JRS Pharma, Germany
Vivapur 101	65	NI	0.26–0.31	
Vivapur 12	180	NI	0.30–0.36	
Emcocel LP200	190	NI	0.25–0.37	

[a-c] Different batches of the same type of MCC; NI – no information.

from Merck (Germany). The buffer solution of KH_2PO_4 was prepared in a concentration of 0.136 mg mL^{-1}, which was adjusted with H_3PO_4 to pH 2.0.

Determination of acidity and moisture of microcrystalline cellulose

Acidity and moisture content of MCCs were determined according to the monograph of MCC in European Pharmacopoeia (4). The pH was measured with a pH meter (Seven Multi, Mettler Toledo, Switzerland). Moisture content – loss on drying (*LOD*) was determined with an oven (SP-105 C, Kambič, Slovenia) in triplicate.

Determination of particle size and specific surface area of microcrystalline cellulose

Particle size of the different types of MCC was determined by laser light scattering (Mastersizer S, Malvern, UK) with a 300RF lens with a QS small volume sample dispersion unit for measuring liquid dispersion. Specific surface area (*SSA*) was calculated automatically by the laser diffraction system software from the equation, based on the assumption that the particles were perfectly smooth, solid spheres:

$$SSA = (6\ \Sigma(V_i/d_i))/(\rho\ \Sigma V_i) = 6/(\rho\ D[3.2])$$

where V_i is the relative volume in class i with a mean class diameter of d_i, ρ is the density of the material, and $D[3.2]$ is the surface area weighted mean diameter (18).

Inverse gas chromatography

For the IGC analysis of MCCs, a commercial gas chromatograph (HP 5890A, Series II, Hewlett-Packard, USA) equipped with the flame ionization detector (FID) and Chem-Station software was used. Dry helium (Messer, Slovenia) was used as carrier gas with a flow-rate of 7 mL min^{-1}. Glass columns (0.2 m long and 3.0 mm i.d.) were packed by tapping the powder for 10 min in a tap density tester (VanKel, Cary, USA). Prior to measurements, filled columns were conditioned overnight with helium at a constant flow of 7 mL min^{-1} at 30 °C. Two injectors and detectors, which enabled measurements of samples simultaneously, were heated at 150 (injectors) and 250 °C (detectors). Samples of MCC were analyzed at 30 °C. The probes, described under *Materials*, were injected automatically from a 10.0 μL Hamilton syringe using an Agilent Technologies (USA) 7683 series auto injector.

The dispersive component of total surface free energy of the solid phase (γ_s^d) and polar characteristics of the surface (K_a, K_b) were calculated from the retention times of the probes measured at a series of concentrations and extrapolated to infinite dilution. The theoretical background of the IGC method is described in the literature (19–21).

Water vapour sorption of microcrystalline cellulose

A dynamic vapour sorption (DVS) method (DVS-1, Surface Measurement Systems Ltd., UK) was used to determine MCC water sorption. The analyses were performed at controlled room temperature (25 °C). A powder sample of about 14 mg was dried to a stable weight on a balance by a stream of dry nitrogen gas at a rate of 200 mL min^{-1}. The sample was then subjected to a series of relative humidities from 0 to 90 % and back in 9 steps each way. Relative humidity (RH) from 0 to 90 % is controlled through a DVS-1 instrument. No special chemicals were used, except water and N_2. Equilibrium was assumed to be achieved when there was < 0.002 % min^{-1} mass increase under the given relative humidity. One complete cycle for each sample of MCC was performed.

Stability study of PER or EM alone and in binary mixtures with different types of MCC

In the stability study, different types of MCC powders from three different manufacturers (FMC, Blanver, Brazil and JRS Pharma, Germany) and three different batches of the same type of one MCC, Avicel PH-101, were used. Individual mixtures of PER or EM with each MCC were prepared by mixing the constituents for 10 minutes. Mixtures of 12 g were prepared in 1:5 (m/m) ratio of PER or EM to MCC.

Each API/MCC mixture was divided into two equal parts. One part was placed in an open Petri dish and the other was filled into an HPLC vial (cca 700 mg of mixture per vial), which was then closed. These two samples are referred to throughout the paper as being under 'open' and 'closed' conditions. Samples were stored in a climatic chamber (KK-1000, Kambič, Slovenia) at 40 ± 2 °C and 75 ± 5 % RH. Samples were withdrawn at different time points (Table II). At each time point, two vials of each binary mixture and about 800 mg of each binary mixture were withdrawn from the Petri dish. Accurately weighed samples, of about 360 mg, of mixtures with PER and of about 120 mg of mix-

tures with EM were then dissolved in 20 mL of the corresponding buffer solution of pH 2.0 in order to obtain solutions having about 3.0 mg of PER per mL or 1.0 mg of EM per mL. Duplicate samples were prepared and analyzed for degradation products by two HPLC methods as described in ref. 13. An HPLC instrument (1100 Series, Agilent Technologies, Germany) with a variable UV detector and column thermostat, fitted with a Hypersil ODS, 5-μm particles, 250 x 4 mm *i.d.* column (Thermo Scientific, Waltham, USA) was used.

Stability of APIs was tested in open Petri dishes and in closed vials in a climatic chamber at 40 °C/75 % RH in the same manner as binary mixtures.

Table II. Time of sample withdrawal for all binary mixtures with different types of MCC

Conditions	Binary mixtures with PER	Binary mixtures with EM
40 °C/75 % RH-open	0, 4, 7 and 14 days	0, 4, 7, 14 and 28 days
40 °C/75 % RH-closed	0, 7, 14, 28, 56 and 84 days	0, 14, 28, 56 and 84 days

RESULTS AND DISCUSSION

Physicochemical properties of MCC powders that could influence drug stability in binary mixtures

Some physicochemical properties of MCC were investigated in detail according to their potential influence on the stability of API. On the basis of the MCC monograph in *Ph. Eur.* (4), acidity, loss on drying and particle-size as functionality-related characteristics of MCC were measured. In addition, the influence of specific surface area, energy surface properties determined by IGC (γ_s^d, K_a, K_b) and water vapour sorption determined by DVS of MCC on the stability of APIs were included in the study.

The results on acidity (pH of water suspension of MCC), *LOD*, average particles size and specific surface area are compiled in Table III. The differences in acidity and *LOD* between different types of MCC are small, with the exception of *LOD* results of Avicel PH-200 LM. The results for pH are from 5.88 to 6.85 and for *LOD* from 4.12 to 5.22 %, with the exception of *LOD* results of Avicel PH-200 LM (2.15 %).

The results on average particles size are in accord with the specified limits of the manufacturers. The results on specific surface area are from 0.254 to 0.903 $m^2\ g^{-1}$.

The results on the dispersive component of the total surface free energy (γ_s^d) of different types of MCC (Table III) show some differences in the nonpolar parameters of MCC (from 42.9 mN m^{-1} for Avicel PH 105 to 56.0 mN m^{-1} for Avicel PH 200). The results on K_a are from 0.086 to 0.104 and K_b 0.341 to 0.558. Higher surface energy parameters can be attributed to increased amorphicity of the sample as known from the literature on lactose or indomethacin (22, 23).

One of the simplest means of studying the interactions of water molecules with powdered polymeric materials are moisture sorption isotherms obtained by the dynamic vapour sorption analysis (24). The results on water vapour sorption on all the measured MCCs are in good agreement with previously published results. Adsorption isotherms can be described as the type II (BET) adsorption isotherms (25, 26). The results on sorption, desorption and hysteresis obtained from the DVS results at 75 % relative humidity (Table III) were used in the study of the influence of adsorbed water on MCC on the stability of PER and EM in mixtures with different types of MCC. Experimental conditions of 75 % RH were chosen in relation to ICH stability testing conditions of 40 °C/75 % RH (27).

Table III. pH of water suspension, LOD, *particle size, specific surface area, IGC and DVS analysis of MCC*

		IGC results						DVS results at 75 % RH		
Type of MCC	pH[d]	*LOD* (%)	*APS* (μm)	*SSA* ($m^2\ g^{-1}$)	γ_s^d (mN m^{-1})	K_a	K_b	Sor (%)	Des (%)	Hyst (%)
Avicel PH-101[a]	6.54	4.55	73.7	0.567	50.1	0.094	0.414	10.40	13.28	2.88
Avicel PH-101[b]	6.60	4.42	74.7	0.596	50.7	0.094	0.430	10.38	13.22	2.84
Avicel PH-101[c]	6.51	4.64	71.3	0.549	50.7	0.092	0.441	10.03	12.86	2.83
Avicel PH-102	6.85	4.74	112.2	0.790	47.7	0.086	0.397	10.16	12.92	2.77
Avicel PH-105	6.26	5.06	26.8	0.903	42.9	0.069	0.516	9.97	12.09	2.12
Avicel PH-112	6.16	4.14	110.7	0.543	46.3	0.085	0.464	9.52	12.37	2.85
Avicel PH-200	6.85	4.12	173.3	0.412	54.4	0.095	0.558	9.52	12.37	2.85
Avicel PH-200 LM	6.34	2.15	183.3	0.254	56.0	0.099	0.453	10.00	12.66	2.66
Microcel MC-102	5.99	4.81	131.6	0.439	52.0	0.090	0.527	9.53	12.30	2.78
Microcel MC-250	6.28	4.91	174.7	0.453	52.7	0.094	0.534	9.21	12.10	2.89
Microcel MC-200	6.19	5.22	159.9	0.480	45.5	0.077	0.341	9.57	12.16	2.59
Vivapur 102	6.33	4.22	122.9	0.408	53.3	0.104	0.389	9.94	12.39	2.45
Vivapur 101	6.18	4.32	72.4	0.507	48.1	0.092	0.406	9.87	12.26	2.39
Vivapur 12	6.36	4.53	162.8	0.400	49.4	0.087	0.454	9.65	12.25	2.59
Emcocel LP200	5.88	4.38	179.0	0.350	55.5	0.098	0.549	9.79	12.04	2.26

[a-c] Different batches of the same type of MCC; [d] pH of water suspension.
LOD – loss on drying, *APS* – average particle size, *SSA* – specific surface area, γ_s^d – dispersion component of surface free energy, K_a – parameter that describes the ability of the surface to act as an electron acceptor (acid number), K_b – parameter that describes the ability of the surface to act as an electron donor (base number), Sor – sorption, Des – desorption, Hyst – hysteresis.

Stability of PER and EM alone and in binary mixtures with different types of MCC

Degradation of PER and EM in mixtures with MCC follows first-order kinetics, which is in good agreement with previously published results. The first-order degradation lines for PER and EM in a mixture with Avicel under closed and open conditions

are presented in Fig. 3. The kinetic constants for degradation of PER and EM are presented in Figs. 4 and 5, for APIs alone and for all mixtures. Most correlation coefficients were above 0.9, except for the hydrolytic degradation of PER and EM in mixtures with MCCs and the degradation of pure APIs under closed conditions. This can be explained by low degradation rates of APIs under these conditions and therefore greater influence of experimental errors.

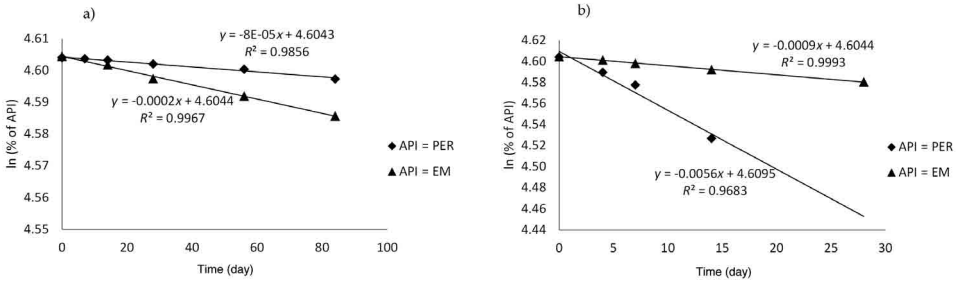

Fig. 3. First-order kinetics for degradation of PER and EM in a mixture with MCC Avicel PH-101 under: a) closed and b) open conditions. ln (% of API) presents ratio of the amount of API at a given time point and the amount of API at the beinning of experiment.

Results of stability measurements under both conditions showed that the influence of MCC on APIs is in general destabilizing when they are in contact (Figs. 4 and 5). Under open conditions, EM in mixtures decomposed mainly into diketopiperazine, while the degradation of PER resulted in almost equal proportions of diketopiperazine and perindoprilate. Under closed conditions at 40 °C/75 % RH, both APIs in mixtures with all types of MCC decomposed mainly to diketopiperazine (Fig. 5), while a small proportion of hydrolytic degradation product and even less of other degradation products were detected. Previous studies have shown that the degree and pathway of degradation of EM depend on the acidity of the drug-excipient mixture (EM decomposes mainly into diketopiperazine when it is in contact with an excipient with acidic properties), temperature, and humidity (19). The acidic nature of MCC has been confirmed, since the main degradation product was diketopiperazine. In contrast, the good stability of EM alone was confirmed, since there was almost no degradation of API after 3 months under closed conditions (Fig. 5b), and degradation of 0.1 % after 1 month under open conditions (Fig. 4b). The stability of EM alone was significantly better than the stability of EM in a mixture with MCC and the stability of PER alone and in mixtures with MCC. Interestingly, the stability of EM in a mixture with MCC was lower than that of PER in a mixture with MCC under closed conditions (Fig. 5).

Comparison of the kinetic constants for degradation showed differences in the stability of APIs when in contact with different types of MCC, but no significant differences were observed when APIs were in contact with different batches of the same MCC type.

Under open conditions at 40 °C/75 % RH, significant differences in the stability of PER and EM in binary mixtures with different types of MCC were observed (Fig. 4). The

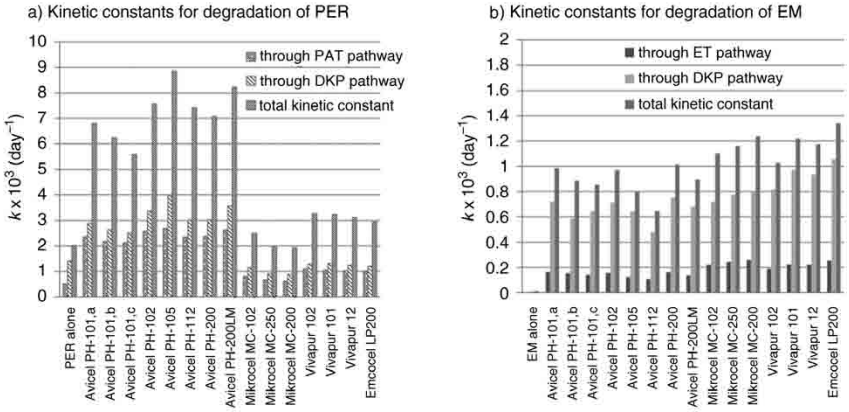

Fig. 4. First-order kinetic constants for degradation of: a) PER and b) EM determined in the stability study under open conditions at 40 °C/75 % RH (a, b, c: different batches of the same type of MCC).

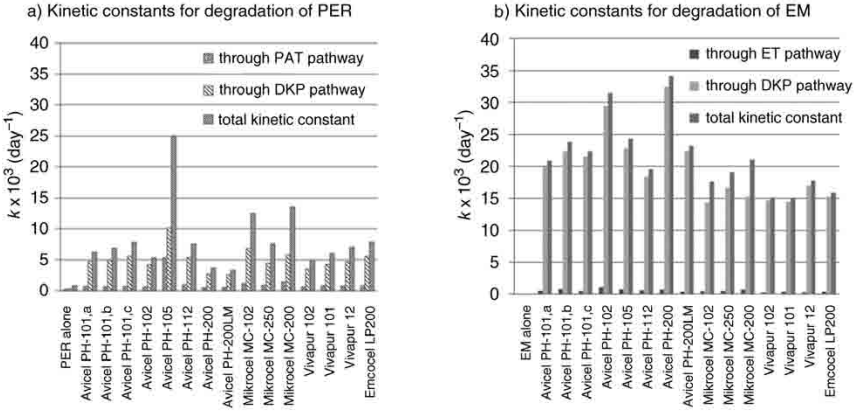

Fig. 5. First-order kinetic constants for degradation of: a) PER and b) EM determined in the stability study under closed conditions at 40 °C/75 % RH (a, b, c: different batches of the same type of MCC).

kinetic constants differed by a factor of 4 for PER degradation and by a factor of 2 for the degradation of EM. The highest stability was observed with MCC Microcel MC-200 for PER and with MCC Avicel PH-112 for EM. On the other hand, the lowest stability was observed with MCC Avicel PH-105 for PER and with MCC Emcocel LP200 for EM. In general, the degradation of PER was higher in mixtures with MCCs from the manufacturer FMC than from manufacturers Blanver and JRS Pharma. The situation was reversed with EM, which is most stable in a mixture with MCC from the manufacturer FMC.

Conclusions of the stability study under closed conditions differed from those obtained under open conditions. Also, under closed conditions significant differences in the stability of PER and EM in mixtures with different types of MCC were observed. The

differences were larger for PER than for EM. The kinetic constants for the degradation of APIs in mixtures differed by a factor of 8 for PER and 2 for EM. PER showed the highest stability with MCC Avicel PH-200 LM and the lowest with MCC Avicel PH-105. EM showed the highest stability with MCC Vivapur 101 and the lowest with MCC Avicel PH-200.

The influence of MCC on the stability of API is complex as several parameters together are determining the stability for each API. In our stability study, the conclusions from open conditions did not reflect the results obtained under closed conditions. In stability studies, closed conditions are more relevant for the pharmaceutical development; however, the results of experiments under open conditions are obtained faster.

We expected that the stability of APIs in binary mixtures under closed conditions would depend on the particle size and surface energy of the MCC powder. MCC powder with larger particles and smaller surface area should have less influence on the stability of API than the MCC powder with smaller particles and larger surface area. The stability of APIs in a mixture could depend on the surface energy of MCC powder, since less water is available for hydrolysis in case of MCC powder with higher surface energy. In order to determine the main properties of MCC that influenced the stability of API, the results of all measured parameters of MCC (pH of water suspension, loss on drying, particle size, specific surface area, water vapour sorption and surface characteristics determined by inverse gas chromatography) were correlated with the kinetic constants for degradation of both APIs. The best correlations were found if the results were divided into two groups. The first group consisted of the results of stability studies of drug mixtures (PER or EM) with MCCs from the manufacturer FRC. In the second group were the results of stability studies of drug mixtures with MCCs from manufacturers Blanver and JRS Pharma.

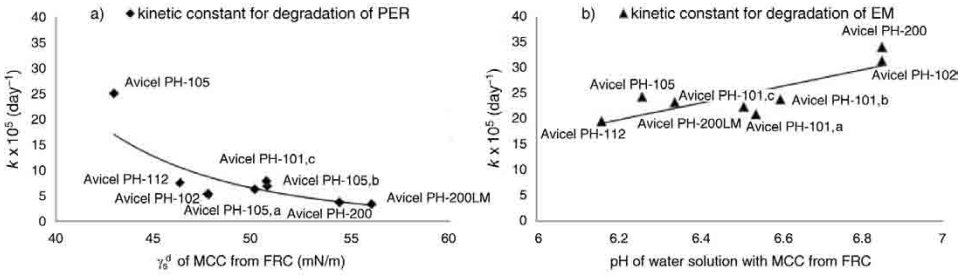

Fig. 6. Kinetic constants for degradation of: a) PER in relation to the dispersion component of surface free energy (γ_s^d) of MCC and b) EM in relation to pH of water suspensions of MCC. Kinetic constants were determined in the stability study with MCCs from the manufacturer FRC under closed conditions at 40 °C/75 % RH.

Correlations from the first group indicated that the surface energy characteristics of MCCs (with PER) and acidity of MCCs (with EM) had major influence on the stability of APIs. The experimental results showed that the kinetic constants for PER degradation predominantly correlated with the results on particle size, specific surface area and IGC

of MCCs (Fig. 6a). The stability was greater with MCCs, which had larger particles, lower specific surface area and higher nonpolar part of surface free energy. The highest correlation of kinetic constants degradation for EM with pH of water suspension of MCC was found under both stability conditions. As already proven (15), the stability of EM is better in an acidic environment (Fig. 6b).

Furthermore, the results in the second group indicated that under closed conditions unbound water of MCC had major influence on the stability of PER or EM in mixtures. The highest correlations of kinetic constants were found with the results on *LOD* and results of DVS analysis. The stability of APIs was higher when less unbound water was available (Fig. 7).

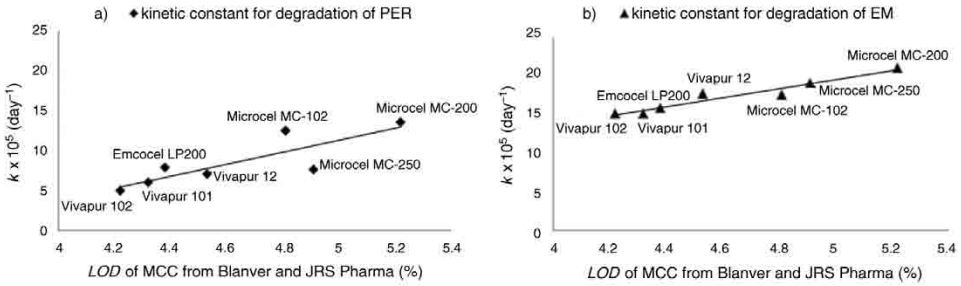

Fig. 7. Kinetic constants for degradation of: a) PER and b) EM determined in the stability study under closed conditions at 40 °C/75 % RH in relation to *LOD* of MCC from manufacturers Blanver and JRS Pharma.

CONCLUSIONS

This study showed differences in the stability of PER and EM when in contact with different types of MCCs that comply with the requirements of *Eur. Ph*. Addition of MCC to PER and EM increased the quantity of degradation products, especially the products of cyclization reaction under closed conditions. Even in case of structurally similar substances, the influence of different types of MCC on their stability is specific for each API. When excipient and API are in contact, both them determine which properties of the excipient would be dominant for the degradation of API. It is reasonable to perform stability studies of API with different types of the same excipients differing in physicochemical properties. The findings of the present study may be specifically helpful in case of very unstable APIs in contact with MCC, where the stabilization in formulation with other excipients is not satisfactory and/or the amount of MCC in formulation is very high. The stability problem could be simply solved with a different type of MCC that is also suitable for the same technological procedure.

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P O V Z E T E K

Vpliv različnih tipov komercialno dostopne mikrokristalne celuloze na razpad erbuminijevega perindoprilata in enalaprilijevega maleata v binarnih zmeseh

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V raziskavi smo proučevali vpliv nekaterih tipov komercialno dostopne mikrokristalne celuloze (MCC) na stabilnost izbranih zdravilnih učinkovin, kadar sta učinkovina in pomožna snov v stiku. Uporabili smo dve strukturno sorodni učinkovini, znana zaviralca angiotenzin-konvertaze, erbuminijev perindoprilat in enalaprilijev maleat. Izmerili smo najpomembnejše lastnosti mikrokristalne celuloze, ki bi lahko vplivale na stabilnost posamezne zdravilne učinkovine in določili povezavo med temi lastnostmi pomožne snovi in stabilnostjo zdravilnih učinkovin v binarnih zmeseh. Stabilnost obeh učinkovin se je razlikovala pri posameznih eksperimentih in je bila odvisna od tipa uporabljene mikrokristalne celuloze. Na stabilnost erbuminijevega perindoprilata so najbolj vplivale površinske značilnosti enega izmed proizvajalcev mikrokristalne celuloze, na stabilnost

enalaprilijevega maleata pa njene šibko kisle lastnosti. V primeru ostalih dveh proizvajalcev mikrokristalne celuloze je na stabilnost obeh zdravilnih učinkovin najbolj vplivala nevezana voda.

Ključne besede: mikrokristalna celuloza, erbuminijev perindoprilat, enalaprilijev maleat, stabilnostna študija, binarna zmes zdravilna učinkovina – pomožna snov

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