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Analysis of surface properties of cellulose ethers and drug release from their matrix tablets

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ABSTRACT

Detailed knowledge based on new developments, especially in analytical techniques, is needed for characterizing polymer excipients. Inverse gas chromatography (IGC) is a useful method for investigating polymer surfaces in terms of thermodynamic parameters. The aim of our work was to study the correlation between polymer surface properties determined with IGC and the mechanisms of release of water-soluble pentoxifylline and vancomycin hydrochloride from cellulose ether matrices. Tablets were made of hydroxypropyl (HPC), hydroxyethyl (HEC) or hydroxypropylmethyl (HPMC) cellulose and contained 25% of drug. Differences in dispersive component of the surface free energy for these polymers were relatively small and ranged from 26 to 33 mN/m. However, polar properties, expressed as specific component of the enthalpy of adsorption and as acid–base properties show larger differences between the polymers and demonstrate their relative polarity in the order HEC > HPMC > HPC, which correlates well with water sorption on bulky polymers and with the swelling degree of polymer matrices. The release of pentoxifylline and vancomycin from HPC is governed mainly by Fickian diffusion, whereas from HEC the relaxation of polymer chains is important too. The analysis of the release profiles in the light of Peppas–Sahlin model lead to the conclusion that the surface properties of the cellulose ethers influence the interactions with water and the release mechanisms of the drug. It was found out, that data obtained by IGC enable rapid inference about the behaviour of polymers in water and the release of water-soluble drugs.

1. Introduction

Investigation of hydrophilic polymers, in particular cellulose derivatives, has attracted considerable attention for the development of controlled release technology in the formulation of pharmaceutical matrix products. Matrix tablets swell on contact with water, and the release of a drug depends on interactions between water, polymer and drug. In the field of controlled release, the influence of carriers on drug dissolution kinetics, which are the result of differently acting mechanisms, was investigated frequently. Usually two main mechanisms are studied, diffusion and erosion. In the case of cellulose ether based matrix tablets, drug release can be described as being controlled by the rate of swelling (Colombo et al., 2000; Lowman and Peppas, 2000; Rodriguez et al., 2000; Peppas and Simmons, 2004). However, drug release in general is not purely swelling controlled, since it occurs mostly as the result of a combination of polymer relaxation and Fickian diffusion (Lowman and Peppas, 2000). Rittger and Peppas (Ritger and Peppas, 1987) proposed an equation to describe drug release kinetics from drug delivery systems controlled by swelling. The equation is based on a power law dependence

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of the fraction released on time and has the following form:

$$\frac{M_t}{M_\infty} = k \cdot t^n \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ the amount of drug released at infinite time, k a kinetic constant and n is the diffusional exponent. The latter can range from 0.43 to 1; it depends on the release mechanism and the shape of the drug delivery device. Based on the value of the diffusional exponent the drug transport in slab geometry is classified either as Fickian diffusion ($n = 0.5$), non-Fickian or anomalous transport ($0.5 < n < 1$), or Case II transport ($n = 1$), where the dominant mechanism for drug transport is due to polymer relaxation during gel swelling. Anomalous transport occurs due to a coupling of Fickian diffusion and polymer relaxation (Colombo et al., 2000; Lowman and Peppas, 2000).

Previous studies of matrix tablets led to the conclusion that the rate and extension of drug release depend on the type of polymer, its viscosity grade, hydration and polymer proportion in the formulation (Williams et al., 2002; Salsa et al., 2003). The cellulose ether derivatives have been widely investigated in our laboratory too. The studies proved that formed hydrogel barriers of different cellulose ether matrix tablets differ in their thickness, viscoelastic properties, concentration profile, the amount of free and bound water molecules and polymer mesh size (Baumgartner et al., 2002a,b, 2005; Sepe et al., 2002). Obviously, these carrier properties influence drug release and correlate with their physicochemical properties.

So, physicochemical characterization and appropriate quality control of excipients are essential to ensure safety and performance of tablets, including efficacy, stability, release profiles and pharmaceutical technological properties. Meeting this objective highlights the need for detailed knowledge, based on new developments in pharmaceutical science and analytical techniques, for the characterization of polymer excipients. Inverse gas chromatography (IGC) is one such technique, which has not yet been utilized for investigation of cellulose ethers powders. The majority of physicochemical adsorption properties studied by IGC refer to the stationary phase and its interaction with known vapor probe. The main object of the investigation by IGC is the stationary phase of the system (in pharmacy most often powder sample), which physicochemical properties, such as enthalpy, entropy and free energy can be measured.

At infinite dilution, the elution peaks are symmetrical, with retention volumes independent on the vapor probe size, indicating that Henry's law region has been reached. When non-polar probes (alkanes) are used, only London interactions are operative between the vapor probe and the solid surface, and the dispersive part of the total surface energy can be determined. The polar character of the stationary phase is studied by the employment of probes that interact through specific forces (Schultz and Nardin, 1992).

It has been known for many years that acid–base interactions are important components of polar forces and play a significant role in adhesion of organic substances to inorganic substrates (Lipatov and Sergeeva, 1974; Sorensen, 1975). IGC has become a widely used method for determining the surface free energy of solids. These data are helpful in judging the technical performance of materials such as polymers and fibers (Schultz and Nardin, 1992; Mukhopadhyay and Schreiber, 1993).

The use of IGC is increasing rapidly in the pharmaceutical field, including its potential for studying batch to batch variability (Ticehurst et al., 1994) and the influence of mechanical treatment on the surface free energy of solid excipients (Feeley et al., 1988; York et al., 1988; Newell et al., 2001a), differences of surface free energy between two isomers (Grimsey et al., 1999), and the influence of humidity on surface free energy of powders (Newell et al., 2001b; Sunskersett et al., 2001). It is possible to use IGC for glass transition determination of powders at defined conditions (Surana et al., 2003; Buckton et al., 2004). An attempt of surface characterization of pharmaceutical polymers was also reported in the literature (Planinšek and Buckton, 2003). However, not much attention has been paid to correlating IGC measurements with the behaviour of powders like polymers or other powdered excipients in particular processes or dosage forms design.

The aim of our work was to investigate the surface properties of cellulose ethers by means of IGC, to formulate matrix tablets and to study release of the drugs. In addition, by correlating the specific component of the enthalpy of adsorption for the polymers with the parameters of drug release, we aimed to assess the appropriateness of IGC as a standard method for the surface characterization of newly developed polymer excipients.

2. Materials and methods

2.1. Materials

The cellulose derivatives used were hydroxyethyl cellulose (HEC, Natrosol 250-HHX, Aqualon, Hercules; $\bar{M}_w \cong 1{,}200{,}000$, molar substitution $\cong 2.5$), hydroxypropyl cellulose (HPC, Klucel 99-HXF, Aqualon, Hercules; $\bar{M}_w \cong 1{,}150{,}000$, molar substitution $\cong 3.7$), and hydroxypropylmethyl cellulose (HPMC, Premium Methocel K4M, Colorcon; $\bar{M}_w \cong 95{,}000$, methoxyl groups = 22.9% and hydroxypropoxyl groups = 9.2%). Pentoxifylline and vancomycin hydrochloride were used as model water-soluble drugs. Pentoxifylline (MM = 278.31, solubility in water at 37 °C 191 mg/ml) was supplied by Krka, d.d., Slovenia and vancomycin hydrochloride (MM = 1485.73, solubility in water at 37 °C more than 100 mg/ml) was a gift from Lek d.d., Slovenia. Probes used for the IGC measurements were non-polar alkanes: from hexane to decane (Fluka, Taufkirchen, Germany), and polar: tetrahydrofuran (THF), acetone (Acet), trichloromethane (TCM) and ethylacetate (EtAcet) (Sigma–Aldrich, Stainheim, Germany). Methane (Messer, Slovenia) was used as a non-adsorbing probe. Powder samples were diluted with Chromosorb W (Carlo Erba, Italy) in mass proportion 1:1.

2.2. Inverse gas chromatography

A commercial gas chromatograph (HP 5890A, Series II, Hewlett-Packard, Palo Alto, CA, USA) equipped with flame ionization detector (FID) and ChemStation software (version 03.34) was used. The injector was heated at 150 °C and FID

detector at 250 °C. Dried helium (Messer, Slovenia) was used as carrier gas with a flow-rate of 7 ml/min. The polymer powders were mixed homogeneously with the Chromosorb, that prevented pressure differences at the column inlet due to possible differences in sample packing, in the ratio 1:1 using mortar and pestle. The glass columns (0.2 m long and 3.0 mm internal diameter) were packed by tapping the powder for 10 min in a Tap density tester (VanKel, Cary, USA). Two injectors and detectors, that enabled measurements of two samples simultaneously, were heated at 150 and 250 °C, respectively. Prior to measurement the filled columns were conditioned overnight with helium at a constant flow of 7 ml/min at 60 °C. Samples were analyzed at 30, 40, 50 and 60 °C. The probe was injected automatically from a 10.0 μl Hamilton syringe using Agilient Technologies (USA) 7683 series autoinjector.

2.3. *Gravimetric water vapor sorption of polymeric powders*

For the quantitative analysis of the water sorption properties of particulate materials a dynamic vapor sorption method (DVS, Surface Measurement Systems Ltd., UK) was used. The method utilized a dual channel carrier gas system, which enabled any desired relative humidity (RH, %) between 0 and 98% to be rapidly established in the system. Gas of a known RH was flowing over a small material sample hanging on a loop attached to a microbalance, which is used to monitor the sample mass as a function of time. The instrument system was controlled via a computer interface.

2.4. *Preparation of matrix tablets*

The polymer and the active substance were mixed homogeneously in such a ratio that each tablet was composed of 75% (w/w) polymer and 25% (w/w) of active substance. Circular flat-faced tablets were prepared by direct compression (Erweka-Apparatebau, EKO, Korsch, Germany) to form tablets of hardness 100 ± 10 N (VanKel VK 200, USA; hardness tester; $n = 6$), with $m = 0.40 \pm 0.01$ g, $2r = 13$ mm.

2.5. *Swelling ability*

For the swelling experiments polymers without drug were compressed into tablets of the same size, shape and weight as for the drug release studies. Swelling ability was evaluated using the standard USP XXVI Apparatus II, paddle dissolution tester (VanKel 7000 Dissolution test station, USA). A stirring speed of 100 rpm was used to agitate the dissolution medium which was kept at 37 °C ± 0.5 throughout and consisted of 900 ml of purified water. Each hour ($t = 8$ h) the tablet mass was measured and the amount of absorbed water determined. The excess of water was gently removed with filter paper. The degree of swelling was calculated using Eq. (2):

$$\text{swelling degree} = \frac{m_t - m_0}{m_0} \tag{2}$$

m_0 is the mass of dry tablet (g) and m_t is the mass of hydrated tablet after the determined time of swelling (g).

2.6. *Drug release testing*

Drug release was studied using the standard USP XXVI Apparatus I, and a basket dissolution tester (VanKel 7000 Dissolution test station, USA) equipped with the automatically dissolution sampling system station (VanKel 8000, USA). Purified water, as the dissolution medium, was kept under the same conditions as for the swelling studies. Samples (10 ml) were withdrawn at defined time intervals and their absorbance measured spectrophotometrically (Hewlett-Packard, HP 8453, Germany) at $\lambda = 276$ nm for pentoxifylline and at $\lambda = 281$ nm for vancomycin hydrochloride. All experiments were performed on six samples.

2.7. *Statistics*

All results were expressed as mean values ± S.D. In order to assess the statistical significance between the data, an analysis of variance (ANOVA) was carried out using the software package SPSS. Significance was tested at the 0.05 level of probability.

3. Results and discussion

3.1. *Theoretical background of the IGC method*

Probes of known properties (Table 1) were injected into the column containing the solid sample. The retention times of these probes, measured at infinite dilution, allow the interactions between the organic molecules and the solid to be determined, assuming that there are no interactions between the probe molecules themselves. The net retention volume V_n was calculated from:

$$V_n = jF(t_r - t_0) \tag{3}$$

where t_r is the retention time of the probe, t_0 the zero retention reference time measured with a non-adsorbing probe such as methane and j is a correction factor taking into account the compression of the gas (Condor and Young, 1979) and given by the following expression:

$$j = \frac{3}{2}\frac{(P_{in}/P_{out})^2 - 1}{(P_{in}/P_{out})^3 - 1} \tag{4}$$

where P_{in} is the pressure at the inlet and P_{out} pressure at the outlet of the column. The free energy of adsorption ΔG_A of alkanes corresponds to dispersive interactions ΔG_A^d only and is given by:

$$\Delta G_A = \Delta G_A^d = -RT \ln V_n + C \tag{5}$$

where R is the ideal gas constant, T the absolute temperature and C a constant depending on the reference state of adsorption. According to the method of Schultz and Nardin (Schultz and Nardin, 1992) the dispersive component of the surface free energy of the solid phase (γ_s^d) can be determined by plotting

Table 1 – Values of $a\sqrt{\gamma_l^d}$ (Schultz and Lavielle, 1989) for the alkanes and polar molecules used as probes and DN and AN* numbers[a] (Santos et al., 2002)

Probe molecule	$a\sqrt{\gamma_l^d}$ (cm^2 (mJ cm^{-2})$^{0.5}$)	DN (kJ/mol)	AN* (kJ/mol)
Hexane	2.21E−16		
Heptane	2.57E−16		
Octane	2.91E−16		
Nonane	3.29E−16		
Decane	3.63E−16		
Tetrahydrofuran	2.13E−16	84.42	2.10
Ethylacetate	1.95E−16	71.82	6.30
Acetone	1.65E−16	71.40	10.50
Trichloromethane	2.24E−16	22.78	0.0

[a] DN is Gutmann's donor number and AN* is Gutmann's modified acceptor number.

$RT\ln V_n$ as a function of the quantity $a\sqrt{\gamma_l^d}$:

$$\Delta G_A = \Delta G_A^d = 2N_{AV}a\sqrt{\gamma_s^d\gamma_l^d} \quad (6)$$

where a is the area occupied by the probe molecule on the surface, N_{AV} is the Avogadro's number and γ_l^d is the dispersive part of the surface tension of the liquid probe (interactions between alkanes and the surface are purely dispersive). Values of $a\sqrt{\gamma_l^d}$ for used probe molecules are listed in Table 1.

The polar character of the stationary phase was studied by employing probes that also interact through specific forces. The "extra part" in the $RT\ln V_n$ value of a polar probe above the "apolar reference line" is attributed to a specific component of the free energy of adsorption, ΔG_A^{sp}, reflecting the polar part of the surface free energy. The specific component of the adsorption energy, calculated at four temperatures for every polar probe, allowed us to calculate the specific component of the enthalpy of adsorption ΔH_A^{sp}:

$$\Delta G_A^{sp} = \Delta H_A^{sp} + T\,\Delta S_A^{sp} \quad (7)$$

The enthalpy of specific interactions between examined surface and test solute results from the acid–base properties of both the surface of polymer and the probe molecule. It may be expressed as follows:

$$-\Delta H_A^{sp} = K_a DN + K_d AN^* \quad (8)$$

where K_a, K_d are parameters describing the ability of the examined surface to act as electron acceptor (acid number) and electron donor (base number), respectively. DN is Gutmann's donor number and AN* is Gutmann's modified acceptor number, corresponding to the polar probes (Table 1) (Gutmann, 1978; Fowkes, 1990). K_a and K_d parameters were calculated from Eq. (8) for the series of selected test probes.

3.2. *Dispersive component of the polymer surface free energy*

Dispersive component of the total surface free energy (γ_s^d) of cellulose ether polymers was first determined at four temperatures. The results show insignificant differences in the non-polar parameters of the polymers measured at the same temperature (Table 2). However, γ_s^d decreases significantly with temperature, since at higher temperatures the interactions are weaker, i.e. less energy is released on adsorption.

The polar interactions of polymers are assumed to be of greater importance for getting into contact with an aqueous solution, wetting at the surface and then penetrating into the dry matrix than the dispersive interactions. This was the reason for the detailed study of the polar character of the polymers.

3.3. *Polar characteristics of the polymer surfaces*

Retention volume of the basic tetrahydrofuran, acidic trichloromethane, amphyphilic acetone, and ethylacetate was determined at four temperatures (30, 40, 50 and 60 °C), with all three cellulose ether samples. The polar character of the sample was calculated using Eq. (7) and results are expressed as the specific component of the enthalpy of adsorption (ΔH_A^{sp}). In contrast to dispersive component of surface free energy, the specific enthalpies of adsorption for every polar probe differed significantly between polymers (Table 3). All values of ΔH_A^{sp} for polar probes are negative, showing exothermal interactions of polar probes adsorption on a polymer. If there was any polymer structural change (like interruption of hydrogen bonds, changes in polymer branching) during measurement, it is expected ΔH_A^{sp} would be positive. The highest specific enthalpy of adsorption, and hence the polarity, was observed for HEC, followed by HPMC

Table 2 – Values of the dispersive component of the total surface free energy (γ_s^d; mN/m) of cellulose ether polymers[a] as a function of temperature

Temperature (°C)	HEC	HPC	HPMC
30	26.0 ± 0.5	28.5 ± 0.1	33.8 ± 2.5
40	21.0 ± 0.1	25.2 ± 0.1	29.5 ± 2.5
50	18.0 ± 0.5	22.5 ± 1.0	25.0 ± 3.0
60	13.3 ± 0	21.0 ± 0.8	22.1 ± 2.1

[a] HEC: hydroxyethyl; HPC: hydroxypropyl; HPMC: hydroxypropylmethyl cellulose.

Table 3 – The average values of specific component of the enthalpy of the adsorption (ΔH_A^{sp}; kJ/mol) of polar probes to cellulose ether[a]

Probe	HEC	HPMC	HPC
Acetone	−49 ± 4	−30 ± 2	−15 ± 2
Tetrahydrofuran	−43 ± 4	−22 ± 2	−18 ± 2
Ethylacetate	−51 ± 4	−41 ± 3	−16 ± 1
Trichloromethane	−25 ± 2	−9 ± 1	−12 ± 1

[a] HEC: hydroxyethyl; HPC: hydroxypropyl; HPMC: hydroxypropylmethyl cellulose.

and HPC. Highest polarity of HEC surface was confirmed also with both acid and base numbers followed by HPMC and HPC (Table 4). The polar character of investigated polymers depends on the nature of the substituent present and the degree of substitution. The hydrophilicity of cellulose ethers increases with a decrease in an alkyl chain length. Thus, it is not surprising that HEC exhibited a considerable higher polarity as compared to HPMC and HPC.

3.4. *DVS on bulky polymers and swelling of polymer matrices*

The results of water vapor sorption on bulky polymers determined by the DVS method are presented on Fig. 1. It is clearly seen that water adsorbs onto the polymers under the same conditions differently, but the adsorption isotherms of HEC, HPMC and HPC have the same shape and tendency. They can be described as the fifth adsorption isotherm (Stahl, 1980), which means that the first layer of adsorbed water molecules enables easier adsorption of the other water molecules. This type of isotherm is characteristic for hydrophilic polymers. It was found out, that the most hygroscopic polymer is HEC, followed by HPMC and HPC. These results are in agreement with IGC measurements.

The ability of cellulose ether matrix tablets to absorb enough water is an important factor in the formation of the gel layer, which controls the drug release. From analysis of the swelling data, it was possible to conclude that the polymers under investigation accept water at different rates. The highest degree of swelling reached at the shortest time was observed for HEC, followed by HPMC and HPC (Fig. 2). The uptake of water into the tablets is highly influenced by the polymer chemical properties, since the procedure of tablet preparation was the same for all polymers, so that any influence of the pharmaceutical–technological properties of the matrix tablets was avoided.

Table 4 – K_a and K_d values[a] of investigated polymers[b]

	HEC	HPMC	HPC
K_a	0.474	0.233	0.204
K_d	1.658	1.652	0.277

[a] K_a describes the ability of investigated polymer surface to act as electron acceptor (acid number) and K_d as electron donor (base number).
[b] HEC: hydroxyethyl; HPC: hydroxypropyl; HPMC: hydroxypropylmethyl cellulose.

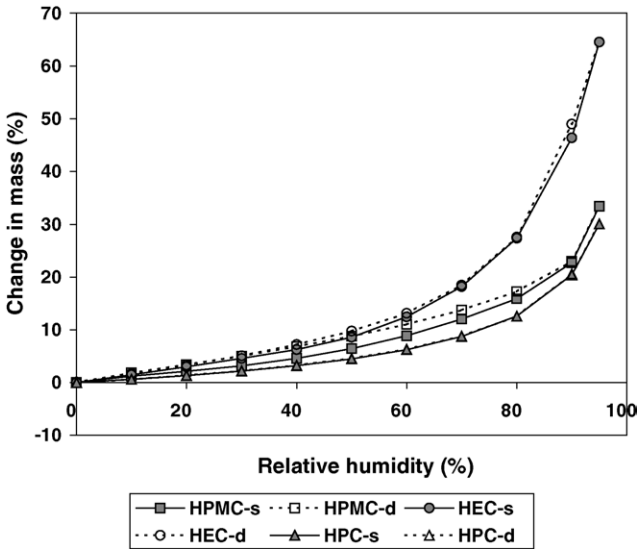

Fig. 1 – The change in mass of bulk polymers HEC, HPMC and HPC in equilibrium under different relative humidity atmospheres employing the DVS method (s: sorption; d: desorption).

The HEC matrices, in particular, displayed a quite different behaviour as compared to the other polymers tested: the presence of small substituent groups in its structure is responsible for interaction with water and faster disentanglement threshold of polymer chains and form network for water uptake. For the HPC-containing matrices the lowest hydration was observed. Roy and Rohera obtained comparative results of swelling for HEC and HPC matrices (Roy and Rohera, 2002). Even more, they concluded that the drug release rate from HEC matrices was higher compared to the release rate from HPC matrices due to relatively higher hydrophilicity of HEC. It is noteworthy that the hydrophilicity of polymers was not evaluated.

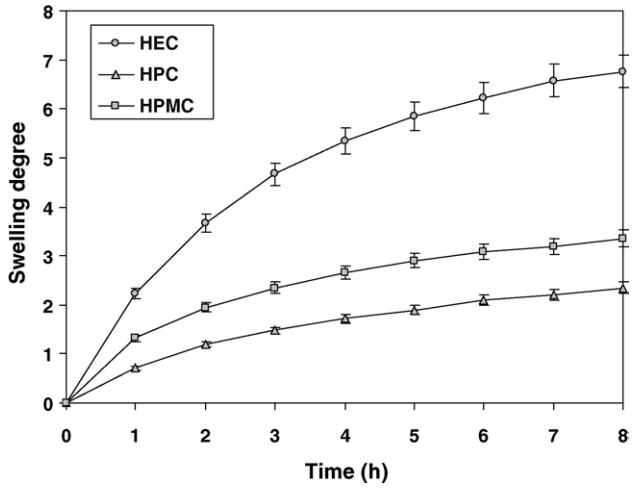

Fig. 2 – Swelling degree of cellulose ether matrix tablets depending on time. Each point is the average of six determinations.

HPMC evidenced a medium specific component of the enthalpy of the adsorption as well as the dynamic sorption of water on bulky polymer and the swelling degree of its matrices. The reason is again the nature of the substituent present in the molecule, where methyl groups enable easier interactions of HPMC with water in comparison with HPC, where interactions between polymers are more pronounced.

However, the specific component of enthalpy of adsorption (Table 3) correlates well with the water adsorption on bulky polymers (Fig. 1) and with the swelling process of polymer matrices (Fig. 2). Here, it must be pointed out, that all IGC parameters were determined for dry cellulose ethers as the experiments were carried out in dry helium. It is clear that during and after vapor adsorption the surface activity of the examined material will change. It means that initial γ_s^d, K_a and K_d are no longer valid. However, the measurements at zero humidity show the potential of the material's surface for interaction with water, for example. Highest K_a and K_d values of HEC in comparison to other two investigated polymers predict stronger interactions with water (higher hygroscopy and water uptake) that result in higher relaxation of polymer chains. As a consequence high water mobility between these chains should enable faster diffusion of a drug from the formed gel.

3.5. *Drug release study*

The aim was to observe whether the surface free energy parameters of the polymers influence the release kinetics and release mechanism of drug molecules with different size. Two freely soluble molecules of different molar volumes were chosen for drug release studies. The molar volume of pentoxifylline was $211.2 \pm 7.0\,cm^3$/mol and its solubility 191 mg/ml at 37 °C; the molar volume of vancomycin hydrochloride was $874.6 \pm 5.0\,cm^3$/mol and its solubility > 100 mg/ml. Molar volumes were calculated using program ChemScetch (ScienceServe GmbH, Germany, version 7).

Release of the drug took place over more than 8 h (Fig. 3A and B). Pentoxifylline was almost completely released in 24 h, except from HPC, where 90% of the drug was released. The release of vancomycin was slower, as expected from the size of the drug molecule. Release from HEC was complete in 24 h, from HPMC 87%, and from HPC 78%.

The influence of differently substituted polymers on the release of pentoxifylline is more evident after the third hour and, in the case of vancomycin, after the fifth hour. However, the release rate of pentoxifylline and vancomycin was highest from HEC matrices, followed by HPMC and HPC (Fig. 3). These results are in accordance with the observed degree of swelling and with some of our previous results on calculated polymer mesh size (Baumgartner et al., 2002a) and polymer profile through the swollen tablet determined by magnetic resonance imaging (Sepe et al., 2002; Baumgartner et al., 2005).

3.6. *Characterization of the mechanism of drug release*

The release mechanism of each drug in all the cellulose ether tablets was initially characterized in terms of the diffusional exponent, n, calculated from Eq. (1). All the exponent values lie between 0.509 and 0.775 (Table 5). Given the geometry of our tablets, these n values signify a non-Fickian or anomalous mechanism of drug release.

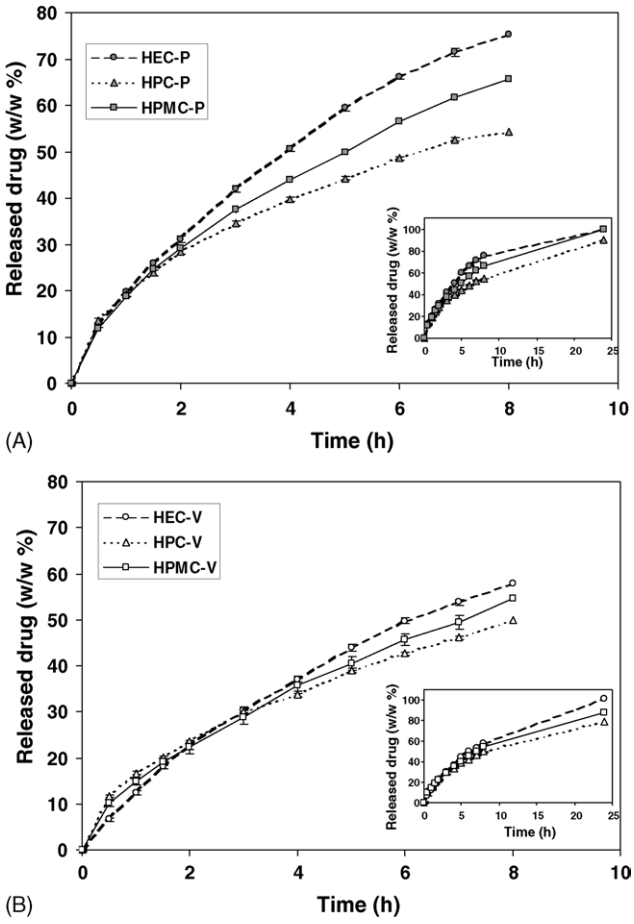

Fig. 3 – Release profiles of pentoxifylline (P) and vancomycin hydrochloride (V) from tablets based on different cellulose ether polymers. Standard deviation <2%.

In the anomalous processes of drug release, Fickian diffusion through the hydrated outer layers of the matrix and polymer chain relaxation/erosion are both involved as reported many authors (Colombo et al., 2000; Lowman and Peppas, 2000; Dürig and Fassihi, 2002; Ferrero et al., 2003). The contribution of these two mechanisms to the overall release are considered to be additive. A well-known empirical model that describes

Table 5 – Diffusional exponent n (Eq. (1)), diffusional k_1 and relaxational k_2 kinetic constants (Eq. (9)), and Pearson's coefficient (R^2) for different cellulose ether tablets with incorporated pentoxifylline (P) and vancomycin (V)

	n	R^2	k_1 (%h$^{-0.45}$)	k_2 (%h$^{-0.90}$)	R^2
HEC-P	0.675	0.9996	11.213	8.575	0.9997
HPMC-P	0.619	0.9991	14.622	4.709	0.9985
HPC-P	0.509	0.9989	18.798	1.207	0.9975
HEC-V	0.775	0.9945	7.771	6.194	0.9932
HPMC-V	0.613	0.9988	11.026	4.108	0.9990
HPC-V	0.525	0.9992	14.844	1.863	0.9991

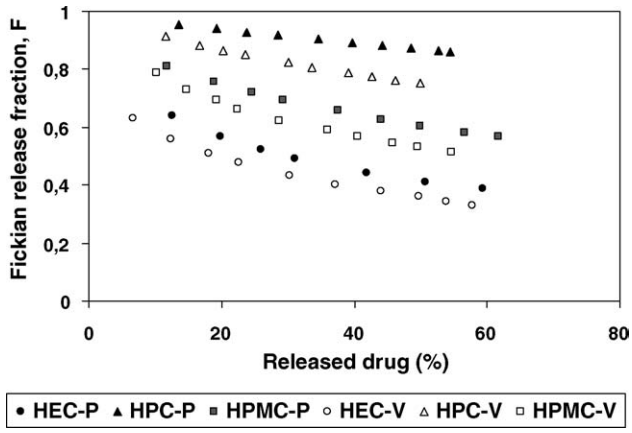

Fig. 4 – Fickian release fraction F (Eq. (10)) as a function of released pentoxifylline (P) and vancomycin (V) from different cellulose ether tablets. Standard deviation < 2%.

these phenomena is that of Peppas and Sahlin (Eq. (9)) (Peppas and Sahlin, 1989):

$$\frac{M_t}{M_\infty} = k_1 \cdot t^m + k_2 \cdot t^{2m} \tag{9}$$

where M_t/M_∞ represents the drug fraction released in time t ($\leq$60%), k_1 and k_2 the kinetic constants associated with diffusional and relaxational release, respectively, and m is the purely Fickian diffusion exponent. For the geometry of our tablets m of 0.45 was appropriate. To calculate the percentage of drug release due to the Fickian mechanism the following equation was introduced (Peppas and Sahlin, 1989):

$$F = \frac{1}{1 + (k_2/k_1) \cdot t^m} \tag{10}$$

F is the Fickian release fraction is the fraction of the drug released due to the Fickian mechanism. The ratio of relaxation to the Fickian contributions can then be expressed as

$$\frac{R}{F} = \frac{k_2}{k_1} \cdot t^m \tag{11}$$

The results of fitting to equation (9) are given in Table 5. From these parameters the contribution of the Fickian diffusion to the overall release (Eq. (10)) and the ratio between relaxation and diffusion (Eq. (11)) were calculated. The results of fitting are presented in Figs. 4 and 5.

The Fickian contribution to the overall release process is observed to decrease with increasing amount of released drug for each of the polymers investigated (Fig. 4). Thus, the relaxation of the polymer chains becomes more pronounced (Fig. 5). This observation was expected, since water is taken up simultaneously with drug release, and this water enables polymer chain relaxation. However, the process of Fickian diffusion is the most important, especially from HPC and HPMC matrices, since the diffusional rate constant k_1 is much larger than the relaxational constant, k_2 (Table 5). For HEC, the two constants have similar values (Table 5).

Comparing the influence of the size of the drug molecule on the release mechanism, the release of smaller pentoxifylline molecule is seen to be more diffusion controlled than the release of vancomycin. Smaller molecules diffuse more easily from these matrices and do not need time for the polymer to relax. On the other hand, vancomycin is larger and the mesh size through which the molecules diffuse should be larger also. Therefore, more time is needed for the polymer to relax and the mesh size to become large enough for vancomycin to be released. The influence of relaxation is seen in Fig. 5, where the curves for vancomycin are above those for pentoxifylline for all the polymers.

HEC polymer relaxation has a larger influence on the release of both drug molecules. This can be the consequence of favorable interactions of the HEC chains with water and therefore relatively easy polymer relaxation and erosion. This relaxation facilitates the release of both drugs, irrespective of molecular size—both HEC curves are substantially above the curves for HPC and HPMC (Fig. 5). In contrast, drug release from HPC is the least relaxationally controlled and HPMC is in-between.

3.7. *Correlation of acid–base numbers of the polymers with the relaxational k_2 kinetic constant*

In the previous section it was seen that there are differences in drug release mechanism between the cellulose ether polymers. Release from HPC and HPMC is mostly diffusion controlled, while relaxation is also involved to a certain extent in the release process from HEC. To test the statement that the reason for different drug release mechanisms is to be found in the interactions between water and polymer, we correlated the relaxational kinetic constant k_2 with the IGC parameters, especially the specific component of the enthalpy of adsorption for tested polar probes and with the sum of acid (K_a) and base (K_d) numbers, which also represent the polarity of the polymers.

The specific component of the enthalpy of adsorption was highly negative for HEC, followed by HPMC and HPC (Table 3). Even more, acid–base numbers calculated from specific interactions show the highest base number for HEC, followed by

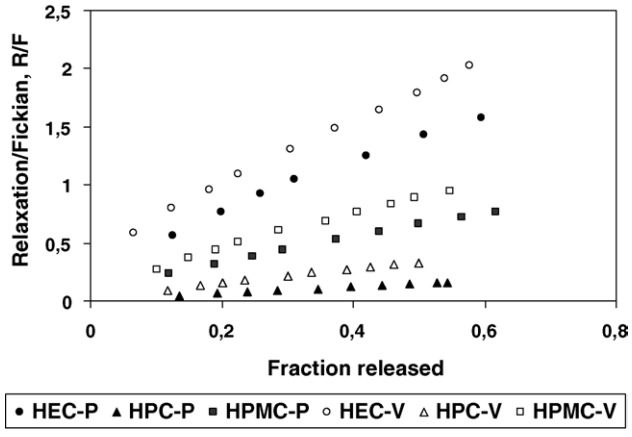

Fig. 5 – Ratio between relaxational (R) and diffusional (F) contributions to release of pentoxifylline (P) and vancomycin (V) from different cellulose ether tablets. Standard deviation < 2%.

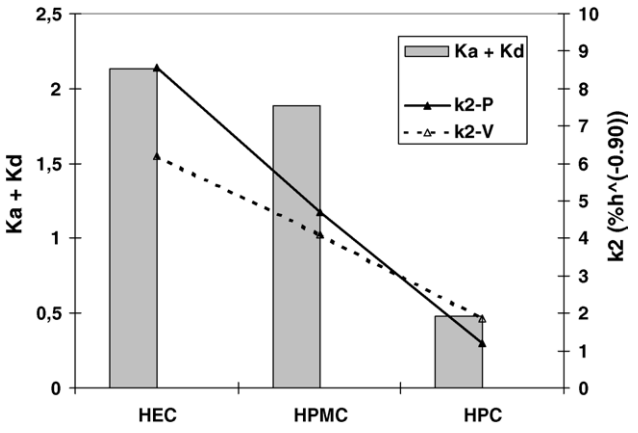

Fig. 6 – Correlations between the sum of acid (K_a) and base (K_d) numbers of cellulose ether polymers and the relaxational kinetic constants k_2 for release of pentoxifylline and vancomycin from those polymer tablets.

HPMC and HPC. The same trend was observed for acid numbers, but those were substantially lower (Table 4). From these results it can be predicted that hydrophilic basic sites of the polymers are responsible for the interactions with the aqueous medium and the interactions of water with HEC will be stronger than with HPMC and HPC. This prediction was verified by the results of the drug release studies, where the relaxational parameter k_2 was the highest for HEC in the case of pentoxifylline and vancomycin release (Fig. 6). The influence of relaxation and/or erosion of polymer chains on the overall drug release mechanism is more pronounced if water has no difficulties to enter the matrix and relax the chains, since energy is released in the exothermal process. The smaller k_2 shows that relaxation makes a minor contribution to the release of drugs from HPC and HPMC, which correlates well with the lower specific component of the enthalpy of adsorption of both polymers and with lower sum of K_a and K_d (Fig. 6).

4. Conclusion

The surface properties of cellulose ethers HEC, HPMC and HPC determined with IGC show that the dispersive components of surface free energy are not significantly different. Polar parameters, expressed as specific component of the enthalpy of adsorption (ΔH_A^{sp}) show large differences between the polymers and demonstrate their polarity in the order HEC > HPMC > HPC, or regarding the acid–base numbers, HEC showed the highest polarity, followed by HPMC and HPC. Polarity of polymers correlates well with water adsorption on bulky polymers and with the swelling degree of polymer matrices. The release rate of pentoxifylline and vancomycin from the polymer matrices followed the same order as the polarity of polymers. The molar volume of the water-soluble drug influences its release kinetics, shown by the release of the larger vancomycin being slower than the release of smaller pentoxifylline. The analysis of differences in the release parameters show that the release is governed mainly by diffusion from HPC and less so from HPMC, while from HEC the relaxation of polymer chains is important too. The higher polarity of HEC accounts for the easier interactions with water, which result in faster polymer swelling, easier chain relaxation and faster release of drugs from the matrix structure than in the case of HPMC and HPC, where polarities are lower. These results lead to the conclusion that, for the characterization of polymers as excipients for controlled drug release, IGC, in combination with other analytical methods (swelling and erosion studies, MRI, DVS), is appropriate for predicting polymer behaviour in water and for explaining small differences between differently substituted polymers.

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