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Research paper

Drug release from diffusion pellets coated with the aqueous ethyl cellulose dispersion aquacoat® ECD-30 and 20% Dibutyl Sebacate as plasticizer: partition mechanism and pore diffusion

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Abstract

The release of the hydrophilic etofylline and the lipophilic propyphenazone (octanol/water partition coefficient PC = 0.35 and 119, respectively) from diffusion pellets coated with the aqueous ethyl cellulose dispersion Aquacoat® ECD-30 and 20% dibutyl sebacate (DBS) as plasticizer is investigated as a function of pH. The relatively slow release is not constant, due to the broad distribution of different release rates within the pellet population and the non-linearity of the release of each diffusion pellet itself. The release proceeds according to a partition mechanism at a pH < 6. The partition mechanism is not influenced by the osmotic pressure difference between the release medium and the saturated solution within the diffusion pellets. The diffusion coefficients of different drugs in the plasticized coating are in the range 1 to 5×10^{-8} cm^2/s. At a of pH > 6 an additional hydrophilic pathway without partition exists if the diffusion pellets did not have any contact with an acidic medium. This is due to the strongly increased water uptake of more than 20% by the coatings as a consequence of the dissociation of carboxyl groups in the ethyl cellulose.

Keywords: Hydrophylic pathway; Interdiffusion; Osmotic effects; Partition; pH-dependence; Release mechanism

1. Introduction

The aqueous ethyl cellulose dispersion Aquacoat® ECD-30 (with ethyl cellulose about 26.3%, cetylalcohol 2.4%, sodium lauryl sulfate 1.3%, dimethyl polysiloxane as anti-foaming agent in small quantities, particle size 0.1–0.3 μm) is often used as a film forming agent for the production of diffusion pellets (coated pellets, microcapsules). It has been shown that the recommended addition of 10–20% of a plasticizer lowers the minimum film formation temperature (MFT) of about 81°C to a more appropriate range of 20 to 50°C. However, lipophilic plasticizers of low water solubility such as dibutyl sebacate (DBS) need 5–8 h stirring or standing time after the addition to any aqueous dispersion to enter the polymer particles completely [1,2]. Only when this uptake is completed, can the true MFT be measured, the respective films do not show droplets of the plasticizer, the coatings of diffusion pellets are more permeable, and its production has better reproducibility [1,3]. Furthermore, it has been recognized that reaching the MFT during the coating process is not sufficient. To obtain optimally filmed diffusion pellets it is necessary to exceed the MFT by nearly 10°C [3]. Curing of the diffusion pellets at elevated temperatures, eventually together with higher humidity, is often recommended to reach a stable state of the coating [3–7]. The addition of a plasticizer to the polymer enables the coating to take up high percentages of water, making it more permeable to drugs. Lipophilic plasticizers like DBS remain in the film during the release process, more hydrophilic ones like diethyl phthalate are leached out. In both cases the watered films are of a milky opaque appearance, thus the water is not homogeneously incorporated [1].

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The release of drugs like guaiphenesin and theophylline seems to proceed by molecular flow via bulk-like water within the coating (hydrophilic pathway) and by a partition step (lipophilic pathway) [3,8,9]. The primary goal of this study is to clarify which pathway is most important for the drug release from pellets coated with Aquacoat® ECD-30, plasticized with 20% DBS. Two different drugs, a hydrophilic and a lipophilic, were used as models: etofylline and propyphenazone. In addition, insight should be gained into the influence of the swelling of the coating and the osmotic pressure on the release.

2. Experimental

2.1. Materials

2.1.1. Etofylline pellets

Etofylline, Knoll AG, D-Ludwigshafen; method of manufacturing: rotating fluidized-bed process, binder solution: 1.5% potato starch [10], particle size 800–1000 μm, drug content 98.9%.

2.1.2. Propyphenazone pellets

Propyphenazone, Hoechst AG, D-Frankfurt; method of manufacturing: Marumarizer process [11], particle size 800–1000 μm; drug content: 87.0%, microcrystalline cellulose Avicel® PH 101, Lehmann and Voss, D-Hamburg: 11.7%, povidone, Kollidon K 90, BASF, D-Ludwigshafen: 1.3%

2.2. Methods

2.2.1. Coating of the pellets

A mass of 186 g of undiluted Aquacoat® ECD-30 is mixed with 14 g of dibutyl sebacate (DBS, Rilanit®, Henkel AG, D-Düsseldorf) while stirring (30 min) and is then left to stand for at least 5 h. The MFT is then 29 ± 1°C [1], determined with the Thermostair BL-MFT'D' gradient test device (Coesfeld GmbH, D-Dortmund). The pellets are coated in the fluidized bed device, Strea I, Aeromatic, CH-Muttenz with a plastic spray tower and a two-way nozzle [3,12]: fill charge, 260 g; air flow, 186–190 m^3/h; bed temperature, 40°C; spraying pressure, 0.06 MPa; spraying rate, 1 g/min (1st–10th min) and 2 g/min (10th min onwards); spraying time, up to 3 h; amount of dispersion, 150 g; amount of film coating, 20%; resulting coating thickness h_d (n = 10 pellets × 5 microscopic measurements), 27 ± 9 (etofylline) and 26 ± 7 μm (propyphenazone); indicating almost quantitative deposition of the coating material [12] and thus ensuring complete and defectless coating.

2.2.2. Curing of the coated pellets

The diffusion pellets are stored on a tray in a ventilated drier for 1 h at 68°C to complete the film forming process [3,12].

2.2.3. Release of drug

The paddle apparatus Ph. Eur. 1997 is used with 1000 ml of different media with an ionic strength of μ = 0.1 at a temperature of 37 ± 1°C; release media: 0.1 N-HCl, formate buffer pH 4.4, phosphate buffer 5.9 and 7.5, borate buffer pH 9.0. The stirring speed of 170 min^{-1} prevents the diffusion pellets from sticking to each other [3]. The UV absorption of the solution is measured after passing a reagent filter (Braun-Lübbe, D-Norderstedt) in a continuous flow cell every 6 min at the isosbestic points: etofylline 267 nm ($A^{1\%}_{1\ cm}$ = 381.0), propyphenazone 246 nm ($A^{1\%}_{1\ cm}$ = 396.2).

2.2.4. Evaluation of the release parameters

The mean values of the quantities released from 150 mg counted diffusion pellets at time t are determined in parallel or repeated tests and a linear regression is performed between t = 0.5 and 4.8 h (n = 6 at least). The permeability coefficients P are calculated from the respective zero order release rate constants k^0_r [3], taking the surface area of the 150 mg diffusion pellets (A) into account, as well as the film thickness of the swollen coatings h_s and the drug solubility c_s

$$P = k^0_r \times h_s / (A \times c_s) \quad (1)$$

h_s is calculated with the water contents of the swollen coatings V_s after 5 h swelling and the coating thickness of the dry diffusion pellets h_d

$$h_s = 100 \times h_d / (100 - V_s) \quad (2)$$

A is calculated according to Eq. (3) [13]

$$A = n \times 4\pi r_p \times r_{DPs} \quad (3)$$

where n = number of diffusion pellets in 150 mg, r_p = mean radius of the uncoated pellets; r_{DPs} = mean radius of the coated diffusion pellets after swelling of the coating. r_{DPs} is calculated according to Eq. (4)

$$r_{DPs} = \sqrt[3]{\frac{3m_{DP}}{4\pi \times n \times \rho}} + (h_s - h_d) \quad (4)$$

m_{DP} is the mass of the investigated diffusion pellets (150 mg); ρ, the apparent density of the diffusion pellets, is determined by the volume titration method (13); r = 1.12 and 0.97 for etofylline and propyphenazone diffusion pellets, respectively.

2.2.5. Drug release from only one particular diffusion pellet

Four etofylline diffusion pellets of different size are selected and weighed precisely. The release of each is measured within a 1 cm thermostated quartz cell with 3 ml of release medium pH = 9.0 at 37 ± 1°C. Mixing is performed by the movement of the automatic change of the cells every 60 s.

2.2.6. Partition coefficients

Ten to fifty milliliters of drug solutions up to a concentration of 0.18 g/100 ml in water or formate buffer are shaken for 24 h at 37 ± 1°C with 1–20 ml of *n*-octanol or DBS, 0.5–5.0 g ethyl cellulose particles (Ethocel® ST 10 Premium, Dow Chemicals, USA-Midland) and ethyl cellulose/DBS 20% films, respectively. The remaining concentration in the aqueous phase is determined spectrophotometrically after filtration. In the case of ethyl cellulose and ethyl cellulose/DBS films blanks are measured and the absorption of the drug solutions is corrected. The partition coefficients are calculated according to

$$PC = \frac{(\text{drug amount in the lipophilic phase} \times \text{volume of the aqueous phase})}{(\text{drug amount in the aqueous phase} \times \text{volume of the lipophilic phase})}.$$

The volumes of ethyl cellulose particles and the ethyl cellulose/DBS films are determined by use of the respective weights divided by the densities. In the case of ethyl cellulose/DBS films, the volumes of the two components are assumed to behave additively. A distinct dependence of the experimental results on the amount or concentration of the drug could not be detected.

2.2.7. Swelling of Aquacoat® ECD-30 films with 20% DBS

After 5 h standing time the plasticized dispersion is poured out onto glass plates to form wet films approximately 800 mm thick. The plates are dried at 68°C for over 2 h to a constant weight, the resulting film thickness is about 300 μm, measured with a micrometer calliper. Pieces of 2 × 4 cm, dried over silica gel and weighed precisely (m_o) are placed in the swelling medium at 37 ± 1°C and carefully shaken. The films are taken out after 5 h, any surface water is removed and the swollen films are weighed precisely (m_s) and then dried until the weight is constant (m_e). The extracted components (EXC, %) can be calculated using the formula: $EXC = 100\ (m_o - m_e)/m_o$. The water content of the films V_s (% v/v) is calculated under consideration of the densities of the polymer (1.13 g/ml), the plasticizer DBS (0.994 g/ml) and water, assuming that DBS is not extracted under these conditions [1,12].

3. Results and discussion

3.1. General release behavior

The reproducibility of the drug release within one batch and between batches is investigated with etofylline diffusion pellets at pH 4.4. The permeability coefficient for six determinations of one batch is $P = 29.9 \pm 2.5 \times 10^{-10}$ cm^2/s. This batch and a second one give $P = 27.6$ and 26.8×10^{-10} cm^2/s, both after a storage time of nearly 1 year. Thus, the reproducibility is rather high. However, a slight decrease of the release rate takes place with increasing storage time as already observed with guaiphenesin diffusion pellets [1,8]. This might be due to the squeezing out of a fraction of the emulsifying agents cetyl alcohol and sodium lauryl sulfate, detected during film aging with scanning electron microscopy and analytical procedures [1].

The drug release is generally very slow. During the first 5 h only 10–36% of etofylline and propyphenazone, respectively, are released with a constant rate in acidic media. After that time the release rates slow down gradually, leading to a 35–90% release after 24 h in the case of etofylline at the different pH-values. This non-linearity may be explained as follows. Fig. 1 shows the complete release curves of four different etofylline diffusion pellets of a weight between 0.338 and 0.547 mg at pH 9.0. The diffusion pellet with the lowest weight releases the drug the fastest and vice versa. A lag-time was hard to detect. All four release curves are not linear. Non-linearity is to be expected only when the percentage of drug released decreases the drug concentration in the coated pellets below saturation (release of about 90–99%, respectively).

The fast release of the small diffusion pellet is first of all a consequence of the thinner coatings of small pellets in comparison to larger pellets [14]. In addition, the area/volume ratio is higher in the case of the small pellets. Furthermore, the summation curve of a broad distribution of different release rates from a diffusion pellet population gives a curvilinear release [3]. This is even more emphasized if every diffusion pellet itself shows a non-linear release. The reason for the gradually decreasing release rate of the four different etofylline diffusion pellets might be a further improvement of the film formation (further gradual coalescence) after contact with water, water acting as plasticizer [8,9] and during the slow release of sodium lauryl sulfate from the films [15].

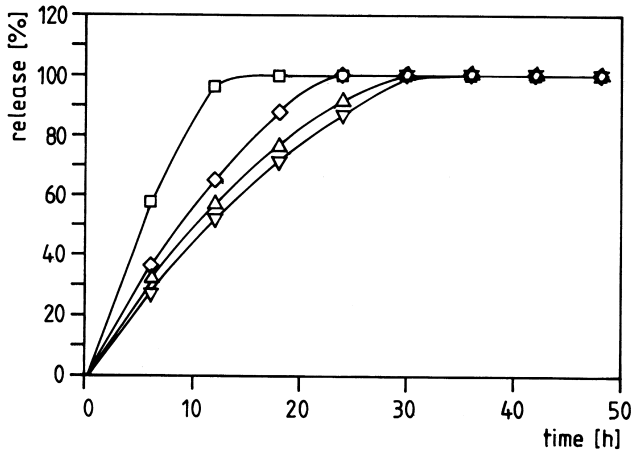

Fig. 1. Release of etofylline from four different diffusion pellets, coated with Aquacoat® ECD-30 and 20% DBS after an 8 h standing time of the dispersion; borate buffer pH = 9.0, μ = 0.1; 37 ± 1°C; measurements every 6 min, marking every 6 h. The mass of the diffusion pellets: □, 0.338 mg; ◇, 0.379 mg; Δ, 0.491 mg; ∇, 0.547 mg.

Table 1

Standardized zero order release rate constants k_r^{0*} and permeability coefficients P of etofylline diffusion pellets, solubilities c_s of the drug and water contents of swollen free films V_s as function of the pH. Temperature = 37 ± 1°C, n is related to k_r^{0*} and P, respectively

pH	k_r^{0*} (mg/h (μm/cm^{-2}))	P (10^{-10}cm^2/s)	c_s^a (g (100 ml)$^{-1}$)	V_s (% (v/v))	n
1.2	10.5 ± 1.2	27.9 ± 3.2	10.51[b]	18.1	27
4.4	10.3 ± 1.4	30.4 ± 3.9	9.38[c]	19.7	85
5.9	11.7 ± 1.6	34.5 ± 4.7	9.38	15.6	22
7.5	17.7 ± 1.5	52.5 ± 4.5	9.38 [c]	24.9	15
9.0	43.1 ± 1.2	127.7 ± 3.5	9.38[c]	30.3	9

[a]pK_a = 0.28 at 37°C [17].
[b]Calculated according to the pK_a.
[c]Taken from pH = 5.9.

3.2. Release of etofylline at different pH-values

Table 1 shows the pH-dependent standardized zero order release constants k_r^{0*} ($k_r^{0*} = k_r^0 \times h_s/A$), related to an area of 1 cm^2 and a coating thickness of 1 mm for different release media. Furthermore, P-values, solubilities c_s of etofylline and water content V_s of swollen free films are given. As already observed for guaiphenesin [3], k_r^{0*} and P are rather independent of pH at pH 1.2–5.9 in accordance with the only slightly changing solubility. Increasing the pH from 5.9 over 7.2–9.0, k_r^{0*} and P increase up to the four-fold, with about a two-fold increase in the water content of the film and the solubility staying constant.

The increased permeability and higher water uptake of the coating at pH-values above 6 are a consequence of dissociating carboxyl groups in the ethyl cellulose [3]. The proposed influence of sodium lauryl sulfate with a pK_a of 1.2 on the pH-dependence of the release process [6] seems without importance in this study. Fig. 2 shows the water uptake as a function of pH after 5 h being nearly the endpoint of the water absorption process. There is an inflection point at pH = 7.6. This is in very good agreement with the change in the permeability of guaiphenesin diffusion pellets as a function of pH with an inflection point at pH 7.5 [3]. The pK_a of the carboxylic groups in the ethyl cellulose of the Aquacoat® ECD-30 dispersion with 20% DBS is 6.2 [1]. The difference between these values can be explained by the change in the degree of dissociation not being transferred in proportion to the increasing water uptake of the films and the increasing permeability coefficient of the coatings, respectively. The highest permeability measured at the highest pH with the highest observed water content in the film gives a hint to a release via aqueous regions in the coating. In contrast, the release rate at pH-values < 6 seems to be rather independent of the water content in the coating. This is further demonstrated with release experiments in sodium chloride solutions of different concentration (0–1 M): The water content in the film is reduced to less than half in the 1 M sodium chloride solution but the permeability coefficient decreases only less than 20%. This behavior could be an indication for a lipophilic release pathway at water contents of the coating <20% (pH < 6) and an additional hydrophilic pathway at water contents >20%.

3.3. Release of propyphenazone at different pH-values

Table 2 gives the standardized k_r^{0*}- and P-values for the release of propyphenazone together with the solubilities c_s of the drug and water contents V_s of the films. The k_r^{0*}-values are nearly three times higher than those for etofylline in the acidic region and the P-values more than 80 times. This could not have been expected if the diffusion had proceeded via hydrophilic regions or pores. In this case propyphenazone with the low solubility in water of 0.291 g/100 ml should be slowly released in comparison to a highly soluble drug such as etofylline with a solubility of 9.38 g/100 ml.

There does not seem to be any pH-dependence of the release rate. This is also true for the permeability coefficient P, if it is calculated at pH 1.2 on the basis of the solubility of the undissociated drug. With the higher overall solubility (undissociated and dissociated drug) P would drop down unreasonably to one third at pH 1.2. This indicates that only undissociated, more lipophilic drug molecules are able to cross the coating. Therefore, the more lipophilic propyphenazone exhibits higher permeability coefficients than the hydrophilic etofylline. At pH > 6 the swelling increases (Table 2, Fig. 2), opening up the hydrophilic pathway. However, the poor solubility of undissociated propyphenazone of 0.291 g/100 ml cannot improve the release rate significantly.

3.4. Release of sucrose and guaiphenesin, influence of osmotic pressure

The behavior of the Aquacoat® ECD-30 coating with

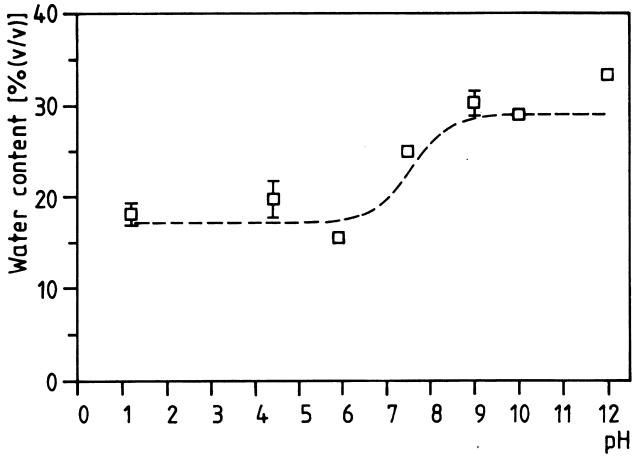

Fig. 2. Water content V_s of Aquacoat® ECD-30 films with 20% DBS after 5 h swelling as a function of the pH of the swelling medium; $x \pm s$, n = 4–12; 37 ± 1°C.

Table 2

Standardized zero order release rate constants k_r^{0*} and permeability coefficients P of propyphenazone diffusion pellets, solubilities c_s of the drug and water contents of swollen free films V_s as function of the pH. Temperature = 37 ± 1°C, n is related to k_r^{0*} and P, respectively

pH	k_r^{0*} (mg/h (μm/cm^{-2}))	P (10^{-10} cm^2/s)	c_s^a (g (100 ml)$^{-1}$)	V_s (% (v/v))	n
1.2	28.6 ± 1.9	2730 ± 180[b]	0.897	18.1	10
4.4	27.3 ± 1.4	2610 ± 130	0.291[c]	19.7	10
5.9	25.2 ± 1.2	2410 ± 110	0.291	15.6	10
7.5	27.8 ± 2.0	2660 ± 170	0.291[c]	24.9	10
9.0	27.4 ± 1.4	2620 ± 140	0.291[c]	30.3	10

[a]pK_a = 1.27 at 37°C [15].
[b]Calculated with the solubility of the undissociated drug.
[c]Taken from pH = 5.9.

20% DBS as a heterogeneous lipophilic partition membrane at pH < 6 and as a partition membrane with an additional hydrophilic pathway at pH > 6 is further substantiated by release experiments with coated sucrose pellets (2.5 g sucrose diffusion pellets in 25 ml 0.1 N-HCl, formate and borate buffer at 37 ± 1°C; careful shaking of the glasses; gravimetrical determination of the released amounts). At pH 1.1 and 4.4 there is only 1.5% release after 5 h due to the hydrophilic character and the low partition coefficient of sucrose. However, 90% is released at pH 9.0 in the same time period, because the hydrophilic pathway is now open.

If the release mechanism at pH < 6 is based on the partition of the drug between the coating and the saturated solution in the core of the diffusion pellet, P-values of different drugs should increase with increasing lipophilicity. Table 3 shows the mean P-values of etofylline and propyphenazone of this study together with the P-value of guaiphenesin of a similar study from the literature [3]. It is obvious that the P-values increase with increasing partition coefficients. However, other factors like interactions of the drugs with the coating materials and resulting structural changes, different molecular volumes of the drug molecules and the lower DBS-content of the coating in the case of guaiphenesin may obscure a perfect correlation.

Nevertheless, calculation of the effective diffusion coefficients of the drugs in the coatings according to $D_{eff} = P/PC$ give values at least in the same order of magnitude: $D_{eff} = 1.12 \times 10^{-8}$ cm^2/s for etofylline, 5.03×10^{-8} cm^2/s for guaiphenesin (with 19.4% DBS in the coating) and 1.07×10^{-8} cm^2/s[1] for propyhenazone. These relatively high values are the consequence of the presence of the plasticizer in the coating [16]. For etofylline diffusion pellets it is also possible to calculate the diffusion coefficient for the release along the hydrophilic pathway D_{hydro}. The permeability at pH > 6 is the sum of the permeabilities of the lipophilic and the hydrophilic pathway. Taking into account the additional water uptake at pH > 6 (Table 1) as volume or area fraction respectively for the diffusion through the hydrophilic pathway and assuming a PC of 1 between the aqueous solutions in the hydrophilic region of the coating and in the diffusion pellets, $D = 1.4 \times 10^{-7}$ cm^2/s. This value is 62 times smaller than the diffusion coefficient in pure water [17], which does not seem to be unreasonable.

The release of the drugs according to a partition mechanism at pH < 6 is demonstrated by also looking at the influence of osmotic pressure differences $\Delta\Pi$ between the saturated drug solution in the pellet core and the release media. The relatively high permeability coefficient of propyphenazone is independent of the sodium chloride concentration, even when the swelling of the coating is reduced (see release of etofylline). In these experiments $\Delta\Pi$ is nearly 0 MPa for the release in water and is −5 MPa for the release in 1 M sodium chloride solution. Furthermore, with a positive $\Delta\Pi$ of almost 6 MPa in the case of coated sucrose pellets (saturated sucrose solution in the respective diffusion pellets and release in 0.1 N-HCl and formate buffer 4.4) there is hardly any release. Looking at these results, again the partition mechanism is supported. An osmotically driven transport is only possible in the presence of pores, allowing a bulk flow of drug solution [9]. This is postulated for Aquacoat® ECD-30 films with 24% DBS. Using urea as an osmotic agent, an inverse-linear relationship was found between the release rate of phenylpropanolamine and the osmotic pressure in the release medium. However, the effect of urea on the solubility of the drug and the swelling of the coating was not investigated [18].

Table 3

Permeability coefficients P and partition coefficients PC between organic phases and water of different drugs (formate buffer if not indicated otherwise), 37 ± 1°C, n = 3–12

Drug	P	PC			
	(10^{-10} cm^2/s)	n-Octanol	DBS	Ethyl cellulose	Aquacoat® ECD-30, DBS 20%
Etofylline	30.4 ± 3.9	0.35 ± 0.01[b]	0.044 ± 0.014[b]	0.94 ± 0.15	0.30 ± 0.18
Guaiphenesin	79 (76–81)[a]	3.7 ± 0.2[b]	0.42 ± 0.01[c]	3.3 ± 0.37[c]	1.57 ± 0.21
Propyphenazone	2610 ± 130	119 ± 4[b]	27 ± 1[b]	30 ± 2	23 ± 1

[a]19.4% DBS [3].
[b]Aqueous phase: 0.1 mol/l NaCl.
[c]Aqueous phase: water [8].

4. Conclusions

In acidic media the drug release from pellets coated with the aqueous ethyl cellulose dispersion Aquacoat® ECD-30 with 20% DBS as plasticizer proceeds by a partition mechanism. Thus, lipophilic compounds which are able to dissolve to a high extent in the heterogeneous but lipophilic coating are released relatively fast, regardless of their low aqueous solubility. At pH $>$ 6 an additional hydrophilic pathway exists, with rather high release rates and permeabilities for hydrophilic compounds.

In practice, however, diffusion pellets always have first contact with acidic media (0.1 N-HCl in vitro and gastric juice in vivo). During this contact with an acidic solution, the ethyl cellulose chains of adjacent pseudolatex particles are able to interdiffuse further, water acting as an additional plasticizer. Consequently, adjacent polymer particles are anchored to each other so strongly that the dissociation of the acidic groups of the ethyl cellulose which occurs when the pH increases (pK_a = 6.2), will no longer cause the opening of the hydrophilic pathway by the formation of pores and cracks [3].

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