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Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion

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Summary

Guaiphenesin pellets are coated in a fluidized bed with aqueous ethyl cellulose dispersions (Aquacoat ECD-30) containing different amounts of dibutyl sebacate (DBS) as plasticizer. Optimal film formation and zero-order release rates are obtained if the produced microcapsules (MC) are treated with heat about 10 °C above the minimum film forming temperature (MFT). The permeability of the MC coats can be primarily influenced by the plasticizer content (permeability coefficient $25-53 \cdot 10^{-10}$ $cm^2 \cdot s^{-1}$), permeability increasing additives are needed to enhance the release rate further. During storage of 1–8 days of the ready-to-spray plasticizer containing dispersions DBS migrates to a higher extent into the ethyl cellulose particles and loosens better the previous compact structures. Thus, the permeability of the resulting MC increases by up to 23%. The permeability of the MC coats is pH-dependent because the ethyl cellulose used has a few carboxylic groups in its molecule. At pH values > 6 the release rates increases (2.5 times in case of MC with optimal formed films). At 25 °C of the release medium the coats of the MC with a MFT of 40–50 °C are in the glassy state, thus the permeability is extremely low.

Introduction

Aqueous ethyl cellulose dispersions like Aquacoat ECD-30 (with ethyl cellulose about 26.3%, cetylalcohol 2.4%, sodium lauryl sulfate 1.3%, dimethyl polysiloxane as antifoaming agent in small quantities, particle size 0.1–0.3 μm) * are highly important as film-forming agents for diffusion barriers of controlled-release dosage forms. A primary goal of this study is to clarify whether approximately linear release curves are obtained for coated drug pellets, and the release rates can be adjusted by varying the influential parameters plasticizer content and manufacturing temperature in the manner needed for oral controlled-release dosage forms. In addition, insight should be gained into the mechanism of the drug diffusion through ethyl cellulose films from pseudolatex dispersions containing lipophilic plasticizers: it is especially interesting to determine whether the drug release takes place via a distribution pathway. Dibutylsebacate (DBS) which is almost insoluble in water and does nearly not migrate out of the film (Sutter, 1987) is used as the plasticizer. Furthermore it is

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* Manufacturer: FMC Corporation, Philadelphia, U.S.A.

necessary to clarify the influence of the storage time of the plasticizer-containing dispersions and of the nature of the release medium. Using the expectorant guaiphenesin ((*R*,*S*)-3-(2-methyoxyphenoxy)-1,2-propanediol, Mr = 198,2) as a model drug, it is possible to test the advantages of the use of aqueous dispersions on a drug having a very high solubility (c_s in water = 33.5 g/100 ml, ionic strength $\mu = 0.1$, 37 °C) (Sutter, 1987). The results can be compared to those obtained with the less readily soluble theophylline (Lippold et al, 1989) and conclusions can be drawn for practice concerning the control of the drug release from MC of this type.

The daily dosage of guaiphenesin is $3–4 \times 200$ mg for respiratory tract disorders. This indicates that in view of the very rapid absorption ($t_{max} = 15$ min) and the rapid elimination ($t_{1/2e} = 1$ h) after oral administration of a solution (Maynard and Bruce, 1970), constant blood levels are desirable. A further prerequisite for efficiently retarding guaiphenesin is the pH-independent absorbability of the drug. Due to the absence of dissociating groups in the molecule, the absorption is guaranteed during the entire transit through the stomach and the small intestine. 385 mg was calculated as maintenance dose (Sutter, 1987) which is within acceptable limits for a single dose of highly concentrated drug pellets. They should be released with a zero-order rate constant k_r^0 of about 80 mg/h.

Materials and Methods

Pellet preparation

The following formulation proved to be suitable: guaiphenesin (Brunnengraeber, Luebeck), 4.0 kg; microcrystalline cellulose (Avicel PH 101, FMC Corp.), 0.2 kg; aqueous solution of 5% polyvinyl pyrrolidone (Kollidon K 90, BASF, Ludwigshafen), about 1 kg.

The humid mass is extruded, perforated disk diameter 1.1 mm, model EXD-60 extruder, Elanco, Bad Homburg) and spheronized (device built by Sanol, Monheim), adding small amounts of the solid mixure of the formulation. After drying the pellets are sieved with a screen fraction 1.0–1.25 mm.

Coating conditions

DBS in the respective amounts was added to Aquacoat ECD 30, stirred for 30 min at 400 rpm and was ready to spray. It is necessary to select a high air flow to prevent the MC from sticking together. The drying temperature should not be raised above 45–49 °C, because immediate sticking of the microcapsules would otherwise occur. The optimal spraying conditions for the principal experiments are as follows in the fluidized bed device, Strea I, Aeromatic, Muttenz, Switzerland, with plastic spray tower and two-way nozzle:

Charge	200–300 g
Air flow	186–190 m^3/h (air outlet maximally opened)
Spraying pressure	0.04–0.06 MPa
Spraying rate	3 g/min (1 g/min at the beginning)
Spraying time	40–60 min

Air flow was measured with Testovent 4300 plus hydrometric vane (Testoterm KG, Lenzkirch), the inlet and outlet temperatures via the sensors located in the fluidized bed device, the bed temperature via thermocouple T 432-1 (installed 180 mm above the perforated bottom) and the indicator Therm 4201 (Ahlborn Mess- und Regelungstechnik, Holzkirchen), continuous temperature recording by means of a Servogor 310 recorder Metrawatt, Nuernberg). A final drying is then carried out for 5 min in the fluidized bed. The microcapsule formulations produced are listed in Table 1 together with the spraying conditions. The quantity of dispersion sprayed (relative to the pellet charge) averages 14.6% to obtain a film thickness of about 25–50 μm (Bauer and Osterwald, 1979). A thickness of 10 μm seems to be the absolute lower limit for coatings with dispersions (Lehmann, 1985). The average loss during spraying is about 2.6% (1.7–4.6%, measured by weighing), the drug content of the MC is 81.7% (theoretically 82.1%). Film thicknesses (Table 2) lie between 33 and 38 μm according to microscopic determinations.

Filmforming, thermal posttreatment

Part of the product is screened and stored without any further treatment, the rest is subjected to additional thermal posttreatment for 1 h on a

TABLE 1

Detailed spraying conditions for preparing the guaiphenesin in MC

Formulation	DBS added to 100 g of the dispersion (g)	Storage time of dispersion with DBS (d)	SCD (%)	Inlet temp. (IT) outlet temp. (OT) bed temp. (BT) (°C)	Pellet weight (g)	Quantity of coating material sprayed per pellets (%)
A	9.0	57	35.8	IT 40; OT 40; BT 38.0	300	15.3
B	4.5	8	32.6	IT 40; OT 40; BT 40.5	300	13.9
C	6.0	10	34.7	IT 40; OT 40; BT 40.8	300	14.7
D	4.5	0	32.6	IT 40; OT 42; BT 40.6	200	14.3
E	6.0	0	34.7	IT 40; OT 43; BT 40.7	200	14.9

SCD = substance content of the dispersion including DBS

tray in a ventilated drier. The MC which stick to the tray or to each other, especially in the case of high plasticizer content and high heat treatment temperatures, are then screened (1.0–1.25 μm).

The different formulations A–E and posttreatments as well as the storage times of the microcapsules (in d, m, a for days, months, years) are indicated as follows, e.g. B – 1 h 68°C – 20/41 d; this means formulation B with a post-treatment 1 h at 68°C, storage time of the microcapsules until release study 20–41 days.

Minimum film formation temperature (MFT)

The dispersions are spread on the surface of the metal block with a temperature gradient (15–51.2°C) and the MFT is determined according to DIN, ISO and ASTM as the temperature where the film is complete and without cracks; instrument: Thermostair, Type MFT "D" with 20 test stations, Coesfeld, Dortmund.

TABLE 2

Properties of guaiphenesin in MC tested

Formulation	DBS/SCD [a] (%)	Film thickness *d* (range) (μm)	Thermal post-treatment per 1 h (°C)
A	23.1	37 (33–40)	o.T. [b], 50, 68
B	11.5	33 (28–38)	o.T., 50, 68; 54 [c]
C	19.4	38 (35–40)	o.T., 50, 68
D	11.5	35 (30–40)	o.T., 40, 50, 68
E	19.4	38 (33–43)	o.T., 40, 50, 68

[a] Equals DBS content in the coat.

[b] o.T. = without thermal posttreatment.

[c] Thermal post-treatment in the fluidized bed for 20 min, additional spraying of water (7 g/min) prevents sticking.

Release studies

Measuring system

Dissolution system according to USP XXI/Ph. EUR. "Easi Lift" (Hanson, Northridge, U.S.A.); the paddle is used for the release tests (exception: basket for changing pH conditions), and no difference can be observed in terms of the release rates between the basket and the paddle (Sutter, 1987); rotational speed: 170 rpm. Release media: unless otherwise specified, one liter of deionized and degassed water of 37°C (pH = 6.1).

Buffers used ($\mu = 0.1$): Gastric Fluid USP XXI without pepsin, pH 1.2; formate buffer, pH 4.4; intestinal fluid USP XXI without pancreatin, pH 7.5; borate buffer, pH 9.1; borate buffer, pH 10.0; carbonate buffer, pH 10.0.

Experimental procedure and sampling

The MC (corresponding to 385 mg of guaiphenesin) are placed onto the releasing liquid; they sink to the bottom of the vessel. During continuous sampling, the solution is filtered through a reagent filter (Technicon, Bad Vilbel), measured with the spectrophotometer PMQ III (Zeiss, Oberkochen) at 248.9 nm. The connecting tubes are made from PTFE, the squeeze tube from Tygon R 3603 (sorption cannot be measured). The pumping rate is 9 ± 1 ml/min.

Stirring speed

The stirring speed is consistently 170 rpm in all releases. This is necessary because the MC would otherwise begin to stick in the releasing vessel shortly after they are put in, especially in the case of formulations with high plasticizer content in the coating; a cone in which the individual MC is no longer able to freely move is formed on the bottom. However, a comparison with lower stirring speeds with MC containing 15.7% DBS shows no dependence of the release on the rpm (Sutter, 1987). This is in agreement with previous studies carried out with the same release apparatus (Lippold and Förster, 1982); k_r^0 decreases only beginning from a very low rpm (30 rpm), i.e., the adhering layer building up reduces the release of the drug.

Evaluation of the release characteristics

The mean values of the quantities released at time t are first determined in repeated or parallel tests, and the linear regression is performed thereafter. The release is investigated during a period of nearly 5 h according to the transit time for the stomach and small intestine (Davis et al., 1984; Davis, 1985). The zero-order rate constants k_r^0, obtained from such drug-rich MC (Lippold et al., 1981; Lippold and Förster, 1982), are calculated from the linear sections of the release curves after an initial phase of 30 min, during which the saturation concentration c_s builds up in the core and the steady state is reached. The constant release must end as soon as 71% of the drug (273 mg) has been released, because then the concentration within the MC is below saturation. The k_r^0 values are therefore determined at most until the corresponding point in time. The reproducibility of the release is good (s_{rel} of $k_r^0 = 5.2\%$, $n = 20$).

The permeability coefficients P can be calculated from the k_r^0 values, taking the MC surface area A, the drug solubility c_s and the film thickness d into account:

$$P = k_r^0 \cdot d/A \cdot c_s \qquad (1)$$

($d = 36\ \mu m$, $A = 16.7\ cm^2$, as mean values)

Reproducibility of the MC preparation

The very similiar release data (P-values) of two differently prepared batches prove the sufficient reproducibility of the fluidized-bed production process (Sutter, 1987).

Results and Discussion

The influence of the thermal posttreatment, plasticizer content, storage time of the ready-to-spray dispersion, pH and temperature of the release medium on the permeability of the MC coats will be demonstrated (Table 3) and discussed below.

Thermal post-treatment and permeability

Fig. 1 shows some of the release curves (mean values from $n = 2$–6 tests) and Figs. 2 and 3 and

TABLE 3

Permeability coefficients ($10^{10} \cdot cm^2/s$, mean values P and extreme values P_{min} and P_{max}) of guaiphenesin for MC shells at pH 6.1 (storage time of the MC: 20–41 d)

Formulation	Thermal post-treatment temp.	P	(P_{min}/P_{max})
A, 23.1% DBS,	o.T.	64	63/65
storage time	50 °C	82	single value
of dispersion:	68 °C	89	single value
57 days			
B, 11.5% DBS,	o.T.	237 [a]	221/252
storage time	54 °C	39	38/39
of dispersion:	68 °C	35	35/36
9 days			
C, 19.4% DBS,	o.T.	55	53/58
storage time	50 °C	78	76/79
of dispersion:	68 °C	79	76/81
9 days			
D, 11.5% DBS,	o.T.	222 [a]	212/240
storage time	40 °C	135 [a]	136/140
of dispersion:	50 °C	36	35/38
0 days	68 °C	40	39/40
E, 19.4% DBS,	o.T.	44	41/46
storage time	40 °C	54	53/56
of dispersion:	50 °C	68	68/68
0 days	68 °C	65	65/66

[a] Linear regression between 30 and 60 min.

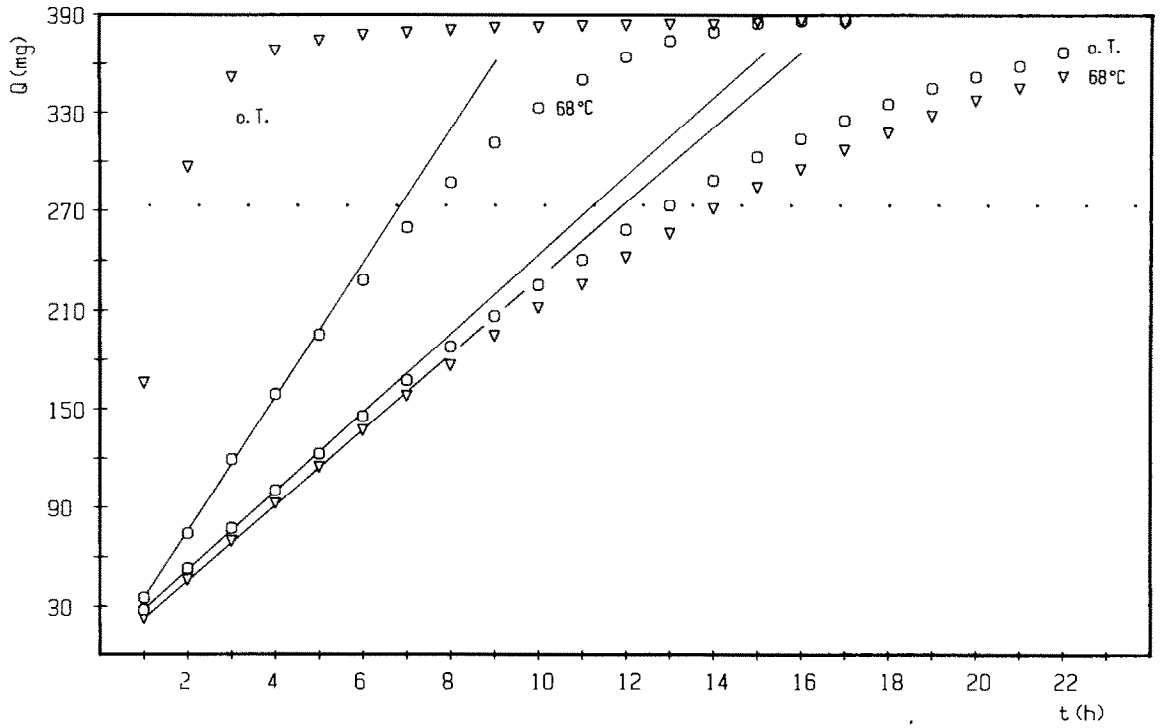

Fig. 1. Release of guaiphenesin MC as a function of the thermal posttreatment for different plasticizer content of the coat. Storage time of the dispersion: 0 d, storage time of the MC: 64–69 d, release conditions: paddle, 170 rpm, 1 liter water, 37 ± 1° C. ▽, formulation D, 11.5% DBS; ○, formulation E, 19.5% DBS.

Table 3 *P* values as a function of the thermal post-treatment for different plasticizer contents and different storage times of the plasticizer-containing dispersion. Most of the release curves are linear during the 5-h period and even longer, but they are curved in some cases at the end (Fig. 1).

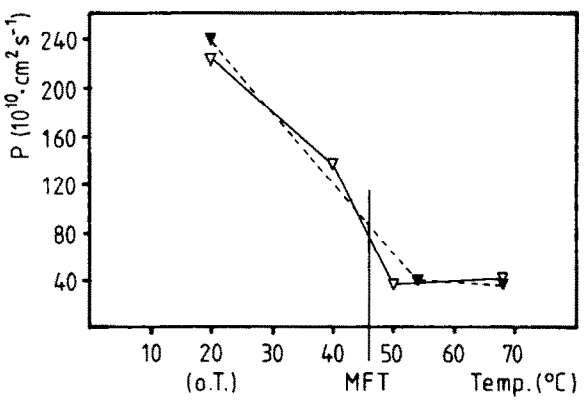

Fig. 2. Permeability coefficients of guaiphenesin for MC coats as a function of the thermal posttreatment for different storage times of the dispersion. DBS content: 11.5%; storage time of the MC: 20–30 d. ▼, formulation B, storage time of the dispersion: 9 d; ▽, formulation D, storage time of the dispersion: 0 d.

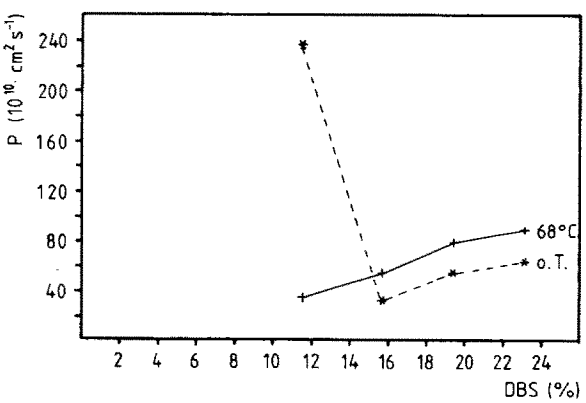

Fig. 3. Permeability coefficients of guaiphenesin for MC coats as a function of the plasticizer content for different thermal posttreatments. Storage time of the dispersion: 4.5–57 d; storage time of the MC: 20–50 d. *, without thermal post-treatment (o.T.); +, 1 h at 68° C.

Deviations from the linear course appear even if the percentage of the drug released is still below the limit value of 71% (= 273 mg, dotted line in Fig. 1 and others); this also applies to most of the other curves if the overall course of the curves is considered. The curvilinear release is the summation curve of a broad distribution of different release rates of a MC population (Hoffman et al., 1986; Lippold et al., 1981; Thoma and Gröning, 1975).

The effect of thermal posttreatment appears most clearly when the *P*-values are considered obtained for formulations containing 11.5% DBS (A,D) without thermal post-treatment (o.T.) or with thermal post-treatment at 40 °C (Table 3). The *P*-values are very high, the steep slope of the release curve in Fig. 1 reflects the presence of cracks (macropores). Furthermore, the release curves of these formulations show a greater variation than those obtained for the MC with lower *P*-values. Retardation of release is achieved only at higher temperatures. Fig. 2 shows the *P*-values as a function of the heat treatment temperature, and the MFT values are also marked there. It is apparent that the MFT (46 °C for 11.5% DBS) must be exceeded so that a continuous film which controls the release (fusion at the molecular level in terms of the theory of adhesion and interdiffusion-optimal film formation, Sutter et al., 1988) is able to form. As most cracked coatings, which cause rapid release, are formed below the MFT, some of the MC even burst during release. The fact that low *P*-values are obtained with 19.4% and 23.1% DBS contents in the shells even without thermal post-treatment (Table 3, o.T. = 20 °C) results from the bed temperature (40 °C) during the spraying and drying.

Above the MFT the permeability either reaches a plateau (11.5% DBS) or still increases (19.4% or 23.1% DBS) with rising thermal posttreatment temperature (Table 3). This can be explained as follows: it is possible for the plasticizer to penetrate into the ethyl cellulose particles more rapidly and completely at elevated heat treatment temperatures and to break the interactions there between the individual ethyl cellulose chains in addition to the heat effect (the MFT is exeeded), thus increasing the flexibility of the chains. After cooling, the ethyl cellulose molecules will then remain in a loosened, metastable state (Spurlin et al., 1946; see also Conclusions).

Plasticizer content in the ready-to-spray-dispersion and permeability

Fig. 3 shows the *P*-values as a function of the DBS content at different heat treatment temperatures. The storage time of the dispersions are in the ranges which permit a comparison of the *P*-values (see next part). Without thermal treatment, microcapsules containing 11.5% DBS show extremely high *P*-values, which can be attributed to insufficient film formation. At heat treatment temperatures above the MFT, the permeability coefficients increase with increasing plasticizer content, due to decreased interaction of the polymer chain in presence of the plasticizer. The water content, which increases with increasing plasticizer concentration (Sutter, 1987; Lippold et al., 1989), causes an additional increase in the permeability of the MC shells, water acting as softener.

Storage time of the ready-to-spray dispersion and permeability

Table 3 also shows the influence of the storage time of the dispersion (0–9 days): the permeability increases to ca. 23% with increasing storage time. The longer the time available for DBS to diffuse into the ethyl cellulose particles to plasticize them, the more rapid is the release of the drug after absorption of water by the shell. The effect of the storage time of the dispersion becomes especially noticeable at higher plasticizer contents, because the maximum possible plasticizer effect is reached under the given conditions (degree of nebulization and posttreatment temperature) without storage of the dispersion if the DBS content is low. It can be deduced from this that during heat treatment for 1 h, the DBS present in the films made from freshly prepared dispersion is unable to distribute homogeneously and to exert its optimal plasticizing effect.

It could be expected that if the MC are stored long enough, the differences in the immigration and the distribution of the plasticizer into the coatings prepared after different dispersion storage times would be equalized and would lead to

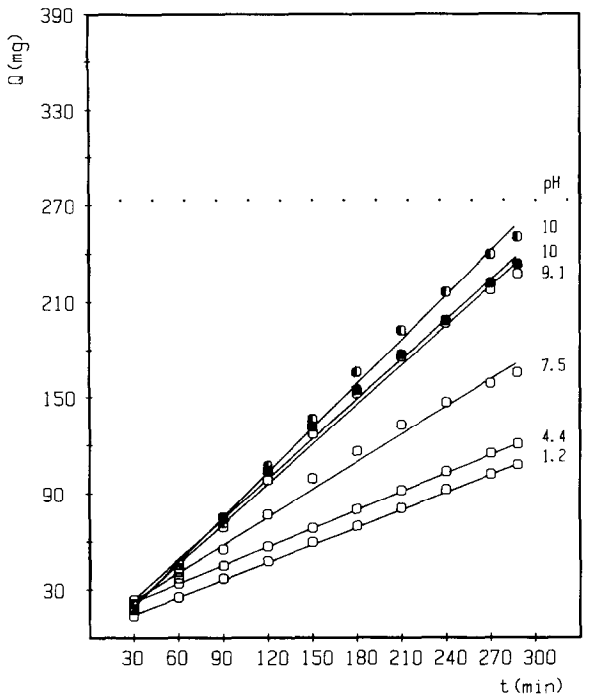

Fig. 4. Release of guaiphenesin MC as a function of pH value. Formulation E, DBS content: 19.4%, storage time of the dispersion: 0 d; thermal posttreatment: 1 h at 68 °C; storage time of the MC 1–1.5a; release conditions: see Fig. 1. ○, Buffer, pH 1.2–9; ● buffer, pH 10, carbonate buffer; ◐ buffer, pH 10, borate buffer.

similar permeabilities. However, this does not happen (Sutter, 1987; Lippold et al., 1989). The plasticizer, which is still in the form of droplets after spraying, is homogeneously distributed in the film during the storage of the microcapsules but this does not lead to the same degree of loosening of ethyl cellulose chains, since the "activation" by elevated temperature is lacking.

pH value of the release medium and permeability

While the release of undissociated drugs from macroporous ethyl cellulose MC prepared from organic solvents is independent of the pH value (Lippold and Förster, 1982), coatings prepared from plasticized dispersions surprisingly behave differently: as is shown by the examples of formulation D, which were heat-treated at 68 °C (Fig. 4 and Table 4), the MC shells show a marked increase in permeability by a factor of 2.5 in the pH range of 4.4–9. Some of the fractions which were post-treated at low heat treatment temperatures (D – 1 h 50 °C – 1/1.5a; E – o.T. – 1/1.5a; E – 1 h 40 °C – 1/1.5a) (Table 4) even show a thirteenfold increase in permeability at pH 7.5 compared to the values measured at pH 1.2 or pH 4.4. The arguments of Goodhart, who also found a pH dependence and attributed the influence of the pH value on the dissociation of sodium laurylsulfate ($pK_s = 1.9$) (Goodhart et al., 1984), is thus refuted. Moreover, most of the sodium laurylsulfate is leaked out after the MC have been stored for 1–1.5 years (Sutter, 1987).

If the P values are plotted as a function of the corresponding pH value (Fig. 5), a sigmoidal curve is obtained which resemble acid-base titration curves. Indeed, investigations on carboxyl groups in microcrystalline cellulose (13 μval/g) and na-

TABLE 4

Permeability coefficients ($10^{10} \cdot cm^2/s$) of guaiphenesin for MC shells as a function of the pH value (Storage time of the dispersion: 0 days, storage time of the microcapsules: 1–1.5 years, n = 1–3)

pH ($\mu = 0.1$)	Buffer	Formualtion D, 11.5% DBS				Formulation E, 19.4% DBS				Formulation A, 23.1% DBS	
		o.T.	40 °C	50 °C	68 °C	o.T.	40 °C	50 °C	68 °C	o.T.	68 °C
1.2	HCl/NaCl	44	32	28	25	36	35	40	39	53	52
4.4	Formate				27	34		35	41		
6.1	NaCl				31				46		
7.5	Phosphate			377	53	405	257	75	62		
9.1	Borate				61				89		
10.0	Borate				68				99		
10.0	Carbonate				71				90		

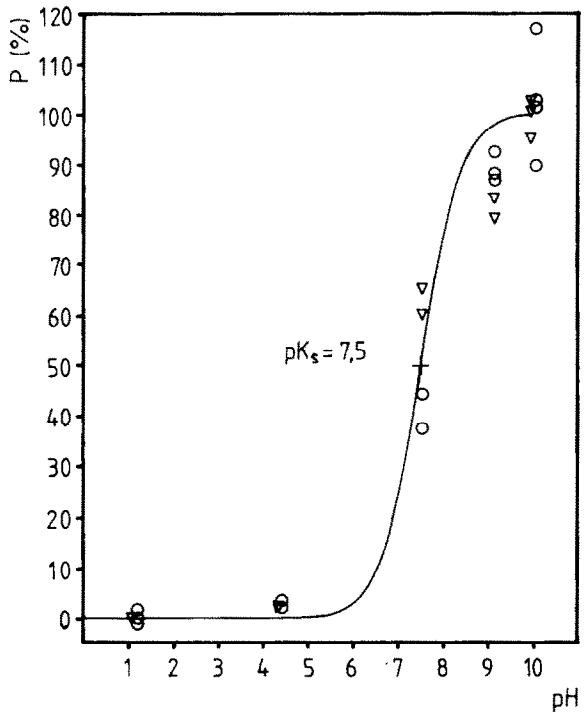

Fig. 5. Change in the *P*-value (%) of guaiphenesin for MC coats as a function of the pH value. Storage time of the dispersion 0 d; thermal post-treatment 1 h at 68 °C; storage time of the MC 1–1.5 a. ▽, formulation D, DBS content: 11.5%; ○, formulation E, DBS content: 19.4%; ———, calculated curve; *P* at pH 1.2 = 0%, *P* at pH 10 = 100%.

tive cellulose (38 μval/g) were reported in the literature (Ullmann and Mansel, 1974); in ethyl cellulose, they can mainly be encountered in the terminal groups of the ethyl cellulose molecules (ca. 80 μval/g) (Evans and Spurlin, 1950). The experimentally determined value is 25 μval/g. However, the IR spectra only weakly suggest the presence of carboxyl groups (Sutter, 1987). The corresponding acid-base titration of an Aquacoat ECD-30 dispersion without DBS has a pK_s value of 6.2 (Sutter, 1987). The difference from the inflection point in Fig. 5 (pK_s = 7.5) can be explained by the change in the degree of dissociation not being transferred in proportion to the increasing permeability of the shell.

Assuming that the carboxyl groups are concentrated on the hydrophilic surface of the particles (Distler and Kanig, 1978), partially at the ends of unfolded ethyl cellulose chains (Sucharewa, 1982), it is imaginable that the release medium primarily penetrates into the shell along the hydrophilic boundary layers between the latex particles (increased carboxyl group and emulsifying agent concentrations) (Distler and Kanig, 1978). The degree of dissociation of the acidic groups is decisive. Intensified hydration and repulsion of the charged groups occur in the case of high degrees of dissociation (pH > 7). Depending on how firmly the ethyl cellulose chains of neighboring latex particles were able to attach to each other during the film preparation, various degrees of loosening and increased permeability will result.

The high degree of linkage in MC formulations showing complete film formation (e.g., D – 1 h 68 °C – 1/1.5a, E – 1 h 50 °C – 1/1.5a and E – 1 h 68 °C – 1/1.5a) (Table 4) leads to more rapid release mainly because of increased hydration, whereas pronounced cracking and consequently extremely high permeability will develop in microcapsule fractions in which the DBS content and the heat treatment are insufficient to bring about linkage between the latex particles via interdiffusion (D – 1 h 50 °C – 1/1.5a; E – o.T. – 1/1.5a; E – 1 h 40 °C – 1/1.5a) (Table 4). Increased pore formation and drug release as a consequence of the increased content of charged groups which mutually repel each other in polymethyl methacrylate films were reported (Okor and Anderson, 1979).

However, if most of the carboxyl groups are in the undissociated form (pH < 5), only slight hydration and no repulsion will occur. The ethyl cellulose chains of adjacent latex particles are able to interdiffuse, water acts as a plasticizer. Consequently, adjacent polymer particles should be anchored to each other after penetration of the acidic buffer so strongly that the dissociation of the acidic groups, which occurs when the pH changes to 7.5, will no longer cause cracks. As is apparent from Fig. 6, the MC shells, which were able to swell in the acidic medium, are prevented from cracking when they are subsequently introduced into a weakly alkaline medium. Nevertheless, the dissociation of the carboxyl groups seems to loosen the shell so much, depending on the degree of film formation, that a deviation from

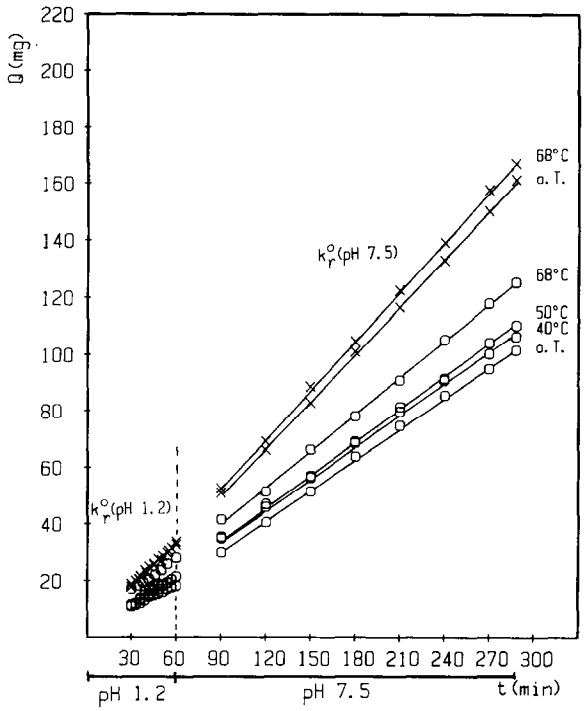

Fig. 6. Release of guaiphenesin MC during a pH change from 1.2 to 7.5 as a function of the thermal post-treatment for different DBS contents. Storage time of the microcapsules: 1–1.5 a; release conditions: basket, 170 rpm, 1 liter buffer, 37 °C ± 1 °C. ○, formulation E, DBS content: 19.4%; storage time of the dispersion: 0 d; x, formulation A, DBS content: 23.1%; storage time of the dispersion: 57 d.

linearity can be observed in the formulations containing only 11.5% DBS: The release curves are bent upward, the release is uncontrolled, presumably due to bursting of individual microcapsules because of inadequate film formation (the plasticizer content and the heat treatment temperature were too low) (Sutter, 1987).

Ionic strength

A pronounced effect of the ionic strength of the release medium on the permeability coefficient was observed: 20% reduction of P by increasing ionic strength from zero to 0.2. This can be considered to be evidence of drug diffusion through areas of the swollen ethyl cellulose film which are rich in water. The NaCl used to set the ionic strength is able to reduce the hydration of the ethyl cellulose chains (salting-out effect). The fact that the effect of the ionic strength on the permeability was not observed in demonstrably porous microcapsules (Förster, 1981) argues against the "bulk flow" hypothesis (Sutter et al., 1988).

Temperature effects of the releasing medium

If the MC are released at 25 °C and the respective curves compared with those at 37 °C (Fig. 1), it is possible to demonstrate an improvement in the film stability in the latter case as a consequence of the interlinking of the polymer chains with each other during the penetration of water having a temperature of 37 °C. Rapid and no longer linear release of the drug occurs at 25 °C in the case of the formulations whose shells did not form optimal films due to the plasticizer content and/or the thermal posttreatment, even though the solubility of guaiphenesin is greatly reduced at 25 °C (37 °C: $c_s = 36.5$ g/100 ml; 25 °C: $c_s = 14$ g/100 ml: Sutter, 1987). In contrast, the release at 25 °C strongly decreases compared to that measured at 37 °C (to ca. 1/6) with the formulations which showed optimal film formation (e.g., E – 1 h 68 °C – 1/1.5a). This cannot be solely attributed to the fact that the solubility of guaiphenesin at 25 °C is much lower, but also to the fact that the film is probably in the glassy state at 25 °C even in the presence of water.

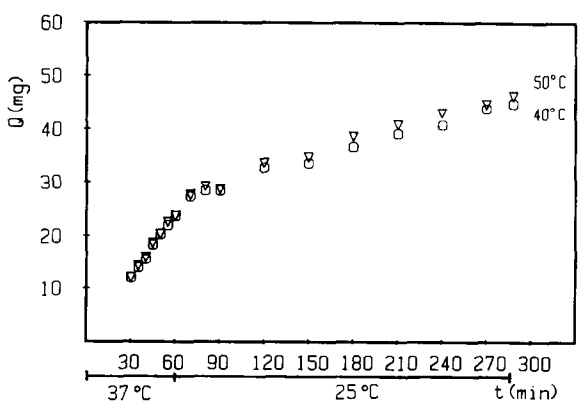

Fig. 7. Release of guaiphenesin MC during a change in the water temperature from 37 to 25 °C. Storage time of the dispersion 0 d; storage time of the MC: 1–1.5 a; release conditions: see Fig. 1. ▽, formulation D, DBS content: 11.5%; thermal posttreatment: 1 h at 50 °C; ○, formulation E, DBS content: 19.4%; thermal posttreatment: 1 h at 40 °C.

If the temperature is lowered from 37 °C to 25 °C during the release in the case of the formulations without optimal film formation (Fig. 7), the release at 25 °C will become appreciably slower than in case of direct release at 25 °C. This can be explained in accordance with the previous chapters: the flexibility of the ethylcellulose chains is sufficient for gradual interlinking at 37 °C in the presence of water; thus, during a subsequent release at 25 °C the MC remain intact.

Conclusions

The formation and the permeability of films prepared from aqueous ethyl cellulose dispersions containing a plasticizer which is nearly insoluble in water show a highly complex picture.

Reaching the MFT with a given plasticizer is the basic requirement of film formation, i.e., of obtaining a film without macroscopically visible cracks. However, reaching the MFT is not sufficient; rather, it is also necessary to subject the microcapsules to heat treatment at temperatures which are ca. 10 °C above the MFT to obtain optimally filmed MC. Only solidified films (thermal posttreatment for one hour at 68 °C) withstand the "dissociation stress" at higher pH values.

The storage time of the ready-to-spray dispersion also exerts a similar, but much weaker effect on the film strength and the degree of loosening as the heat treatment temperature. Thus, the storage time has to be standarized.

The dissociation of carboxylic groups of ethyl cellulose leads to a rise in permeability (by a factor up to 2.5) in the case of optimally filmed shells and even to cracking or bursting in the case of incomplete film formation. This could be viewed as positive with regard to complete release during transit in the small intestine.

In optimally filmed shells, the existence of carboxyl groups in the undissociated form (pH 1.2–4.4) enables the ethyl cellulose chains to compensate the activated state occurring as a consequence of high heat treatment temperatures during the swelling phase.

Microcapsules showing incomplete film formation are even able to partially complete the film formation during the swelling of the film in an acid medium.

Plasticizer content of the film provides for the necessary uptake of high percentages of water (ca. 20% at 23.1% DBS) (Sutter, 1987) and makes it permeable to drugs. The permeability of the shell can be controlled by varying the plasticizer content within technologically reasonable limits (danger of sticking), but only in a range ($P = 25–53 \cdot 10^{-10}$ cm$^2 \cdot$ s^{-1}, $k_r^0 = 15–32$ mg $\cdot$ h^{-1} respectively under acidic conditions) that is too low for the required release rate ($k_r^0 = 80$ mg $\cdot$ h^{-1}). Permeability increasing additives are needed to enhance the release rate further.

In the case of release in an acidic medium the storage time of the microcapsules does not seem to affect the drug release (Sutter, 1987). The release characteristics of theophylline from MC on the basis of Aquecoat ECD 30 confirm the results with guaiphenesin and give further insight in the release mechanism (Sutter, 1987; Lippold et al., 1989).

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