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PROPERTIES OF AQUEOUS, PLASTICIZER-CONTAINING ETHYL CELLULOSE DISPERSIONS AND PREPARED FILMS IN RESPECT TO THE PRODUCTION OF ORAL EXTENDED RELEASE FORMULATIONS

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ABSTRACT

Plasticized aqueous ethyl cellulose (EC) dispersions (Aquacoat^{R} ECD-30) are incompatible with concentrated electrolytes but stable with nonelectrolytes. The minimum film formation temperature (MFT) decreases with increasing plasticizer content, from 81 °C to about 30 °C

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with 20 % dibutyl sebacate (DBS) in the resulting film. The plasticiser has to penetrate completely into the EC particles before film formation to obtain optimal plastification, the lowest film formation temperature and high permeability of the resulting film. This takes more than 5 hours with 20 % DBS. Films prepared from plasticized dispersion with short standing times show craters of former plasticizer droplets. With increasing plasticizer content the sticking point of the films decreases. The plasticizer induce a high water absorption of the films: more than 30 % with 23 - 26 % DBS or diethyl phthalate (DEP). DBS is hardly released from the films within 5 hours, in contrast to DEP. Thus, the absorbed water is completely swelling water in case of DBS and partially also substitution water in case of DEP. The films squeeze out cetylalcohol (CA) and also sodium lauryl sulfate (NaLS) during storage, this may change the permeability of the films. EC contains a small amount of carboxylic groups which explains the pH dependent release of drugs from pellets coated with aqueous EC dispersions.

INTRODUCTION

Aqueous polymer dispersions are increasingly used instead of organic polymer solutions for the coating of drugs or drug preparations to extend the release. To applicate successfully aqueous dispersions in practice (1),

to understand film formation (2), and to control the release (1, 3), different properties such as coagulation stability, minimum film formation temperature (MFT), sticking point, film swelling, plasticizer release, and film aging have to be known. This paper describes important relevant parameters of aqueous ethyl cellulose dispersions and resulting films containing different amounts of the plasticizer dibutyl sebacate (DBS) and diethyl phthalate (DEP).

MATERIALS AND METHODS

Ethyl Cellulose Dispersion

The pseudolatex Aquacoat^{R} ECD-30, FMC-Corporation (USA-Philadelphia) is used, particle range 0.1 - 0.3 µm. The batches investigated contain about 26,3 % ethyl cellulose (EC), 2.4 % cetylalcohol (CA), 1.3 % sodium lauryl sulfate (NaLS) and dimeththyl polysiloxane (DMPS), small quantities.

Ethyl Cellulose

Ethyl cellulose Ethocel^{R} STD 10 IND, Dow Chemical (D-Düsseldorf) is used for comparative studies and essentially corresponds to that used in Aquacoat^{R}. Its characteristics are shown in Table 1, according to the information of the company. Data with an asterisk are experimentally determined (3).

TABLE 1

Physical Characteristics of the Ethyl Cellulose Ethocel^R STD 10 IND

Density	1.13 g/cm^3
Particle size*	88 % 0.5 mm
Ethoxyl content	48.0 - 49.5 %
DS	about 2.5
Average molecular weight, M_n	about 22,000
Viscosity[1)]	9 - 11 mPa · sec
δ	21.1 $\sqrt{J/cm^3}$
T_g*	128 °C
Softening range*	160 - 165 °C
Decomposition range*	180 - 200 °C

1) 5 % solution, 80 parts toluene / 20 parts ethanol, Ubbelohde, 25 °C

* experimentally determined

Plasticizer DBS and DEP

The properties of DBS, Henkel (D-Düsseldorf) and DEP, Merck-Schuchardt (D-Hohenbrunn) are listed in Table 2. Most of the data are from Ref. (4) and (5) , data with an asterisk are experimentally determined (3). The high solubility of ethyl cellulose in the plasticizers is in agreement with the similiar solubility parameters of the compounds.

TABLE 2

Properties of the Plasticizers

	DBS	DEP
Molecular weight	314.5	222.2
Boiling point (°C)	345	298
Melting point (°C)	1	-3
Solidification point (°C)	-4	-33
Glass transition temperature (°C)	-108	-85
Density (g/ml^3)	0.9405	1.1175
Refractive index n_D^{20}	1.4413	1.5000
δ ($\sqrt{J/cm^3}$)	18.8	20.5
Solubility at 20 °C (%)		
in water	0.01	0.15
of water in plasticizer	0.2	0.7
of ethyl cellulose in plasticizer	> 10*	> 10*
Volatility ($mg \cdot cm^{-2} \cdot h^{-1}$)		
at 68 °C	0.03*	0.64*
at 85 °C	0.07*	
at 105 °C	0.58*	2.77*
at 191 °C	63	500

* experimentally determined

Preparation of Plasticizer-Containing Dispersions

After intensively shaking the Aquacoat^{R} dispersion for five minutes in the shipping container, appropriate quantities of dispersion and plasticizer are combined and mixed with a glass blade stirrer for 30 minutes at 400 rpm. A short intermediate stirring with a glass rod guarantees mixing of the plasticizer droplets which adhere to the glass wall.

Coagulation Test

Solutions of substances are added drop by drop to a plasticizer-containing dispersions, or the dispersion is added to solutions of substances. Coagulation of the dispersion will develop as a result of incompabilities.

Preparations and Water Absorption of Films

The plasticizer-containing dispersions are dropped onto a glass plate until a continuous liquid layer is formed; drying is carried out at 68 °C within one hour in a ventilated dryer. After digestion of the films (film sample weight: 250 - 400 mg) in deionized water (37 °C), surface water is removed from the films by placing them briefly between two filter papers under gentle pressure, and their weight increase is determined. For comparison reasons films prepared from solutions of EC and the plasticizer in chloroform are prepared, too. In general 2 - 5 determinations are made, maximum deviation from the mean is 25 %.

Minimum Film Formation Temperature (MFT)

Instrument: Coesfeld Thermostair and Thermostair electronic, Coesfeld GmbH (D-Dortmund), with 20 test stations.

Procedure: According to DIN 53787, ASTM-D 1465, 2354; setting the temperature gradient (usually $\pm$ 10 °C of the expected MFT) the dispersions are spread on the metal bloc covered with an aluminium foil, resulting film thickness about 100 µm. Three films are prepared as parallel strips. MFT is observed without covering the hot plate.

Glass Transition Temperature (T_g)

Determination with the differential calorimeter DSC-4, Perkin Elmer (D-Überlingen): Two analysis are run with each specimen (heating rate 20 °C/min, nitrogen treatment); the second one is evalueted.

Sticking Point

Small pieces of film are placed on the metal block of an apparatus for melting point determination and moved on the surface. The temperature (heating rate 1 °C per minute) at which the film begins to stick to the metal surface is noted. The values are mean values from two to five tests. The maximum variation is 9 °C.

Scanning Electron Microscopy (SEM)

Instrument: Preparation unit Z 400, Leybold (D-Köln), microscope ISI-60, International Scientific Instruments

(D-München) with Microanalysis System Ortec 6230, Ortec (D-München). Procedure: The specimens are sputtered with gold and scanned under vacuum (0.04 Pa) at 30 kV.

Acid-base titration of Aquacoat^R

Charges: a) blank value: 40.00 ml distilled water, treated with nitrogen for 30 minutes plus 2.00 ml 0.1 N NaOH

b) specimen: 2.4257 g Aquacoat^R (= 0.6380 g EC) in 40.00 ml distilled water, treated with nitrogen for 30 minutes plus 2.00 ml 0.1 N NaOH.

Procedure (6,7): 0.1 N HCl is added to the specimen in 50 - 400 µl increments and stirred with a magnetic stirrer until the pH value is stabilized, and the exact pH values are read after stopping the magnetic stirrer (temperature: 25 °C). After the corresponding pH values are plotted against the quantity of HCl added, the differences of HCl consumed can be determined by shifting the blank value titration curve. The half-height of the differential curve thus plotted indicates the pK_S value of the acid function.

RESULTS AND DISCUSSION

Coagulation Tests

These investigations should elucidate how the dispersions behave if they come into contact with drug pellets. Highly concentrated electrolyte solutions show incompatibilities with plasticized dispersions (Table 3), thus film formation may be disturbed on surfaces of readily dissociating drugs. Coagulation does not occur with dissolved nonelectrolytes (Table 3). Thus the coating of pellets of highly soluble nonelectrolytes such as guaifenesin (solubility 36.5 % at 37 °C) is possible without problems (1).

Film Formation and its Dependence on Standing Time of the Plasticizer-Containing Dispersions

Minimum film formation temperature (MFT): Table 4 contains the MFT values of the dispersions as a function of plasticizer content. Below the MFT, the films are cracked and become fragmented during attempts to peel them off. However, the individual fragments are clear and translucent. The MFT values decrease with increasing plasticizer content of the dispersion. To guarantee complete film formation during film coating processes temperatures about 10 °C above the respective MFT have to be applied (1).

TABLE 3

Incompatibilities of Dispersions Containing Plasticizer (DBS) with Solutions of Substances.

Addition of: / Charged in beforehand:	Test solution / Dispersion	Dispersion / Test solution
Sucrose solution[1)]	-	-
Guaifenesin solution[1)]	-	-
NaCl solution[1)]	+	+
Oxalic acid solution[1)]	+	+
1 N HCl	+	not determined
0.1 N HCl	+	not determined
0.01 N HCl	-	not determined

+ Precipitation

- No reaction

[1)] Saturated solutions

The MFT values of dispersions with different storage times show small differences. To investigate the effect of the standing time in a more detailed study, the MFT values of a an other DBS-containing batch are recorded as a function of the standing time after preparation (20 % DBS in the resulting film) (Fig. 1). There is a sharp drop of the MFT values during the

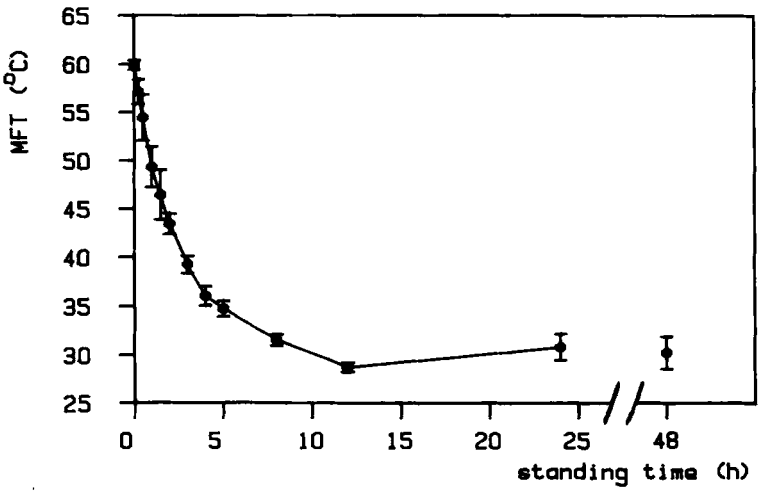

FIGURE 1
MFT values of the EC dispersion Aquacoat^{R} containing DBS (20 % in the resulting film) as function of the standing time; $x \pm s$, $n \cong 2 \times 3$.

first 5 hours of standing time from about 60 to 35 °C, then a plateau is obtained at about 30 °C.

Microscopic investigations: Preliminary microscopic investigations carried out with stained DBS (Sudan III) show that this plasticizer has markedly immigrated into the EC particles after a one-day standing of the dispersion. However, it is only after one week that one can speak of a "homogeneous" dispersion, i. e., the absence of recognizable isolated DBS droplets in both the dispersion and the films prepared from it: the distribution equilibrium has become established. SEM-micro-

TABLE 4

Thermoanalytical Characterization of DBS-Containing EC Films Prepared from Aqueous Dispersions.

DBS/film (%)	0	13,3	18,0	22,0	26,1
MFT (°C)					
unstored disp.	n.d.	46	37	34	29
stored disp. (8 d)	81	46	39	31	n.e.
T_g (°C)					
without thermal treatment	n.d.	31	29	n.e.	n.d.
with thermal treatment	n.d.	46	42	40	n.d.
Sticking point (°C)	n.e.	81	n.d.	64	61

n.e. = not evaluable, n.d. = not determined

graphs (Fig. 2) confirm this. On the day of preparation of the plasticizer-containing dispersions, the plasticizer DBS is unable to diffuse homogeneously into the EC, and plasticizer droplets remain on the films prepared form such dispersions (68 °C, 1 h). After storage of the films up to 1 - 1.5 months at room temperature the plasticizer has diffused into the surrounding polymer so that imprints (= craters) of former droplets

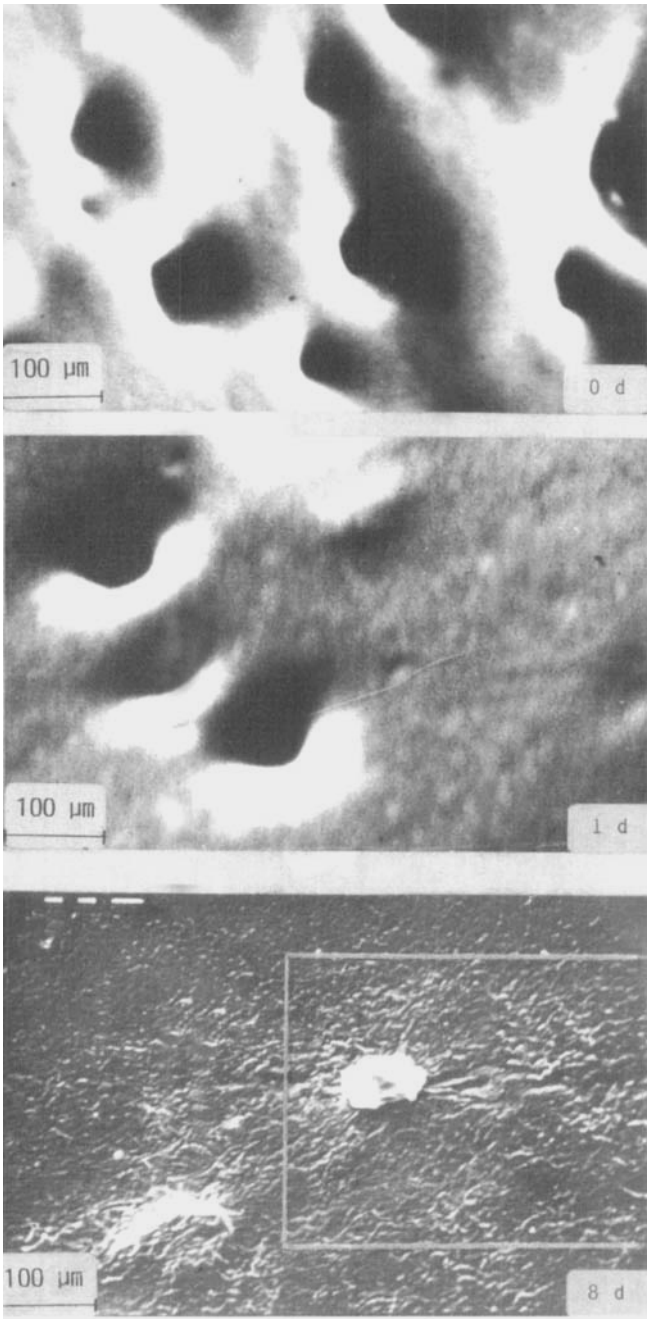

FIGURE 2
Scanning electron micrographs of EC films with standing times 0,1 and 8 days of the dispersion; DBS content: 23.1 %, thermal post-treatment: 1 h at 68 °C, storage time of the films: 1 - 1.5 months.

will remain (Fig. 2). These craters are less frequent in sprayed films (microcapsules) according to the atomization of the droplets during their exit from the spray nozzle. As the standing time of the dispersion increases, the plasticizer penetrates better into the EC particles, so that less craters are observed (1 day, Fig. 2), or homogeneous films are formed (8 days, Fig. 2).

The processes taking place in the dispersion after the addition of the plasticizer until the film preparation have apparently been considered so far to be of secondary importance for the film formation from aqueous dispersions. No studies are known concerning the influence of the standing time of the plasticizer-containing dispersion on the film formation. Bindschaedler (8) was the only author to investigate the immigration of the plasticizer into the film-forming agent in great detail, but he investigated plasticizers with relatively high solubility in water, which penetrate into the investigated cellulose acetate polymer in a short time.

The standing time of the plasticizer-containing dispersions influences not only its MFT and the appearance of the resulting films but also the permeability of the coatings of pellets: Longer standing times give higher permeabilities (1). Thus the standing time has to be standardized to get reproducible release rates from such formulations.

Glass transition temperature (T_g): Table 4 also shows the T_g values of plasticized films (coatings of pellets). The coatings with thermal posttreatment at 68 °C (above the MFT) give T_g values within the range of the corresponding MFT values and of data from literature (9). The T_g values of films without thermal post-treatment are lower (Table 4). All in all DBS seems to be the more effective plasticizer for ethyl cellulose than DEP: According to Rowe et al. (5), the T_g of EC drops to 85, 66 and 52 °C at DEP contents of 20, 30 and 40 % DEP in the films (films prepared from organic solutions) and are about 44, 41 und 39 °C using the aqueous dispersions (9). However, the MFT-values are of more interest if the application of aqueous dispersions is concerned. Especially the plasticizing action of water will be detected by measuring the MFT. Furthermore, T_g values depend on the applied methode and may vary considerably.

Sticking point: As expected, the sticking points are much higer than the respective MFT-values for DBS (Table 4). Sticking of coated pellets (microcapsules) can be expected to occur above these temperatures in the spray tower or during thermal post-treatment. The sticking points of films from organic solutions plasticized with DEP are higher: 106, 80 and 75 °C for 11.5, 19.4 and 23.1 % DEP. This confirms again that DEP is a less effective plasticizer than DBS.

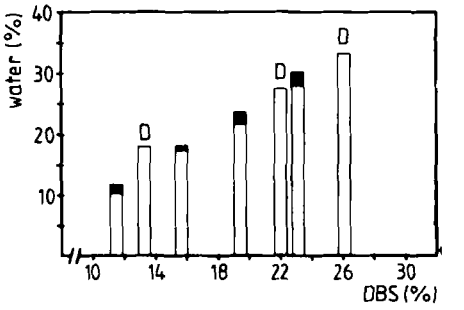

FIGURE 3
Water absorption by DBS-containing EC films prepared from organic solutions or aqueous dispersions (D).
swelling water
water of substitution

Water Uptake and Plasticizer Release of Plasticized Films

Fig. 3 and 4 contain the mean values of the water contents of the films in block diagrams. Both plasticizers cause a considerable absorption of water. The absorption of water is approximately proportional to the plasticizer content and is almost exclusively due to swelling water (percentage increase in weight) in the films plasticized with DBS (Fig. 3). DBS remains almost completely in the films during a five-hour release period (minimum loss of weight after the drying compared to the films used, associated with water of substitution). The behavior of the plasticizer DEP is different in some respects. Along with a continuous increase in extinction at 229 nm, it can be inferred from the great losses from drying that a considerable portion of the DEP leaves the film during the five hour period. The sums of the swel-

ling water and the water of substitution yield almost identical total water contents as in the case of DBS. The percentage of swelling water is markedly lower than in DBS films. While investigations carried out with additives which are readily soluble in water revealed a marked correlation between the volume fraction of the absorbed water and the eluted components (10 - 11), EC membranes absorb proportionally more water with increasing initial DBS and DEP contents, regardless of how high the residual plasticizer content is after watering.

The water absorbed does not seem to occur homogeneously in the membranes, because the watered films are of a milky opaque appearance (12 - 15). The presence of free water ("bulk-like" water) could be inferred from this. The films become clear again only after complete removal of the water at 68 °C or 105 °C. The fact that a considerable portion of the total water is relatively strongly retained by the EC in films which contain DEP as the plasticizer is remarkable: At a drying temperature of 68 °C, the drying does not lead to a complete removal of water, but only after drying for two hours at 105 °C. Similiar distinctions concerning the binding of water were already made in other polymer films (16), and it was inferred that only certain fractions are available for rapid exchange or for drug diffusion. Due to the small amount of water released at 68 °C, DEP-containing films seem to contain a lower percentage of free water than corresponding DBS films. This is impor-

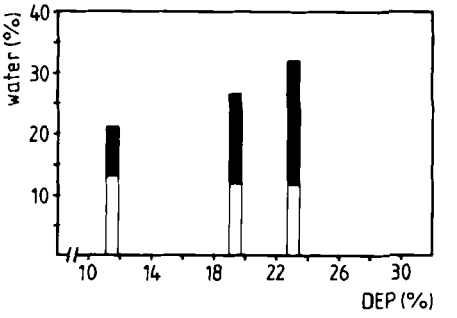

FIGURE 4
Water absorption by DEP-containing EC films prepared from organic solutions
swelling water
water of substitution

tant discussing drug release mechanisms from coated dosage forms (1 - 3).

As Fig. 3 shows, it is irrelevant for the water absorption of the films due to swelling, whether the film is dried from an organic solution (without emulsifying agent) or from an aqueous dispersion.

Film Aging

After storage of films and microcapsules with DBS and DEP, scale-like plates are observed on the surface, which are superimposed to each other in a terraced pattern and cover large areas, together with single crystals (SEM, Fig. 5), independend of the thermal post-treatment (3). The efferences are identified as cetyl-

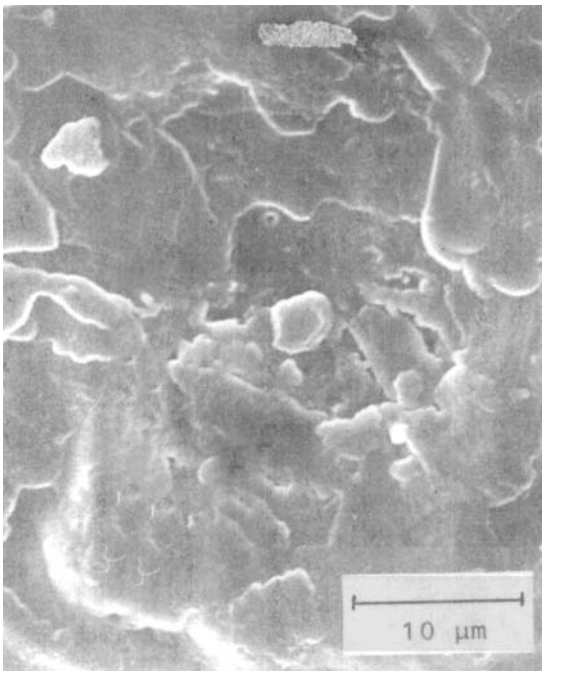

FIGURE 5
Scanning electron micrograph of theophylline microcapsules coated with EC-dispersion; DBS content: 19.4 %, thermal post-treatment: 1 h, 68 °C, standing time of the dispersion: 0 days, storage time of the microcapsules: 3 - 4 months.

alcohol (CA) according to the melting point and to the indentical melting point of a mixture with a reference CA. In some instances sodium lauryl sulfate (NaLS) could be detected with the methode of Bürger (17). In the case of guaifenesin pellets coatet with plasticized Aquacoat^{R} dispersions the release rates decrease during the first 30 days of storage (3). This may be attributed to the squeesing out of the emulsifying agents CA and NaLS.

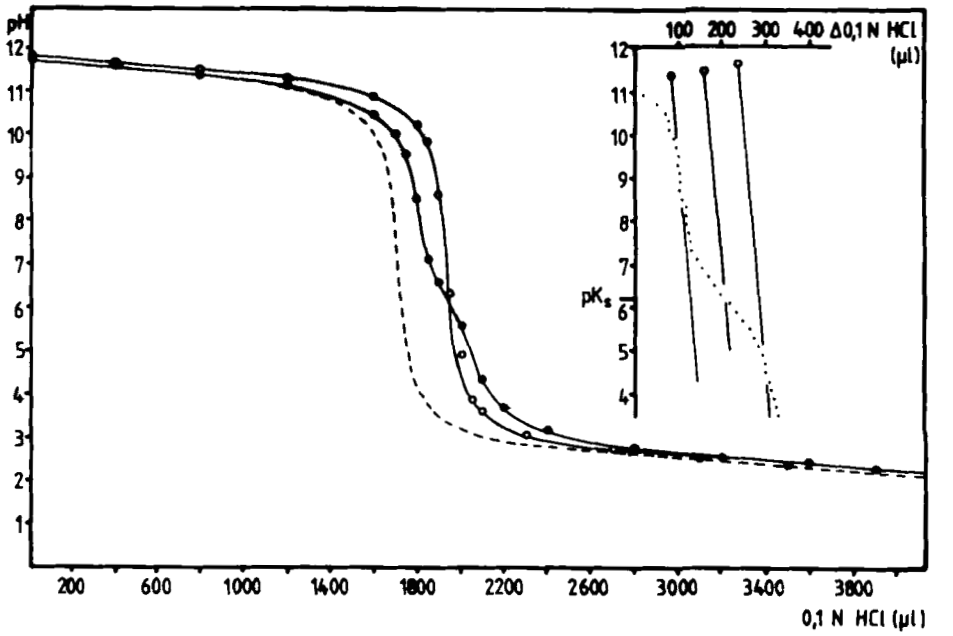

FIGURE 6
Determination of the pK_s-value of the acid function of EC in Aquacoat^R
o——— o Titration curve for 0.1 N NaOH (blank)
------ shifted curve
●——— ● Titration curve for Aquacoat^R in 0.1 N NaOH

Carboxylic Groups in Ethyl Cellulose

The permeability of plasticized EC films is pH dependend. If the permeability coefficients P are plotted as a function of the corresponding pH value, sigmoidal curves are obtained which resemble acid-base titration curves with the highest permeability at pH = 9 and an infection point at pH = 7.5 (1). Investigations on carboxyl groups in microcrystalline cellulose (13 µval/g)

and native cellulose (38 µval/g) were reported in the literature (18); in ethyl cellulose, they can mainly be encountered in the terminal groups of the ethyl cellulose molecules (about 80 µval/g) (19). The experimentally determined value is 25 µval/g, the pK_S = 6.3 (Fig. 6). However the IR and FIR spektra of EC and alkalized EC in comparison to microcrystalline cellulose and sodium carboxymethyl cellulose only weakly suggest the presence of carboxyl groups (3).

Supposing the existence of carboxylic groups its dissociation and hydration may improve the permeability of the coatings (1). The difference of the determined pK_S from the inflection point according to permeability measurements at pH = 7.5 can be explained by the change in the degree of dissociation not being transferred in proportion to the permeability of the shell.

All in all the knowledge of the particular properties of plasticized aqueous ethyl cellulose dispersions and resulting films should help to understand the control of drug release form coated drug preparations such as microcapsules (1, 3, 20).

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