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THE RELEASE OF AN AMPHOLYTIC DRUG FROM ACRYLIC FILMS

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ABSTRACT

Benzyloxiamine was used as an ampholytic drug model to study the in vitro drug release from films in a function of pH. Two films based on commercial acrylic dispersions Scopacryl^{R} and Eudragit^{R} were used as drug carriers. The films investigated were produced by a solvent cast technique. The pH into the films was adjusted at every experiment before cast.

To understand the factors governing the release of the ampholytic drug its protonation/ionization macro- and microconstants have been determined. The protonation macroconstants determined were log K_1= 7.80, log K_2 = 4.26 and log β_2= 12.06. The microconstants calculated were log K^f= 7.79, log K^a= 4.74, log K^f_a= 7.33 and log K^a_f = 4.29.

The release data could be interpreted by taking into account species concentrations calculated by use these

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constants on the one hand and the velocity and diffusion coefficients on the other.

INTRODUCTION

Drugs are often incorporated in acrylic films as part of a transdermal delivery system (2, 6, 8, 14). Following the drug on its pathway from the film into the interphase formed with the horney layer the first step comprises the dissolution and diffusion (1). Higuchi (3) indicated that the chief driving force for diffusion is the thermodynamic activity, which for a weakly acidic drug is inversely proportional to the term 10^{pH}. Pflegel et al. (12) observed an increase in the permeation of an acidic drug through an acrylic film when the pH was decreased and a decrease in the permeation of a basic drug respectivly when the pH was increased.

Summarizing these results one can state that the diffusion respectivly permeation of a drug through an acrylic film occurs by a partition process of the undissociated drug.

It is known that the incorporation of drugs into acrylic films makes possible the preparation of various compositions with an inside pH in a wide scale (2). But the question was not decided how the drug release depends on its ionization degree.

The objective of this study was to determine the influence of pH on the release of an ampholytic drug from acrylic films, using 2-hydroxy-5-carbomethoxybenzyloxyamine as a model compound. For this reason the compound was incorporated in films based on two commercial acrylic dispersions. The pH of the film

has been adjusted by modifying the film forming material before cast. Since Benzyloxyamine may act in four microforms, first we studied its ionization respectivly protonation process at the level of microequilibria.

MATERIALS AND METHODS

Chemicals

Benzyloxyamine was obtained from the Drug Research Institute of Budapest (5). Its good absorption from several dosage forms was stated earlier (13).
Two commercial acrylic copolymers served as film forming materials: PMA, Eudragit E 30 D (Röhm Pharma GmbH Darmstadt, FRG) and PAA, Scopacryl D 340 (VEB Chemische Werke Buna, GDR). The preparation of the films was carried out by a solvent cast technique as described earlier (2).
All the inorganic chemicals were of analytical grade and from Reanal, Budapest, Hungary.

Determination of macro- and microconstants

The pH-metric titrations were carried out at constant ionic strength with 0.1 Mdm^{-3} NaOH and 0.1 Mdm^{-3} HCl solutions as well as 0.4 Mdm^{-3} NaCl as auxiliary electrolyte. The pH was measured by Radiometer pH-M 64 research pH meter and Ingold 104053059 combined electrode. At titrations the temperature was kept constant by ultrathermostat at 25.0 $\pm$ 0.1 ^{o}C.
Spectra were recorded by Specord UV-VIS spectrophotometer, VEB Carl Zeiss Jena, GDR.

Drug release

The drug release was followed as described earlier (2). The amount of drug released was determined spectropho-

tometrically at 258 nm. The amount of drug released was calculated and plotted as a function of square root of time on a personal computer HP 85 (Hewlett Packard Corvallis, Oregon 97330, USA).
Utilizing the slope of the straight line of this plot the apparent diffusion coefficient was determined by a modificated Higuchi equation (4):

$$D = \frac{a^2 \pi}{(2c_o)^2} \qquad \text{(Eq.1)}$$

D = apparent diffusion coefficient ($cm^2 s^{-1}$)
a = velocity coefficient ($M \cdot cm^{-2} \cdot s^{-0.5}$)
c_o = initial drug concentration ($2.8 \cdot 10^{-4} M cm^{-3}$)

RESULTS AND DISCUSSION

Benzyloxyamine may act in four microforms (Figure 1). Consider the complete ionization scheme the macro- and microconstants and their relations (9) are as follows:

$$\beta_1 = K_1 = \frac{[BH]}{[B^-][H^+]} \qquad \text{(Eq.2)}$$

$$\beta_2 = K_1 K_2 = \frac{[BH_2^+]}{[B^-][H^+]^2} \qquad \text{(Eq.3)}$$

$$\beta_2 = k^f \cdot k_f^a = k^a \cdot k_a^f \qquad \text{(Eq.4)}$$

$$K_1 = k^f + k^a \qquad \text{(Eq.5)}$$

$$K_2 = \frac{[BH_2^+]}{[BH][H^+]} \qquad \text{(Eq.6)}$$

$$k^a = \frac{[^-OBH^+]}{[^-OB][H^+]} \qquad \text{(Eq.7)}$$

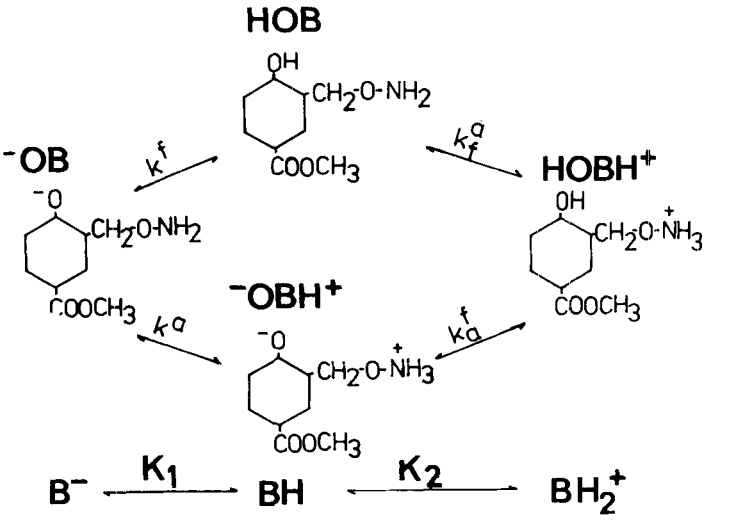

FIGURE 1

Scheme of protonation microequilibria for Benzyloxyamine

$$k^f = \frac{[HOB]}{[^-OB]\,[H^+]} \qquad \text{(Eq.8)}$$

$$k_f^a = \frac{[HOBH^+]}{[HOB]\,[H^+]} \qquad \text{(Eq.9)}$$

$$k_a^f = \frac{[HOBH^+]}{[^-OBH^+]\,[H^+]} \qquad \text{(Eq.10)}$$

The superscripts of k microconstants indicate the protonation group in the given process (a = amino, f = phenolate), while subscripts if any stand for the group holding already proton.

The protonation macroconstants of Benzyloxyamine could be determined by pH-metry:

$$\log K_1 = 7.80 \pm 0.02$$

$$\log K_2 = 4.26 \pm 0.03$$

$$\log \beta_2 = 12.06 \pm 0.05$$

The pH-dependent UV spectra show that the proton dissociation around pH = 7.8 is accompanied by the appearance of a band at 298 nm, while the other band at 256 nm diminishes. On the other hand protonation around pH = 4.26 causes only slight spectral change. On this basis it is obvious that the process at pH = 7.8 can be assigned to the phenolate group. The more than three orders of magnitude difference between the protonation macroconstants indicate that the minor protonation isomer species $^{-}OBH^{+}$ occurs in a very low concentration. For this reason the determination of microconstants is not feasible from pH-metric and spectroscopic data only. Considerations for microconstants of related molecules, namely tyrosine derivatives, are also necessary.

The effect of one group on the basicity of the other group in a molecule is expressed by the difference between the log microconstants of the same group. This valued by Eq.11 for para-tyrosine is 0.38.

$$\Delta \log k = \log k^{f} - \log k_{a}^{f} = \log k^{a} - \log k_{f}^{a} \quad \text{(Eq.11)}$$

The analogous data for meta-tyrosine is 0.42 (7). Consequently, the effect of the meta-para relocation of the phenolic hydroxyl results in an 0.42 - 0.38 = 0.04 increase of $\Delta \log k$. The meta-ortho modification certainly causes a similar change. Accordingly, at Benzyloxyamine the effect of the neighboring group can be estimated as $\Delta \log k = 0.42 + 0.04 = 0.46$. Using this value and the macroconstants, the microconstants could be calculated:

$$\log k^{f} = 7.79 \qquad \log k^{a} = 4.74$$

$$\log k_{a}^{f} = 7.33 \qquad \log k_{f}^{a} = 4.29$$

The microconstants made possible the calculation of microspecies concentrations (Table 1). The relative

TABLE 1

Relative concentrations of Benzyloxyamine microspecies as a function of pH, in $-\log \gamma$ units

pH	OB^-	HOB	$^-OBH^+$	$HOBH^+$
0	12.08	4.29	7.34	0.00002
2	8.08	2.29	5.34	0.0023
4	4.26	0.473	3.52	0.183
5	2.88	0.086	3.14	0.796
6	1.81	0.024	3.075	1.73
7	0.86	0.075	3.12	2.78
8	0.212	0.422	3.47	4.13
9	0.026	1.24	4.28	5.95
10	0.0027	2.21	5.26	7.92
12	0.000027	4.21	7.26	11.92
14	0.00000027	6.21	9.26	15.92

concentrations γ can be converted into concentrations in percentage by Eq.12.

$$C_{rel} = 100 \cdot 10^{\log \gamma} \qquad [\%] \qquad \text{(Eq.12)}$$

The pH at which the zwitter ion concentration is a maximum is known as the isoelectric point. The lines labelled $HOBH^+$ and ^-OB in a $\log \gamma$ versus pH diagram (Fig.2) intersect at the isoelectric point (10). The macroconstants could also be used to calculate the isoelectric point by use Eq.13 (10).

$$pH_i = -\log [H_3O^+]_i = (K_1 K_2)^{0.5} = 6.03 \qquad \text{(Eq.13)}$$

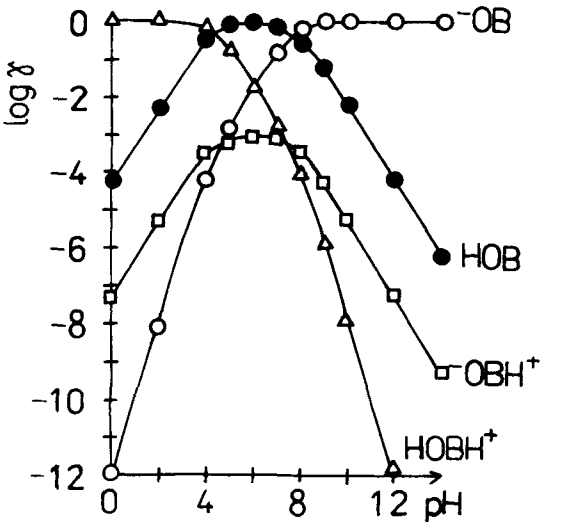

FIGURE 2

Distribution of Benzyloxyamine microspecies ($\log \gamma$) in the function of pH

However, it is important that in biological processes the dominating microspecies is not necessarily the reactive one (11).

A follow-up to this part of the experiment the release properties of the films were determined by means a method described earlier (2). In the time period from 30 to 390 min there was in all cases a linear relationship between the amount of the drug released and the square root of time in accordance with the model proposed by Higuchi (4) (Fig.3).

The slope of the straight lines a, after Kehne et al. (6) also called velocity coefficient, can be used to calculate the apparent diffusion coefficient D (Eq.1). D calculated in this way ranged from 0.17 to $9.78 \cdot 10^{-9}$ for PMA and from 0.35 to $3.29 \cdot 10^{-9}$ $cm^2 s^{-1}$ for PAA.

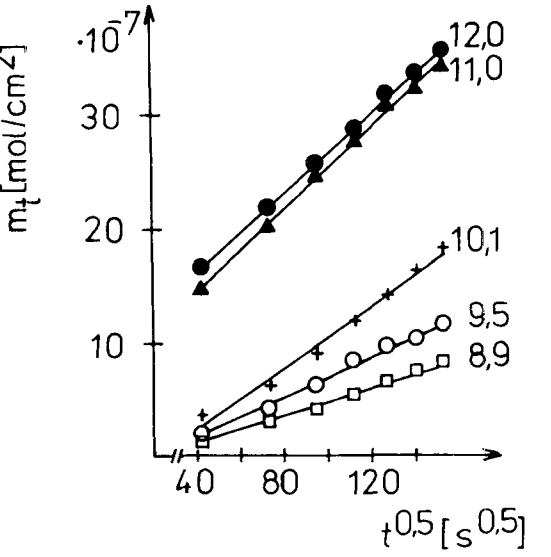

FIGURE 3
Amount of drug released m_t versus $t^{0.5}$ (PAA films)

For both types of films a was plotted as a function of the film pH (Fig.4).
In both cases the curves calculated show in the basic pH range upward tendency at greater pH values. Besides the release from the PMA-films increases again below pH 6. The PAA-films are instable at this pH range.
It was obvious that the change noted in the velocity coefficients depends on the pH and the HOB concentration respectivly the concentration of ionizing drug C_I. C_I was calculated by use Eq.12 and 14 as follows:

$$C_I = 100 - C_{rel}(HOB) \qquad [\%] \qquad \text{(Eq.14)}$$

For the pH range from 7 to 12 and both types of films C_I was plotted as a function of the film pH (Fig.5). In the same way the relative velocity coefficients are plotted. They are calculated by Eq.15.

$$a' = \frac{a}{a_{max}} \cdot 100 \qquad [\%] \qquad \text{(Eq.15)}$$

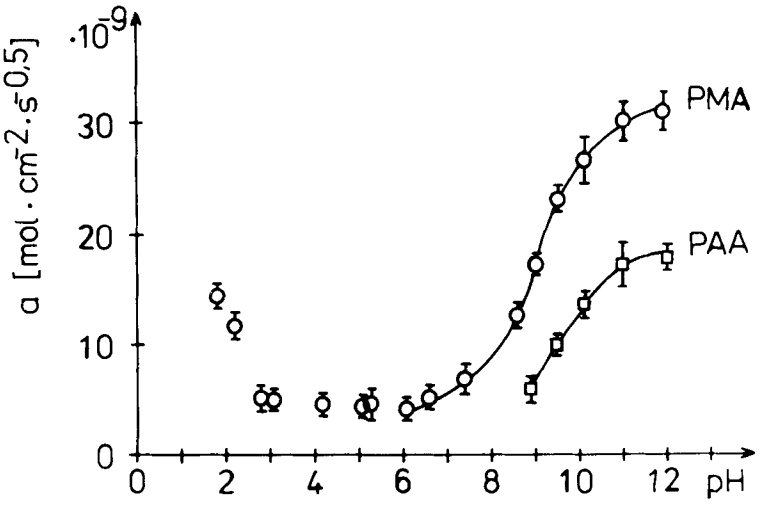

FIGURE 4

Relationship between velocity coefficients a and pH of PMA- and PAA- films

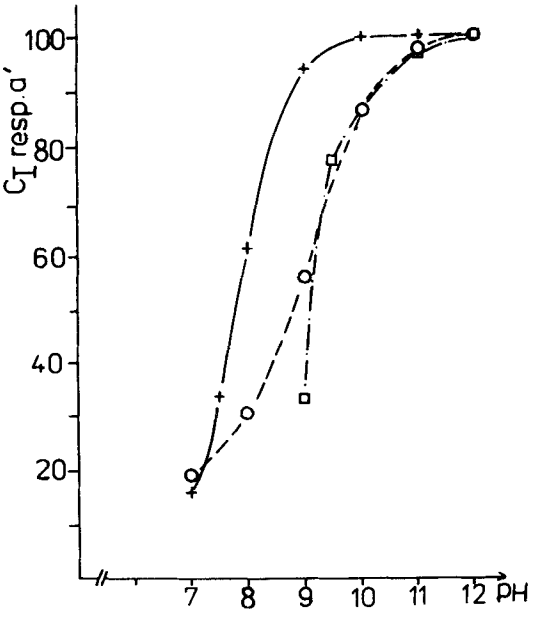

FIGURE 5

Relationship between the concentration of ionizing drug C_I, the relative velocity coefficients a' and pH

C_I and a' are in agreement in their change with the pH similar to a titration curve. These results are in general agreement with the work of Pflegel et al. (12). Whilst the authors have found an increase of permeation rate when the drug ionization was decreased it was just in the release process the other way round.

CONCLUSIONS

On the basis of the microconstants as well as the pH-metric and spectroscopic results the acid-base properties of Benzyloxyamine can be summarized as follows:

- The HOB-form predominating in neutral solution contains phenolic hydroxyl and aminooxy groups, which are able to dissociate and protonate, respectively.
- In basic solution the anionic ^-OB and at low pH the cationic $HOBH^+$ species are in overwhelming majority.
- At neutral pH two isomeric species, the neutral HOB and the zwitterionic $^-OBH^+$ predominate, of which HOB is the more abundant one.

On the basis of our experimental drug release data compared to the results of Pflegel et al. (12) permeation studies on PAA-films the following conclusions could be drawn:

- The velocity coefficients depend on the concentration of the ionizing drug and the higher C_I, the greater a and the rate of the drug released.
- This effect is independent on the film forming material, but at the same pH the release from PMA-films is greater than from PAA-films.
- The data obtained suggest that the drug release from acrylic films follows a dissolution mechanism whilst the permeation through the films follows a such one of partition.

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