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INFLUENCE OF THE BUFFERING CAPACITY OF THE MEDIUM ON THE DISSOLUTION OF DRUG-EXCIPIENT MIXTURES.

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ABSTRACT

The dissolution rates of benzoic acid/salicylic acid (BA/SA) and indomethacin/citric acid (IMC/CA) drug/excipient mixtures in media of different buffering properties were examined. The dissolution rates of the drug from both pure and mixed discs were found to be dependent on the buffering capacity of the dissolution medium. The acid excipient decreased the dissolution rate of the drug. In the presence of the second acid, the enhancing effect of increasing the buffer strength on the dissolution rate of the drug, was lowered. Buffer capacity versus pH profiles prepared for each buffer system showed the shape of these profiles to be an intrinsic property of the buffering agent(s) used. The differences in dissolution profiles observed in media of similar pH but different composition may be explained in terms of the buffering capacity of the medium. The pH-buffering capacity profiles of human duodenal aspirates were also examined. In contrast to the in vitro dissolution media, the human duodenal samples showed relatively constant buffering capacities in the pH range 4-8 and were below 20mm of

HCl/litre. We conclude that the buffering capacity of the medium is an important consideration in the design of dissolution media if successful in vitro-in vivo correlation is to be obtained.

INTRODUCTION

The composition of the dissolution medium is a major variable in the design of dissolution testing procedures. Of particular importance in the case of drugs, which are weak acids or weak bases, is the pH of the medium. The properties of the dissolution medium may also influence the ionisation of formulation excipients which in turn may control the solubility and dissolution rate of the drug. A number of recent reports have shown that the release of quinidine gluconate from controlled release products was highly sensitive to medium pH in the range 1 to 8 and at a given pH was dependent on the buffering agents present in the medium[1,2]. The dissolution rate of weak carboxylic acids, at a constant pH, has also been shown to be a function of the total buffer concentration in the dissolution medium[3,4]. The dissolution rate of weak carboxylic acids in buffered media at a given pH was found to increase asymptotically with increasing buffer concentration and reaches a maximum value when the pH at the interface (pH_o) approaches the pH in the bulk solution (pH_{bulk})[3,4]. Previously we reported that the presence of a second acid retarded the release rate of the acid drug in a buffered medium[5,6]. The retarding effect of the acid excipient on the drug dissolution rate was more pronounced the lower the agitation rate[6].

EXPERIMENTAL

Materials

Benzoic acid, salicylic acid and citric acid (monohydrate) used were of analytical grade (Reidel de Haen). Indomethacin (γ-indomethacin) was of USP grade.

Solubility Determinations

The solubilities of drug and drug/excipient mixtures in a range of media were determined at 37°C as previously described[5]. Equilibrium was achieved within 48 hours and samples were filtered through 0.2μ membrane filters(Gelman Sciences Inc.) . On dilution samples were assayed by UV spectroscopy using a Shimadzu UV160 spectrophotometer.

Dissolution Rate Method

Dissolution profiles were determined at 37°C from compressed discs of drug mounted in paraffin wax as previously described.[5] Powders were ground to a sub 210μ particle size before compression. The pH of the dissolution medium was monitored using a pH meter (PHM82 Radiometer) and when pH control was required a pH-stat (Radiometer) was employed. A stirring speed of 60 r.p.m. was used. Dissolution rates were obtained by linear regression analysis from all the data throughout the dissolution runs. Limiting rates for IMC were obtained from the 60-120 minute data using linear regression analysis.

Buffering Capacity Determinations

The buffering capacity of acetate, Tris and phosphate buffer systems and human duodenal aspirates were measured by titrating 3-5 mls aliquots with HCl solution using an autoburette titrator (Radiometer). The pH of the solution after each addition of HCl was recorded against the total volume of HCl (C_a) added. The gradient at each recorded pH, $(-\partial Ca/\partial pH)$, which is the buffering capacity at that pH, was calculated and corrected for dilution due to the added HCl.

RESULTS AND DISCUSSION

Dissolution of benzoic acid. The dissolution profiles of benzoic acid from pure and 1:1 benzoic acid:salicylic acid discs in distilled water pH 6.05,

Tris buffer pH 7.40 and phosphate buffer pH 7.34 were linear as shown in figure 1 (A & B). The dissolution rates of benzoic acid from both the pure and the mixed discs were faster in the phosphate buffer, the rate being about twice the rates obtained in Tris buffer and in distilled water. Since benzoic acid has a high intrinsic solubility, it will self-buffer the microenvironment at the solid-liquid interface unless the concentration of the buffer base in the dissolution medium is high enough to overcome this effect. Since phosphate buffer has a pK_{a2} at 7.21[7], it is a stronger buffer at pH 7.34 than Tris (pK_a= 8.2)[8] at pH=7.40. The dissolution rates of benzoic acid from the 1:1 benzoic acid:salicylic acid discs were lower than the corresponding rates for the pure acids. The presence of the second acid therefore decreased the enhancing effect of the buffer on the dissolution rate of the acidic drug.

Dissolution of indomethacin. The dissolution rates of indomethacin from pure IMC discs in 0.0334M, 0.0668M and 0.1336M phosphate buffer pH 7.34 were faster than in distilled water pH 6.05 as shown in figure 2. The dissolution rate in the buffered media were forty fold higher than in distilled water. However increasing the buffer concentration at the same pH did not increase IMC dissolution rate. Indomethacin has a very low intrinsic solubility ($3.27*10^{-6}$ M/l) and therefore very little self-buffering capacity. As a result its dissolution rate is more sensitive to the bulk solution pH than is the dissolution rate of benzoic acid. The pH of a saturated solution of IMC in 0.0668 M phosphate buffer pH 7.34 was 7.11 which is equivalent to the pH at the solid-liquid interface[9] and is very close to the pH of the bulk solution (pH_{bulk}). As the pH_o reaches pH_{bulk}, the dissolution rate would reach a maximum. Aunins et al[4] found that the dissolution rate of α-IMC in phosphate buffer pH 7 reached a plateau as the total buffer concentration was increased.

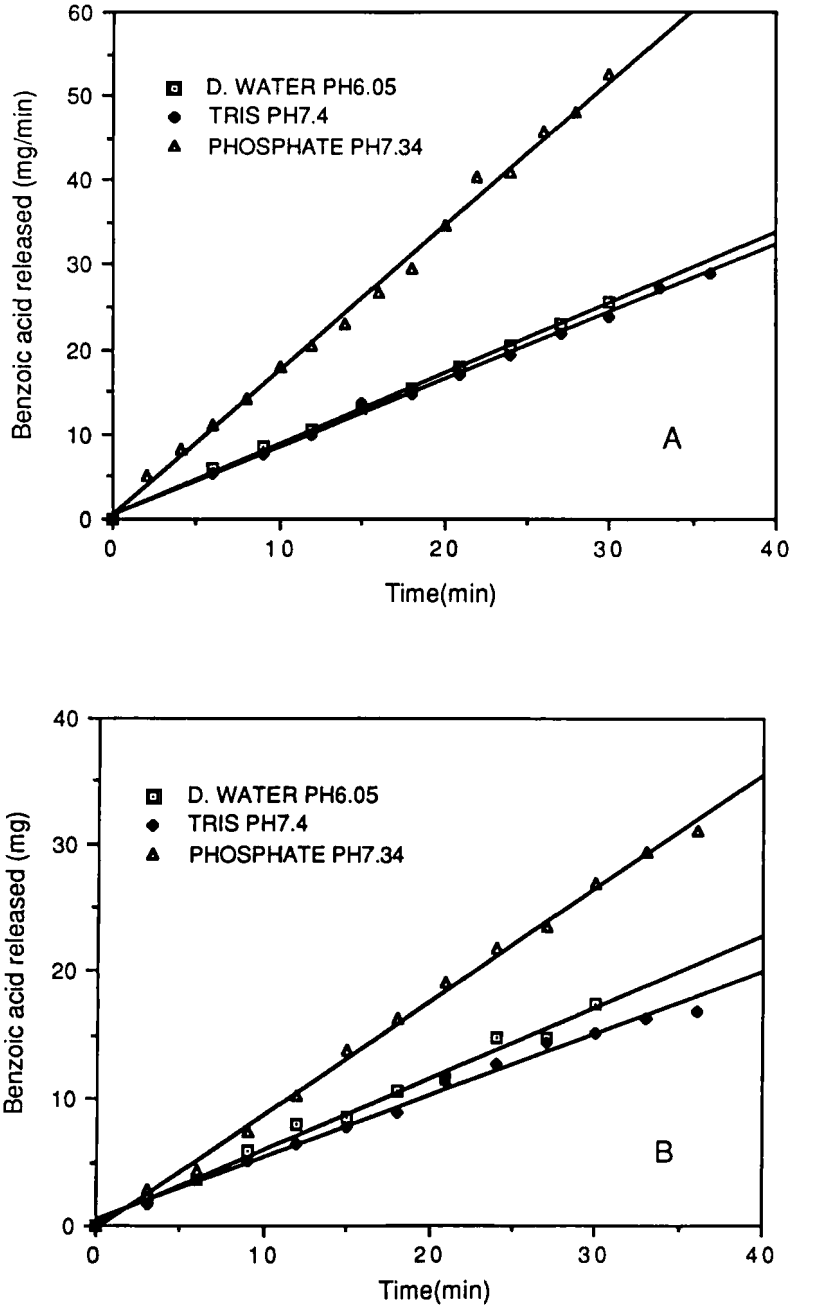

FIGURE 1

Dissolution profiles of benzoic acid from (A) pure benzoic acid and (B) 1:1 benzoic acid: salicylic acid discs dissolving in different media.

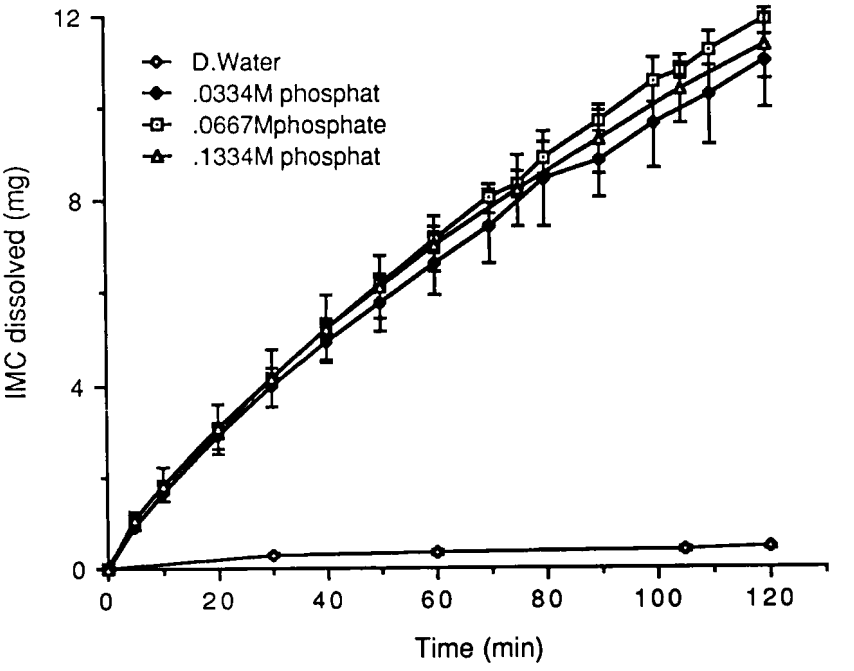

FIGURE 2
Dissolution profiles of IMC from pure IMC discs dissolving in media having increasing buffering strengths.

The dissolution rate of IMC from 1:1 IMC:CA discs increased as the concentration of phosphate buffer was increased as shown in figure 3. The positive curvature observed at certain compositions of IMC:CA reported previously[6] was observed in 0.0334M and 0.0668M phosphate buffer. However the dissolution profile in 0.1336M phophate buffer was linear as shown by the mean and limiting rates given in table 1.

Unlike the dissolution rates of IMC from the pure discs, the dissolution rates of IMC from 1:1 IMC:CA discs increased significantly with increasing buffer concentration. However the dissolution rates of IMC in the presence of citric acid were lower than the rates from pure IMC discs.

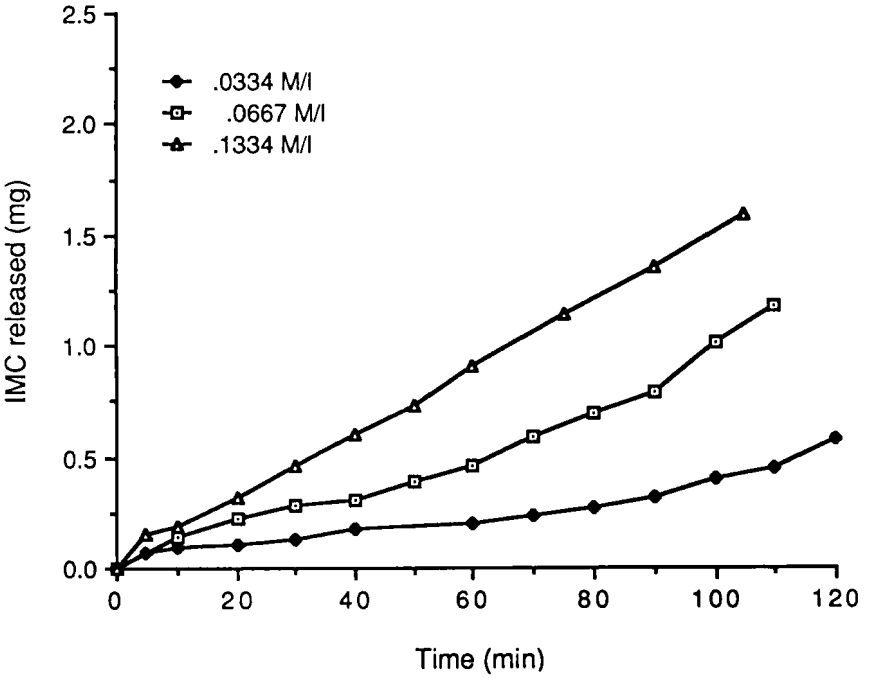

FIGURE 3

Dissolution profiles of IMC from 1:1 IMC:CA discs dissolving in increasing concentrations of phosphate buffer pH 7.34.

TABLE 1

Dissolution rates and limiting rates, X±SD, of IMC from 1:1 IMC:CA disc dissolving in increasing concentrations of phosphate buffer at pH 7.34

[phosphate] (M/l)	dissolution rate (mg/min)	limiting rate (mg/min)
0.0334	0.0045±0.0020	0.0060±0.0010
0.0668	0.0092±0.0020	0.0140±0.0060
0.1336	0.0155±0.0007	0.0154±0.0006

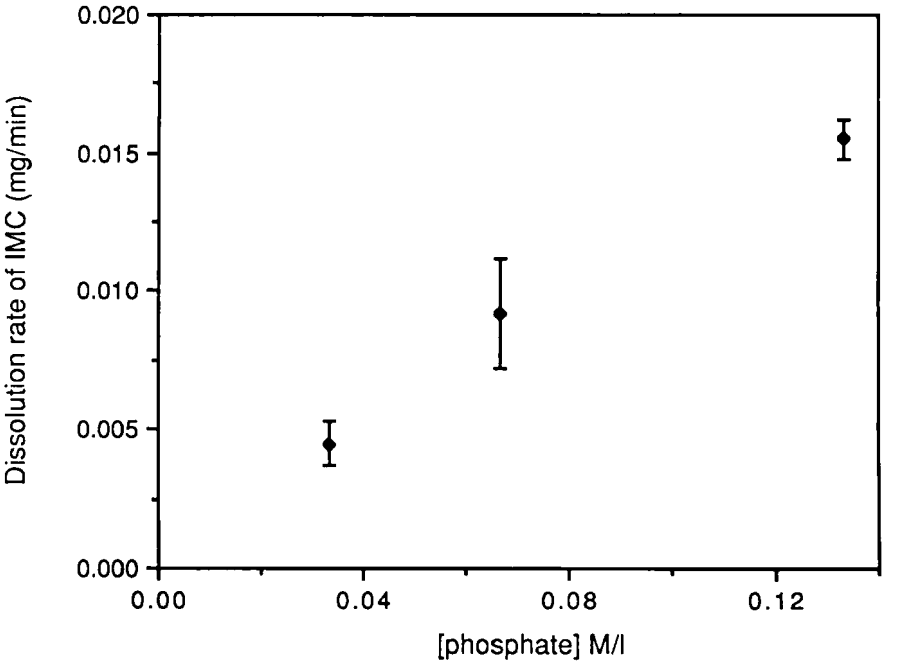

FIGURE 4
Relationship between the dissolution rates of IMC from 1:1 IMC:CA discs and the concentration of the phosphate buffered dissolution media.

This retarding effect of the acid excipient on the IMC dissolution rate was more pronounced at the lower buffer concentrations. A plot of the mean dissolution rates of IMC against buffer concentration (figure 4) shows a nonlinear relationship. A similar relationship was observed for IMC release from 1:1 IMC:CA discs dissolving at increasing agitation rate[6]. As stirring speed was increased, h decreased and therefore the flux of the buffer was increased resulting in a higher pH_o and dissolution rate of IMC. Similarly an increase in the buffer concentration in the bulk solution causes an increase in the flux of the buffer base across the diffusion layer which neutralises the citric acid. As a result the pH at the interface (pH_o) increases and the dissolution rate of IMC also increases, i.e. increasing

the buffer concentration in the bulk solution decreases the suppressing effect of citric acid on IMC release. With increasing buffer concentration, the pH at the interface will increase to a maximum value when pH_o equals the pH of the bulk solution. The dissolution rate of IMC may therefore increase with the surface pH to a maximum dissolution rate at pH_o equals pH_{bulk}.

The dissolution rate of an acid (HA) in an aqueous unbuffered medium depends on the intrinsic solubility of the dissolving acid and the extent of ionisation (i.e. the pK_{aA}) of the acid. In buffered media, however the dissolving acid will also react with the buffer base (B), the extent of this reaction depending on the buffer base concentration which in turn depends on the pK_a of the buffer (pK_{aB}) as shown by the equilibrium:

$$HA + B \rightleftharpoons A^- + BH^+ \qquad \text{eq. 1.}$$

The equilibrium constant, K_{ab}, for the reaction is given by:

$$K_{ab}=[A^-]*[BH^+]/[HA]*[B] \qquad \text{eq. 2.}$$

since $K_{aA} = [A^-]*[H^+]/[HA]$ and $K_{aB} = [B]*[H^+]/[BH^+]$, K_{ab} is also equal to K_{aA}/K_{aB}. Buffers with a high K_{aB} value will tend to favour the formation of the buffer base [B]. The dissociation constant of the buffer also determines the buffering capacity of the buffer at a given pH, the maximum buffering capacity of a buffer occurring when pH equals the pK_a of the buffer:

$$pH = pK_a + \log ([salt]/[acid]) \qquad \text{eq. 3.}$$

The buffer capacity is also described by the Van Slyke's buffer index ,ß, which is defined as $\partial C_b/\partial pH$ or $-\partial C_a/\partial pH$ where C_a and C_b are the

concentrations of the strong acid or base added to the buffer system.[7] For a monoprotic buffer system, neglecting the contribution of the water present, the buffer capacity is calculated using the following equation[7]:

$$\beta = 2.303 * C * [H+] * K_a / (K_a + [H+])^2 \qquad \text{eq. 4.}$$

where C and K_a are the concentration and ionisation constant of the buffer respectively. For a polyprotic buffer system, e.g. phosphate buffer, provided that the successive ionisation constants are not too close i.e. $K_{a2}/K_{a1} < 0.05$, it can be considered as a mixture of monoprotic acid of equal concentration and the buffer capacity may be calculated by[7]:

$$\beta = \beta_{H_2O} + \beta_{H_3PO_4} + \beta_{H_2PO_4^-} + \beta_{HPO_4^{2-}} \qquad \text{eq. 5.}$$

From equation 4, at pHs other than the pKa, ß is a function of both the pK_a and the concentration of the buffer components present. At pH = pKa, ß is proportional to the concentration of the buffer components. Therefore the buffer capacity of a buffer system will increase with increasing buffer concentration and will be greater at pHs nearer the pK_a of the buffer acids. Phosphate buffer has three pK_as[7] : 2.23, 7.21 and 12.32. At pH 7.34, its buffering capacity is greater than that of Tris buffer pH 7.4 (pK_a=8.2)[8]. The experimentally determined dissolution rates of benzoic acid from pure discs and 1:1 BA:SA discs at a given pH (≈7.4) differed depending on the buffer used. From eq. 1 the degree of reaction between the dissolving acid and the buffer and hence the dissolution of the acid is dependent on the pK_a of both the acid and the buffer. The dissolution rates of IMC from 1:1 IMC:CA discs in phosphate buffer pH 7.34 increased with increasing buffer concentration.

Buffering Capacity-pH Profile of Buffers used in Dissolution Studies.

The experimentally determined pH versus buffering capacity profiles of 0.0334M, 0.0668M and 0.1336M phosphate buffers are plotted in

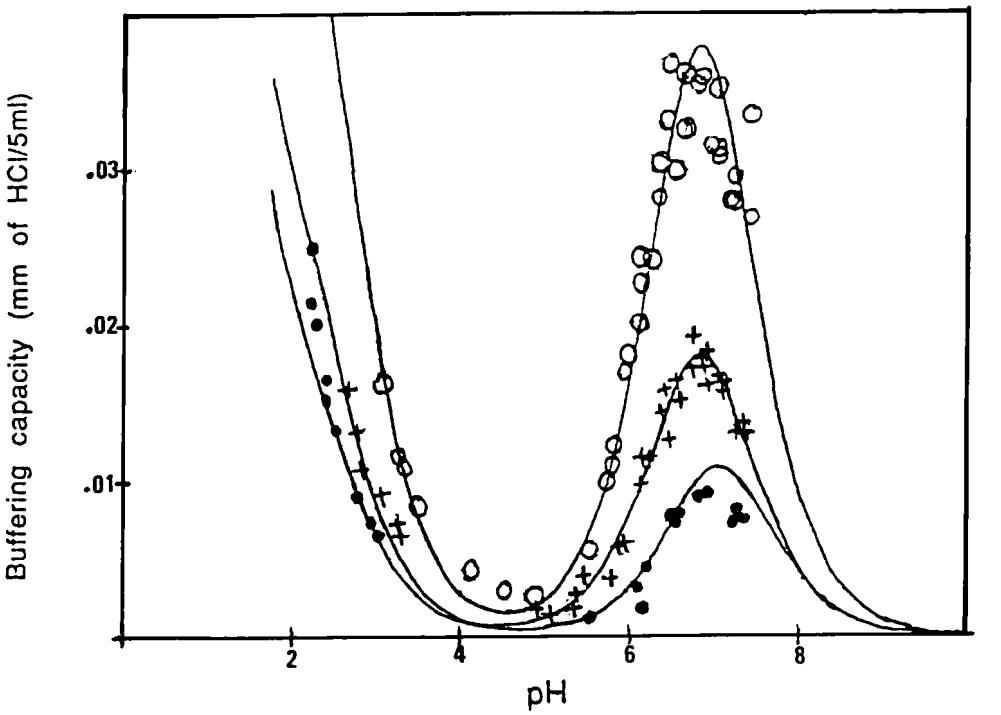

FIGURE 5

pH-buffering capacity profiles of increasing concentrations of phosphate buffers pH 7.34. key: • 0.0334M, + 0.0668M, o 0.1336M, – theoretical fit.

figure 5 together with the theoretical buffering capacities calculated from equation 5 using the pK_a values estimated experimentally. The maximum buffering capacity ($ß_{max}$) occurs at $pH=pK_a$. As predicted by equation 4, the buffering capacity at a given pH increased as the buffer concentration was increased.

Figure 6 show the experimental and calculated buffering capacity-pH profiles of acetate and phosphate buffers pH 5.4 and 0.05M Tris buffer pH 7.4, which have been used as in vitro dissolution test media. From the buffering capacity profiles, phosphate buffer is the stronger buffer in the pH region 6-7.5, i.e. has the greater buffering capacity, while acetate and

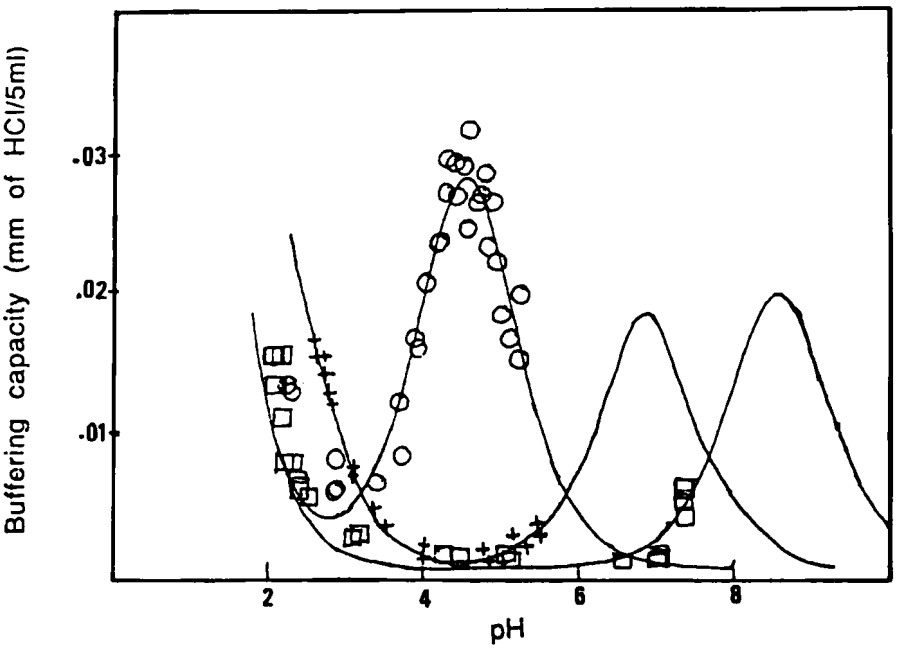

FIGURE 6

pH-buffering capacity profiles of acetate, Tris and phosphate buffers. Key: o 0.10M acetate pH 5.4, + 0.0668M phosphate pH5.4, □ 0.05M Tris pH 7.4 and – theoretical fit.

Tris buffers show poor buffering capacity in this pH region. In the pH region 4 to < 6, acetate buffer (pK_a = 4.75)[7] is the stronger buffer, showing greater buffering capacity than Tris and phosphate buffers at these pH.

The difference in the buffering capacity of Tris and phosphate buffers around pH 7.4 is consistent with the higher dissolution rates of benzoic acid from both pure and mixed (SA:BA) discs in phosphate buffer pH 7.34 compared to Tris buffer pH7.4. The dissolution rates in phosphate buffer were about twice the rates obtained in the Tris buffer i.e. the dissolution rate of benzoic acid was faster in a stronger buffer at a lower pH than in a weaker buffer at a higher pH. The buffering capacity of the

medium may therefore be more important than the pH of the medium in controlling the release rate of solutes. For IMC dissolving from 1:1 IMC:CA discs, increasing the buffer concentration resulted in an increase in its dissolution rate. The buffering capacity versus pH profiles in figure 5 shows an increase in the buffering capacity with an increase in concentration of the buffer. Therefore as the buffer concentration increases, its resistance to pH change increases, i.e. the change in the pH of the microenvironment due to the dissolving acids decreases as the buffer concentration increases.

In the pH region of 4 to <6, acetate buffer has a greater buffering capacity than the phosphate buffer. Skelly et al[2] observed that the dissolution rate of quinidine gluconate from different formulations were higher in acetate buffer pH 5.4 than in phosphate buffer pH 5.4. The higher dissolution rates observed in the acetate buffer may be due to the greater buffering capacity of the acetate buffer at pH 5.4. At that pH the acetate buffer will resist changes in pH to a greater extent than the phosphate buffer. Skelly et al[2] also showed that the difference in the dissolution results obtained in the phosphate buffer pH 5.4 correlated better with the bioavailability differences observed.

Buffering Capacity-pH Profile of Human Duodenal Samples.

In view of the effect of buffer composition on dissolution rate, the pH versus buffering capacity profiles of duodenal samples from human subjects (n=26) were determined. Of the patients, 14 were classified as normal while 12 patients had gastrointestinal disorders (abnormal) at endoscopy. The measured buffering capacities versus pH of the normal and anormal samples are plotted in figure 7 together with the profile of 0.1M bicarbonate buffer calculated using a pK_a value of 6.1. The buffering capacity of the samples, both normal and anormal, were relatively constant in the pH range 4 to 8 and were below 0.1mm of HCl per 5ml (or 20 mm HCl/litre). However the 0.1 N bicarbonate buffer

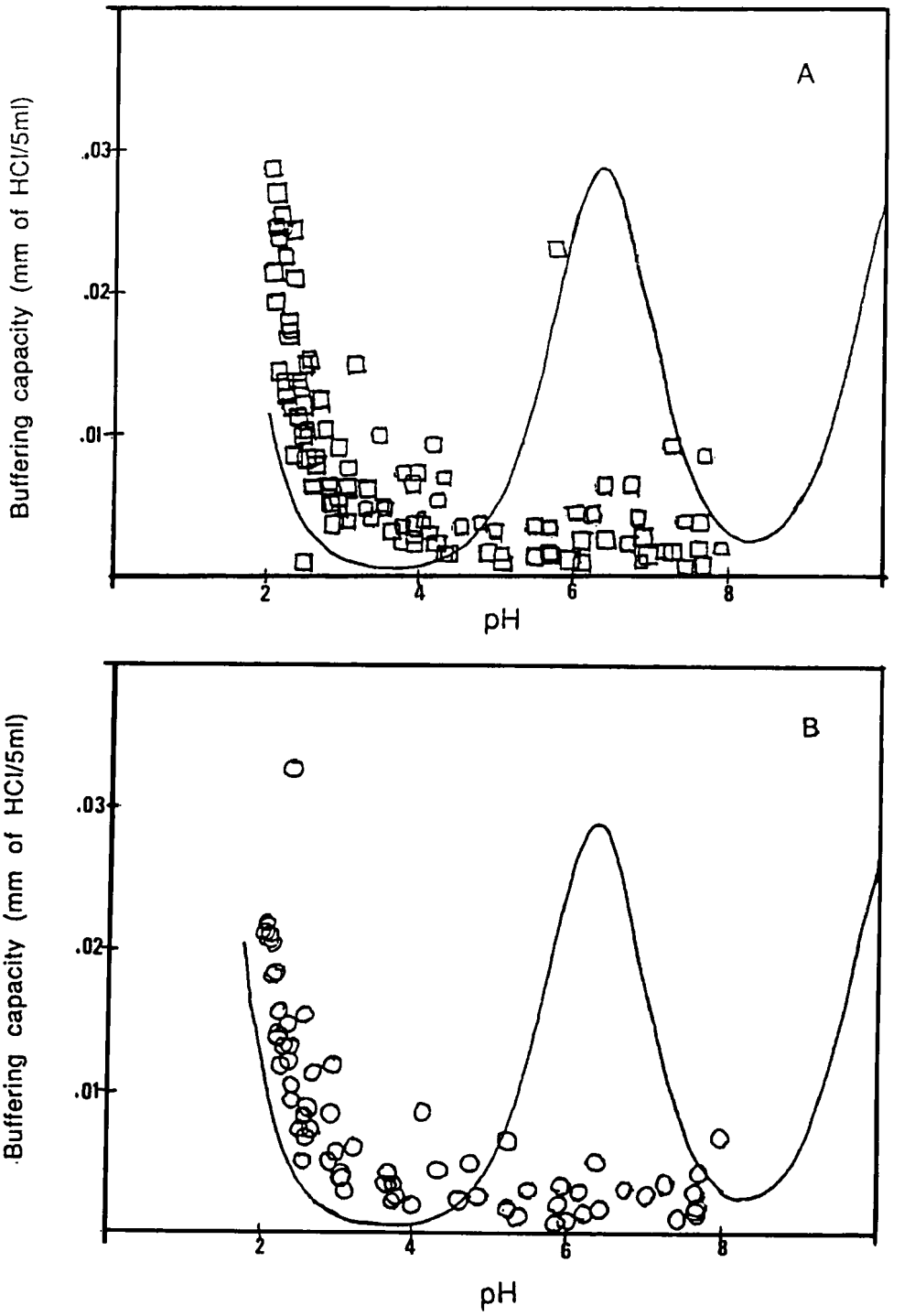

FIGURE 7

Buffering capacities versus pH for (A) normal human duodenal samples (n=14) and (B) abnormal human duodenal samples (n=12). The continuous line is the theoretical pH-buffering capacity profile of 0.1M bicarbonate buffer.

system shows maximum buffering capacity in the pH range of 5-7. This suggests that while bicarbonate is expected to be the buffering system in the duodenal samples other buffer constituents may also be present. The phosphate and Tris buffers had buffering capacity ≤ 0.1mm HCl/5ml in the pH range of 4-6 while the buffering capacity of 0.1M acetate buffer was > 0.1mm HCl/5ml in the pH range of 4-6 with a maximum buffering capacity at pH equals 4.56.

The results obtained show that while the pH of the dissolution medium is an important factor controlling the dissolution rate of solutes, the buffering capacity of the medium may exert a greater influence on dissolution. The buffering capacity of the buffers used vary widely over the pH range and is optimum at certain pHs. In contrast, human duodenal samples showed relatively constant buffering capacity over the pH range of 4-8 and therefore the buffer systems examined did not simulate the in vivo situation.

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