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EFFECT OF AGITATION INTENSITY ON THE DISSOLUTION RATE OF INDOMETHACIN AND INDOMETHACIN-CITRIC ACID COMPRESSED DISCS

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ABSTRACT

The dissolution rates of indomethacin (IMC) and indomethacin-citric acid (monohydrate) 1:1 mixtures under various hydrodynamic conditions were determined in a phosphate buffered medium.Dissolution profiles of the γ form of IMC were nonlinear,the rates decreasing with time.The dissolution rates increased with increasing stirring speed.In contrast α-IMC gave linear dissolution profiles,the rates being higher and more sensitive to agitation intensity than those obtained using the γ-form. The slope of a log dissolution rate versus log stirring speed plot had a value of 0.598 for α-IMC and 0.171 for γ-IMC.Indomethacin dissolution rates from the mixed discs were 5-10 times lower than those of pure γ-IMCin the stirring speed range 180-60 rpm respectively.The dissolution profiles of IMC showed positive curvature at low stirring speed while at high stirring speed the dissolution profiles became linear.The slope of the log dissolution rate versus log stirring speed plot was nonlinear and ranged from >1 at low stirring speed to < 0.5 at high stirring speed.

INTRODUCTION

The relationship between dissolution rate and agitation intensity for single component compressed nondisintegrating systems has been investigated[1]. In general these studies indicate that the dissolution process is diffusion controlled for many pharmaceuticals. However, a number of cases where the surface reaction offers a significant resistance to mass transfer have been reported[2,3]. Furthermore,there have been few if any reports on the effect of agitation intensity on the dissolution rates of such systems containing more than one dissolving component.The dissolution rate per unit surface area(G) of a single compressed component is given by:

$$G = K_{app} \cdot C_S \qquad \text{eq.1}$$

where K_{app} is the apparent dissolution rate constant and C_S is the solubility.The relationship between dissolution rate (G) and stirring speed (RR) may be expressed by:

$$G = K * (RR)^b \qquad \text{eq. 2}$$

where K and b are constants. If mass transfer is transport controlled,b will have a value in the range 0.5-1.0[4].The magnitude of b can be used to characterise the type of agitation in the system i.e. turbulent or laminar[4].A value of 0.5 generally indicates laminar flow,while higher indices are indicative of turbulent flow.In propellor agitated systems,values of b for transport controlled dissolution are normally in the range 0.6-0.8.Values of less than 0.5 generally indicate significant surface control of the dissolution process .In this report we have examined the effect of hydrodynamic conditions on the dissolution rates of IMC and IMC-citric acid 1:1 mixtures using the static disc method.The values of b obtained indicate that the dissolution of α-IMC is diffusion controlled while the value of b for γ-IMC suggests significant surface control for this polymorph .

EXPERIMENTAL

Materials

α-IMC was prepared by a modification of the method of Borka[5] i.e. IMC was dissolved in a minimum amount of ethanol at 80°C and excess cold water at room temperature was added to it.The precipitated crystals were filtered off and dried in a dessicator under vacuum at room temperature.

γ-IMC used was of USP grade. Both polymorphs were characterised by Differential Scanning Calorimetry and X-Ray Diffraction Analysis.Citric acid (monohydrate) used was of analytical grade(Reidel de Haen) .

Solubility Determinations

The solubilities of α-IMC and γ-IMC were determined at 37°C in isotonic phosphate buffer (pH7.34)[6]. The saturated solutions were prepared by stirring an excess of the drug in a water jacketed vessel kept at 37±0.1°C ,using a modified method of Shefter and Higuchi[7].Samples were withdrawn at intervals of time and filtered through 0.2 μ membrane filters(Gelman Sciences Inc.) . On dilution samples were assayed by UV spectroscopy at 266nm 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[8].Dissolution profiles of α-IMC at stirring speeds of 90 ,120 and 155 rpm were determined on the same discs i.e. after sampling over an interval of time (about 40 min) at one speed,the stirring speed was then changed to a different rate. Powders were ground to a sub 210 μ particle size before use.The stirring speed was varied in the range 45-180 rpm.Sink conditions prevailed throughout dissolution.The pH of the dissolution medium was monitored using a pH meter (pHM82 Radiometer).

X-Ray Diffraction Analysis

X-Ray diffraction patterns were obtained using nickel filtered copper radiation (Philips instrument).

Differential Scanning Calorimetry(DSC)

DSC was carried out using a Mettler TA3000 instrument at a heating rate of 10^{o}C/min.

Microscopy

Photomicrographs of disc surfaces and edges were obtained using a scanning electron microscope(Hitachi S520) .

RESULTS AND DISCUSSION

Solubility.The solubilities of α-IMC and γ-IMC at 37^{o}C in phosphate buffer pH 7.34 were 2.34 and 1.87 mg/ml respectively. The α-form of IMC reached equilibrium solubility after one hour and remained constant throughout the 48 hrs sampling interval and γ-IMC reached equilibrium solubility after 5 hrs.The solubility of γ-IMC determined by the sealed vial method [9] as described before[10], was consistent with the solubility after 5hrs using the overhead stirrer.The α-form of IMC was more soluble than the γ-form,the ratio of the solubilities of α-IMC : γ-IMC being of the order of 1.25.This is in agreement with the value of 1.26 ,obtained by Kaneniwa et al[11] , for the ratio of the solubilities of α-IMC to γ-IMC in distilled water at 35^{o}C.

Dissolution of pure IMC.Fig 1 shows the dissolution profiles of α-IMC and γ-IMC obtained at the stirring speed of 60 rpm,in phosphate buffer pH 7.34. The α-polymorph gave a linear dissolution profile,while the dissolution profile of γ-IMC was nonlinear,the rate decreasing with time.The dissolution profiles of γ-IMC at higher stirring speed were all nonlinear as shown in fig.2.The dissolution rates increased with

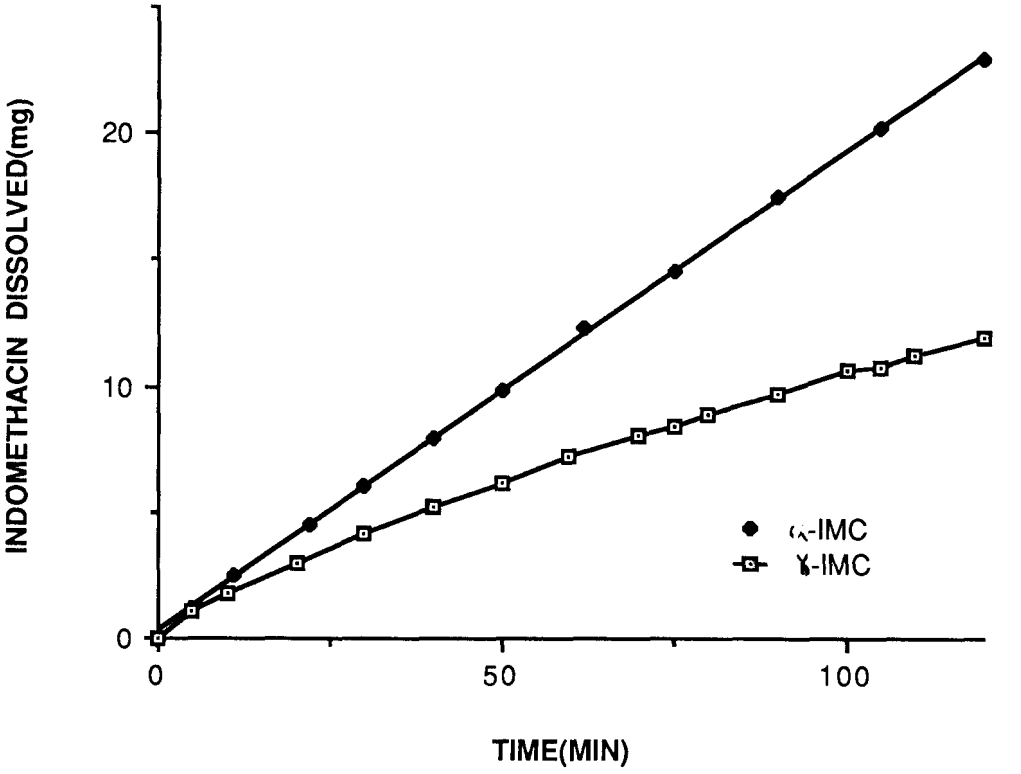

FIGURE 1

Dissolution profiles for α-IMC and γ-IMC in phosphate buffer at 60 rpm and at 37°C.

increasing stirring speed, the ratio of the rate at 180 rpm to the dissolution rate at 60 rpm being 1.24.The ratio of the initial to limiting rates at each stirring speed was of the order of 1.7 . In contrast α-IMC dissolution rates were higher and more sensitive to agitation intensity. The ratio of the dissolution rates at 155 rpm to 60 rpm for α-IMC was 1.76. The dissolution rates , (for the entire sampling interval) for both polymorphs were obtained by linear regression analysis. Initial (5-20 min) and limiting (60-120min) rates for γ-IMC were also obtained using linear regression analysis.The log of the dissolution rates for each

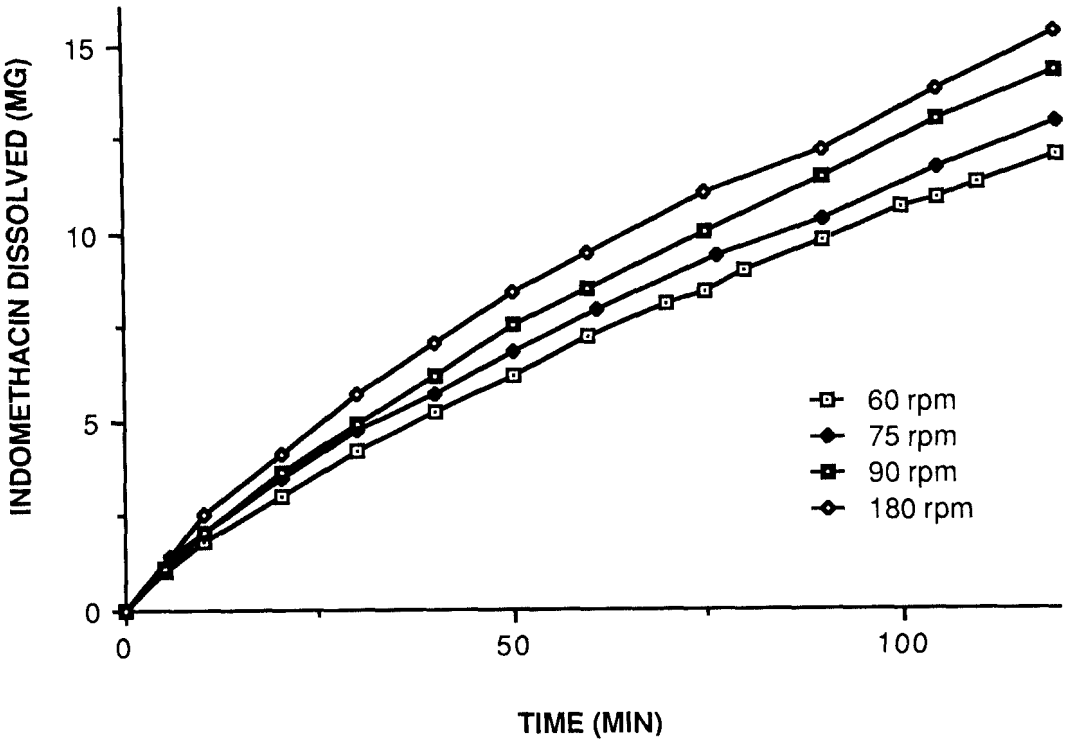

FIGURE 2

Dissolution profiles of γ-IMC in phosphate buffer under various stirring speeds.

polymorph are plotted against the log of stirring speed in fig 3. A slope of 0.598 was obtained for α-IMC .However for γ-IMC,the slope of 0.171 obtained suggests that in the stirring speed range used ,the dissolution of γ-IMC is significantly surface controlled.A slope of 0.61 was previously obtained for compounds having diffusion controlled dissolution process and using a similar dissolution apparatus[12]. Using eq.1 and the solubilities obtained above,the apparent dissolution rate constant ,K_{app}, for the two polymorphs was calculated at each stirring speed.From the relationship:

$$1 / K_{app} = 1/K_d + 1/K_r \qquad \text{eq. 3.}$$

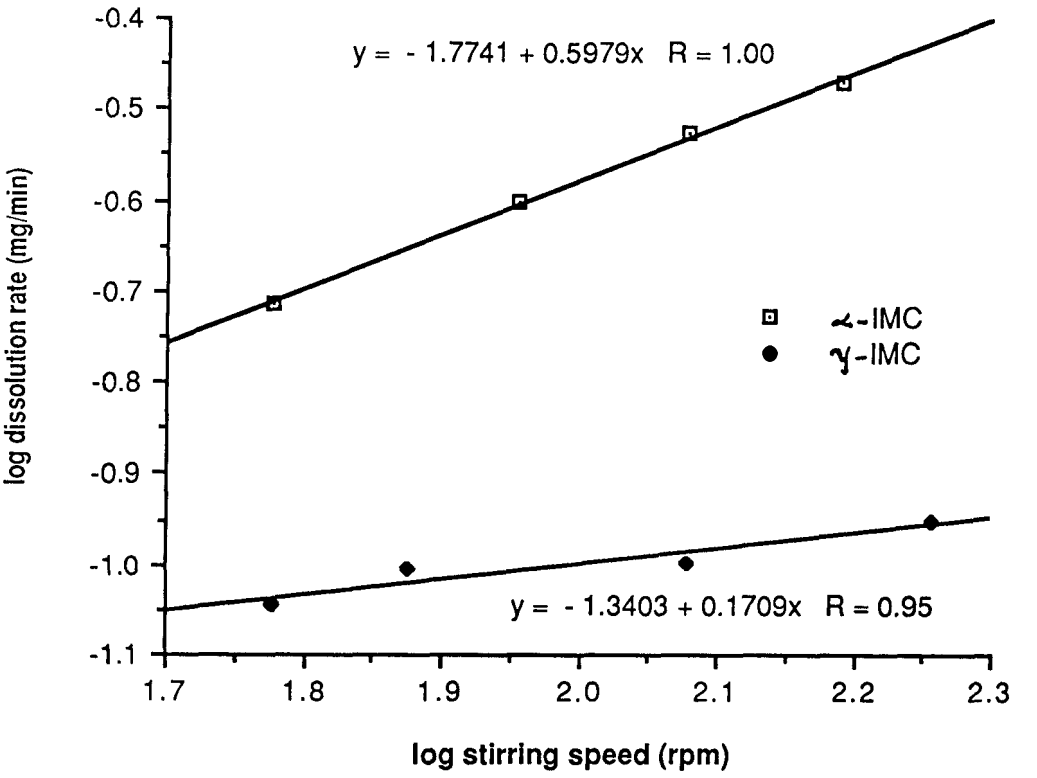

FIGURE 3
Log dissolution rate versus log stirring speed plots for α-IMC and γ-IMC

where K_d and K_r are the diffusion and reaction rate constants respectively[13],the contribution of the surface reaction to the dissolution process for each polymorph can be calculated.Rewriting eq.3 in terms of resistances:

$$R = 1/K_{app} = h/D + R_s \qquad \text{eq.4}$$

where R is the total resistance to mass transfer,h/D is the ratio of diffusion layer thickness and the diffusion coefficient and $R_s = 1/K_r$ is the resistance offered by surface reaction. The effective diffusion layer thickness (h) at each stirring speed was estimated from eq. 2, using a

value of 0.61 for b and a diffusion coeffient of 9.6 x 10^{-6} cm^2/sec for benzoic acid[9],a diffusion controlled compound.The calculated diffusion layer thickness(h) ranged from 4.9 x 10^{-3}cm at 60 rpm to 2.5 x 10^{-3} cm at 180 rpm. The resistance to dissolution due to the surface reaction,in the stirring speed range studied, was found to be of the order of 10% in the case of α-IMC.However for the γ-polymorph, the contribution of Rs to the total resistance, R, was larger,ranging from 47 % for the stirring speed of 60 rpm to 66 % at the stirring rate of 180 rpm. The diffusion coefficient of IMC used was 5.6 x$10^{-6}$$cm^2$/sec[9]. Recently Kaneniwa et al[14] reported the dissolution behaviour of IMC polymorphs in the stirring speed range of 200-600rpm and at various temperatures(20-50°C).The dissolution rates were measured in phosphate buffer pH6.8 over a10 minute sampling interval.At these high stirring speeds,they reported linear dissolution profiles for both polymorphs.They also concluded that the dissolution of IMC proceeds with two processes ,one reaction and the other diffusion.

Dissolution of IMC:citric acid compressed discs. The dissolution profiles of IMC from mixed γ-IMC:citric acid 1:1 discs in the stirring speed range of 45-180 rpm are shown in fig.4.The dissolution profiles at the lower stirring rates (45-60 rpm) show positive curvatures, the rates increasing with time. Previously we reported that the presence of an acid excipient such as citric acid significantly retards the dissolution rate of IMC in buffered media and at certain compositions give dissolution profiles with positive curvatures[15] .These positive curvatures were explained in terms of pH changes occurring at the solid-liquid interface i.e.as citric acid dissolves , it lowers the pH at the dissolving surface suppressing the release of IMC. With time, citric acid recedes from the surface and the interfacial pH rises and hence the dissolution rate of IMC increases.At higher stirring speeds,the dissolution profiles became linear and the rates higher.The ratio of the dissolution rates at the stirring speed of180

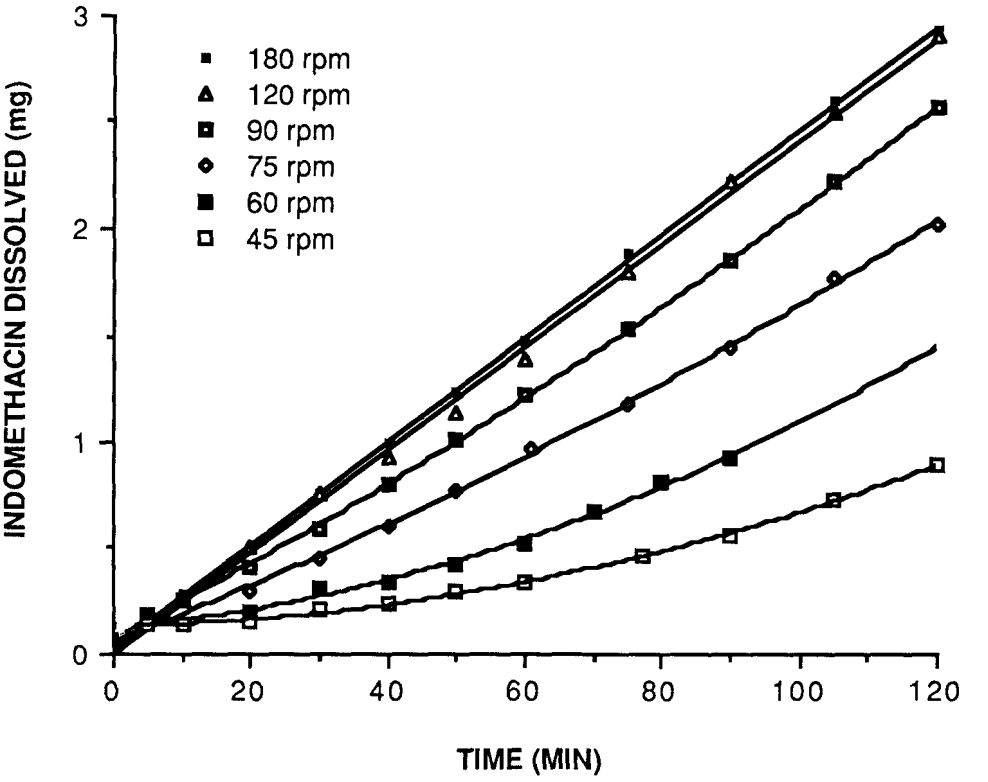

FIGURE 4

Dissolution profiles of IMC from γ-IMC:citric acid 1:1 discs dissolving in phosphate buffer,under various stirring speeds.

rpm to 45 rpm was 3.78. The dissolution rates were lower than the rates obtained from pure IMC discs at the same stirring speed.The ratio of the rates from pure : mixed discs was 10:1 at 60 rpm and decreased to 5:1 at 180 rpm.If at high stirring speeds the surface pH is higher then IMC dissolution rates should also be higher.A plot of log IMC dissolution rate versus log stirring speed is shown in fig 5. A nonlinear relationship is evident,the slope being >1in the lower stirring speed range(45-90 rpm) and < 0.5 at 120-180 rpm.

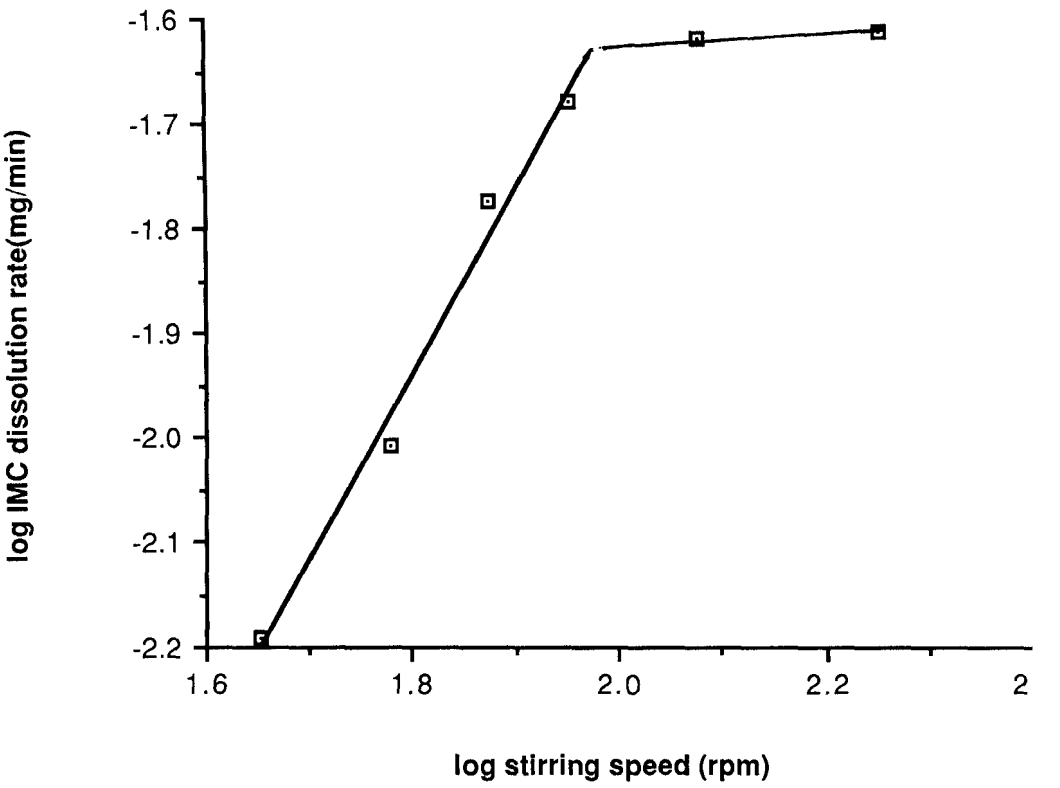

FIGURE 5

Log dissolution rate versus log stirring speed for IMC from γ-IMC:Citric acid 1:1 discs.

The surfaces of 1:1 IMC-citric acid mixed discs before and after dissolution at 60 rpm were examined using X-Ray diffraction analysis and scanning electron microscopy.X-Ray diffraction patterns from a 1:1 γ-IMC:citric acid disc after dissolution reveals very little citric acid on the surface of the disc i.e. citric acid had dissolved away from the surface during dissolution.The pattern obtained was similar to that of γ-IMC with the exception of a single citric acid peak at $2\theta=15.2^{o}$. Photomicrograph of the surface and edge of the same disc is shown in fig.6. The porous

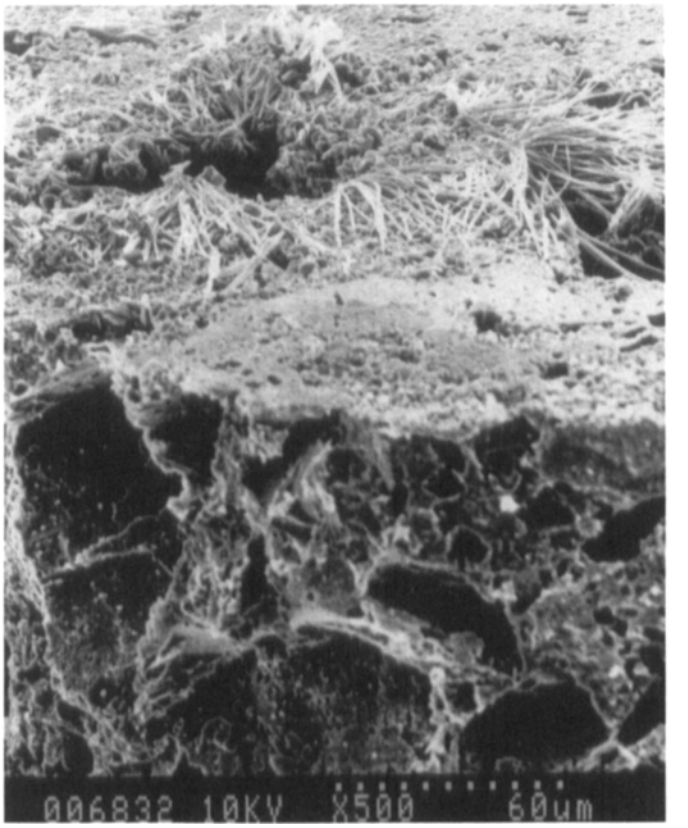

FIGURE 6
Photomicrograph of the surface and edge of a 1:1 γ-IMC:citric acid disc after disolution at 60 rpm.

nature of the surface of the disc is evident. Moreover fine needle-shaped crystals seem to have formed around the pores on the surface .Such crystals are characteristic of the α-form of IMC.The photomicrograph of the surface of a 1:1 α-IMC : citric acid disc after dissolution (fig.7) shows that needle-shaped crystals cover the surface of the disc.However no α-IMC peaks were evident on the X-Ray diffraction pattern.This is not surprising due to the low intensity of the peaks of this polymorph.If as

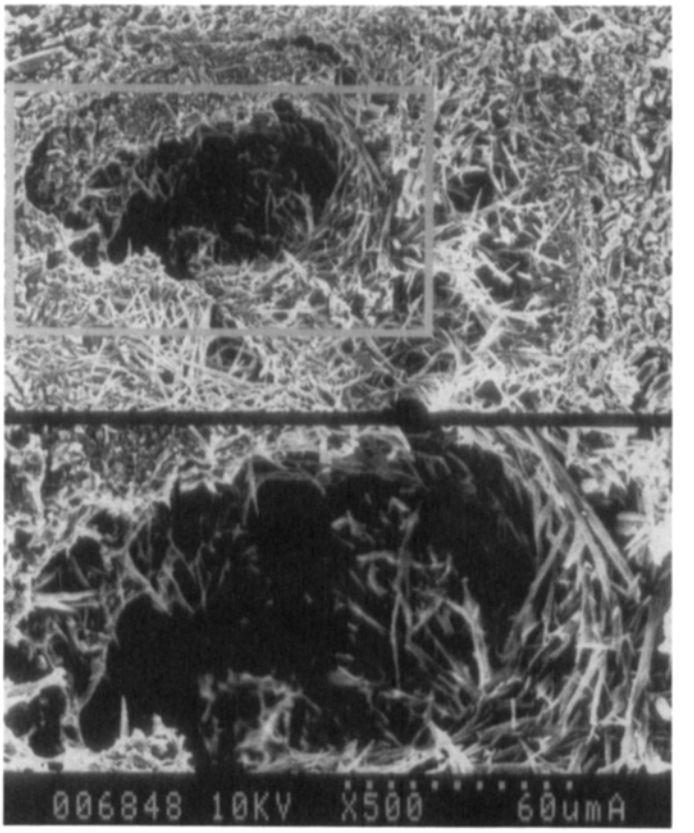

FIGURE 7

Photomicrograph of the surface of a 1:1 α-IMC:citric acid disc after dissolution at 60 rpm.

suggested by Kaneniwa et al[16], amorphous IMC is formed on grinding and / or compression,recrystallization of the α-form on the disc surface is possible.However we have not detected amorphous IMC in ground and / or compressed mixtures because of interfering citric acid peaks.Furthermore when concentrated citric acid solution was added to phosphate buffer saturated with IMC,the precipitate formed contained amorphous IMC.Amorphous IMC readily converts to needles of the α

phase[16].The reasons for the appearance of needle-shaped crystals on the surface of mixed discs of γ-IMC and citric acid during dissolution is being investigated further.

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