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THE RELEASE OF ANTIBACTERIAL AGENTS FROM GLYCEROLGELATIN GELS

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The rigidities and dissolution times have been compared for a range of glycerogelatin gels prepared from both acid and alkali processed gelatins. A statistical linear correlation between these parameters was observed for gels containing proflavine hemisulphate provided the melting point of the gel exceeded the dissolution temperature. However, when phenol was included as the drug then a marked decrease in gel rigidity was observed and no correlation between dissolution time and rigidity was apparent.

INTRODUCTION

Glycerogelatin or glycogelatin has been used for many years as a water miscible gel base for the delivery of medicinal agents to body surfaces and cavities. Because the gel dissolves in body secretions it is particularly suitable for the administration of anti-bacterial agents.

In addition, it is perhaps best known for its use in the form of a suppository whichhas a laxative action due to a direct effect on the rectal mucosa.

The official monograph on gelatin[1] states that the bloom strength (6 2/3%) must be greater than 150. The gelatin may be acid or alkali processed and since no upper limit of bloom strength is given then a wide range of high grade gelatins would be acceptable. Selection of different grades of gelatin by manufacturers has lead to a variation in the solution time of suppositories[2]. Recently, therefore, a solution test has been adopted and a maximum dissolution time of one hour at 37^{o} is permitted[1].

However, little information is available on the release of drugs from such bases. The current search for prolonged action dosage forms together with the fact that regulatory bodies favour innocuous formulation aids has lead to an increased use of gelatin in such devices[3,4,5]. For example, glycerogelatin has been used in the form of strips to administer such drugs as prednisolone, oxytetracycline and nystatin to the oral mucosa[4]. Such dosage forms produced continuous release of drugs at a site which is notoriously difficult in terms of drug administration. Similarly, gelatin discs have been included in devices for the delivery of 15 S 15-methyl-$PGF_{2\alpha}$ methyl ester to the vagina[5].

It was, therefore, considered valuable to obtain a better understanding of drug release from gelatin based systems. In this work we have compared the effect of gelatin type on drug release from glycerogelatin gels.

MATERIALS

The gelatins were commercial acid and lime processed ossein samples (Croda Ltd.) considered suitable for pharmaceutical use. The physical characterisation and properties of these samples have been reported previously[6,7] and are summarised in Table 1.

Proflavine hemisulphate B.P. (Macarthys Ltd.) and glycerol (Analar, BDH Chemicals Ltd.) were used as supplied. Chromatography grade phenol, p-methyl-phenol (BDH Chemicals Ltd.) and p-ethyl-phenol (Koch Light Laboratories Ltd.) were recrystallised twice from ether.

METHODS

Glycerogelatin gels containing 2-14% gelatin and 70% glycerin were prepared by heating with distilled water at 50^{o} for 1 h. Antibacterial agents were dissolved in the molten gels immediately prior to pouring into the molds or the apparatus used for the physical measurements.

TABLE 1
Properties of Gelatins

	ACID	ALKALI
pH	5.3	5.6
Bloom, g at 6.66%	249	243
Molecular weight (Mn)	40,300	53,800
I.E.P.	6.0-6.2	5.6

Dissolution tests were carried out using cylindrical blocks of gel weighing approximately 3.25 g into 2 l of distilled water 37°. The fluid was stirred at 110 r.p.m. and 5 ml samples were withdrawn every 240 s from a fixed point in the medium[8]. Each sample was analysed for proflavine content at 443 nm or phenol at 269 nm.

Rigidities were determined at 25° using the modified gelometer described by Timson and Kelly[9]. The solutions were poured into 1.5 cm diameter tubes, allowed to cool to 4° and aged for 21 h. Apparent viscosities were determined using an Epprecht Rheomat 30 automatic viscometer (Contraves Ltd., Zurich) with concentric cylinder geometry.

RESULTS

The dissolution curves obtained for the release of proflavine hemisulphate from 2, 5 and 14% acid and alkaline gels are shown in Figure 1.

All the curves were of similar shape although the time to release a given amount of drug increased with increasing gelatin concentration. Only a slight difference was observed between the release from the acid and alkaline samples; the acid sample showing the fastest release at low gelatin concentrations and the alkaline at higher concentrations. When the time to release 75% of the drug is plotted as a function of gelatin concentration (Figure 2) then the crossover can be seen to occur at the 4% level. Above this concentration a linear relationship exists for each of the gelatins.

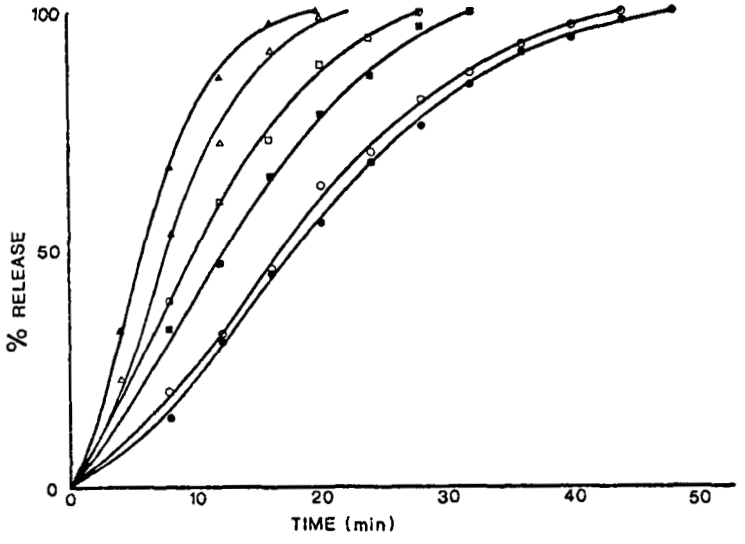

FIGURE 1

Dissolution curves for the release of proflavine from 2 (Δ), 5 (□) and 14 (O) per cent acid (closed symbols) and alkaline (open symbols) gelatins.

The effect of altering the glycerin concentration between 50 and 70% in 7% acid blocks is shown in Figure 3. Although there is a tendency towards increased release time with increase in glycerin concentration the differences are not significant and the times taken to release 100% of the drug are the same.

The relationship between gel rigidity and gelatin concentration for both gelatins is shown in Figure 4 and is non-linear over the concentration range 2-14%. At any particular concentration the acid gels are more rigid than those prepared from alkaline gelatin. Nixon et al[10] showed a linear correlation between gelatin concentration and rigidity for glycerin contents

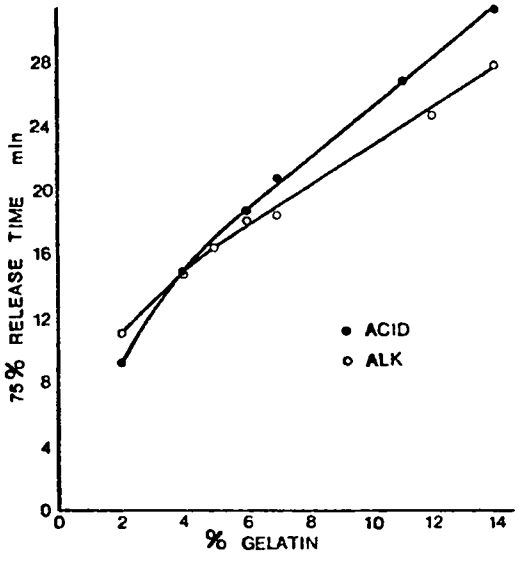

FIGURE 2

The effect of gelatin concentration on release time.

of up to 40% but could find no such correlation for higher glycerin concentrations. This is particularly significant since the highest grade gelatin used by these workers had a bloom strength of 250 which is similar to that of the gelatins used in this work.

When the time to release 75% of the proflavine was plotted as a function of gel rigidity then a significant linear correlation ($r=0.9954$) was found for formulations containing greater than 7% gelatin (Figure 5). Moreover, this relationship is obeyed by both the acid and the alkaline samples indicating an independance of the manufacturing process. The gels

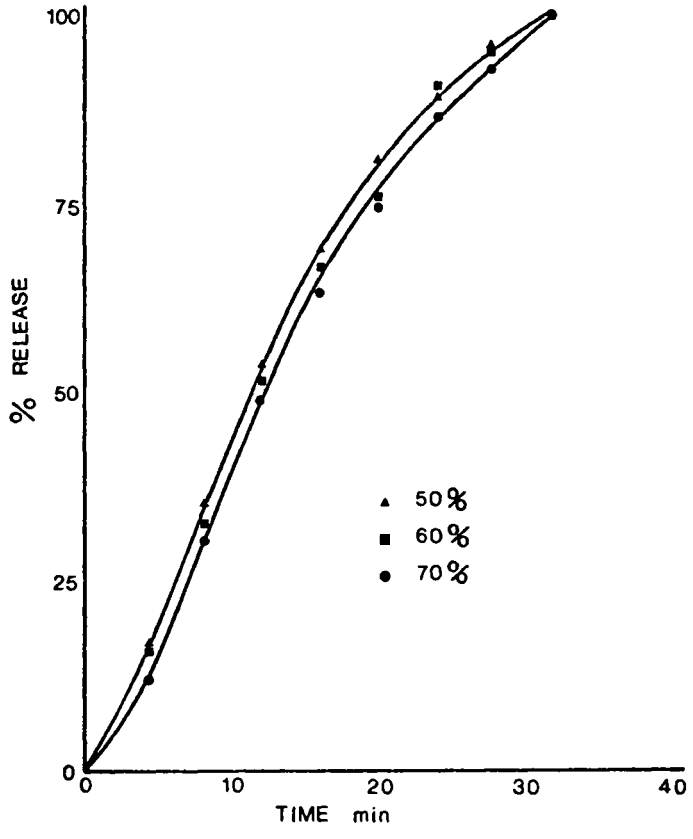

FIGURE 3

The influence of varying glycerin concentration on release time.

which did not obey this relationship contained 2 and 4% gelatin and Figure 6 indicates that the linear relation between melting point and release time which holds at higher concentrations is not obeyed at the lower concentrations. Correlation again appears to depend upon gelatin type.

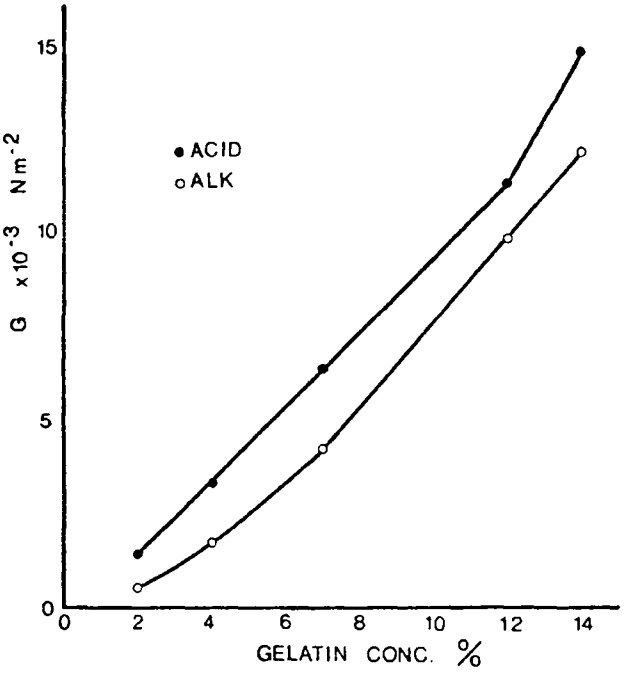

FIGURE 4

The relationship between rigity modulus (G) and gelatin concentration.

When phenol was added to the gels then profound differences in the rigidity were observed (Figure 7). Once the phenol concentration reaches 5-6% then the rigidity has been reduced to such a level that the resultant gels are pharmaceutically unacceptable. Also, at higher phenol concentrations the gels appear opalescent even at 37°.

The data in Table 2 indicates that the melting point of the gel also decreases with increase in

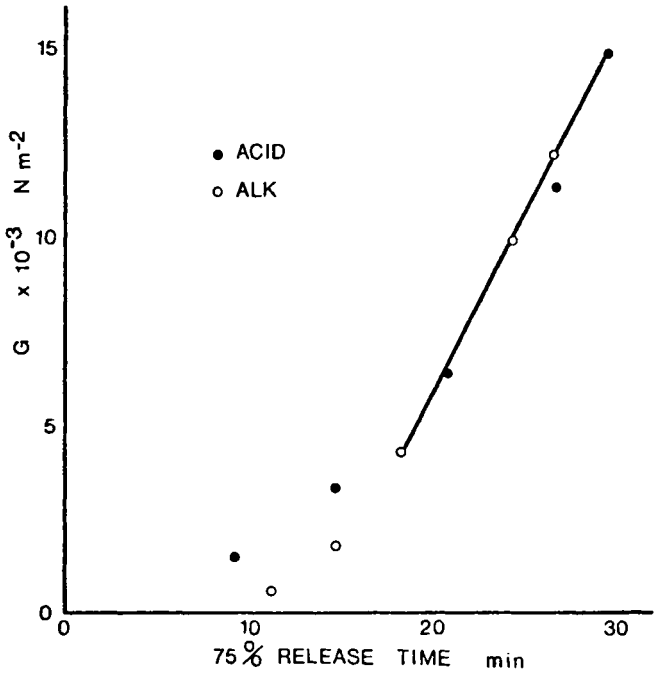

FIGURE 5

Release times as functions of gel rigidity modulus (G).

phenol concentration. The time to release 75% of the phenol has also been included in Table 2 and it is apparent that this release is not a function of gel rigidity for gelatin concentrations up to 3.2%. However, once the rigidity is markedly reduced and as the gel melting point approaches 37°, then the release time falls. The irregular pattern in these results may well be due to the fact that these higher concentration gels were opalescent and presumably the phenol was present in a different physical state. These

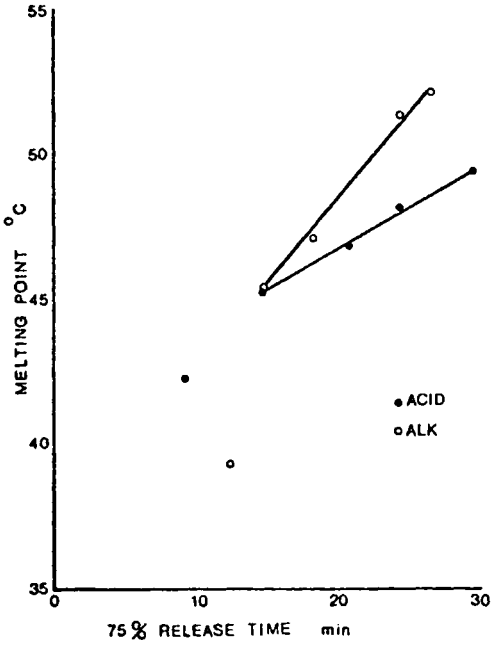

FIGURE 6

The relationship between release time and gel melting point.

changes in base characteristics and state of the drug probably explain the small differences in release which were obtained with the substituted phenols from 7% alkaline gels (Figure 8). Since the higher members of the series are more potent disrupters of gel structure then the release times might be expected to be reduced.

DISCUSSION

The release of the water soluble proflavine hemisulphate from glycerogelatin can be predicted from

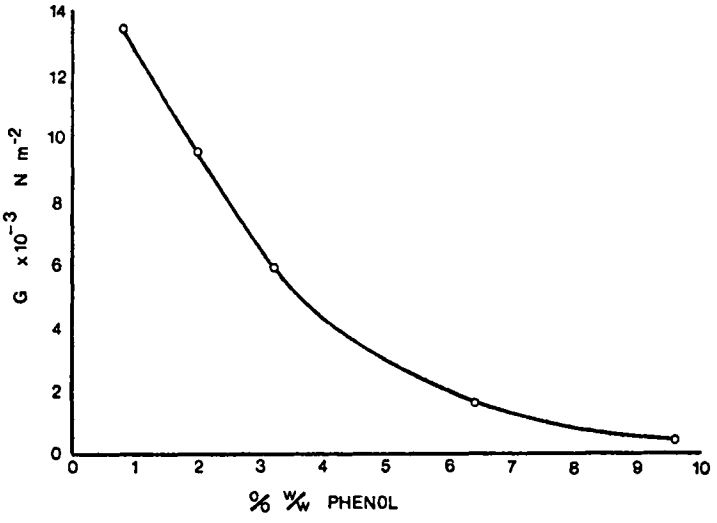

FIGURE 7

The effect of added phenol on the rigidity modulus (G) of alkaline gelatin.

TABLE 2

The Effect of Phenol on Gel Rigidity and Release Time

% w/v Phenol	Melting Point °C	75% Release Time min
0	48.0	-
0.8	45.4	20.6
2.0	43.2	21.0
3.2	41.7	20.6
6.4	36.9	15.6
9.6	34.6	16.6

the gelatin concentration used (Figure 2). However, the relationship does depend upon the gelatin type and therefore is not independent of the manufacturing process. When the release time is expressed as a

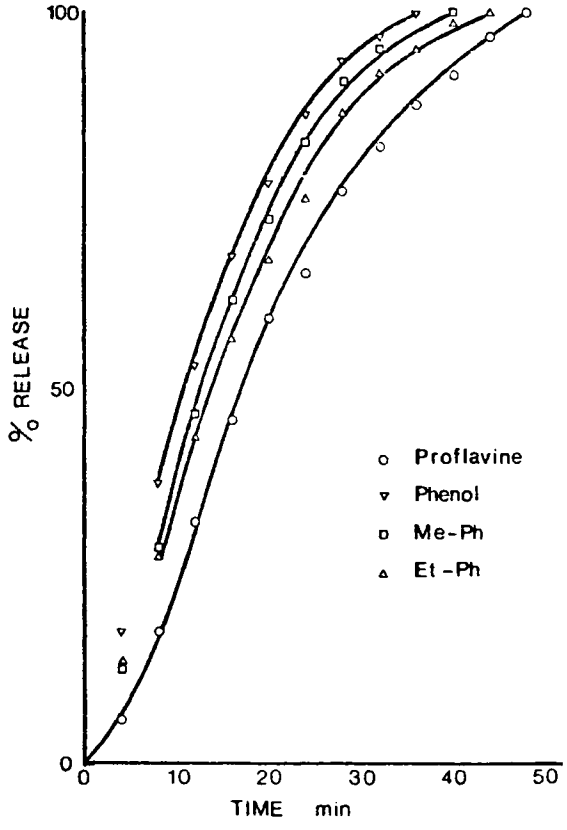

FIGURE 8

Dissolution curves for phenols from 7% alkaline gels.

function of gel rigidity then the relationship is independent of the method of manufacture. This may be due to the fact that both gelatins are ossein and such correlation may not have been apparent if gelatins from different sources had been used.

The release of proflavine is also independent of the glycerin concentration in the base (Figure 3). Nixon and others[11] have examined the diffusion of methy-

lene blue from 10% glycerogelatin blocks containing 0-60% glycerin. Diffusion was measured from 200 g blocks into 200 ml of water at 25^{o} and a dependence upon glycerin concentration was found with maximum diffusion occurring at 10% glycerin. The different experimental conditions and lower concentrations of glycerin might account for the differences, but it would appear that the proflavine release is not governed by the rate of diffusion through the block.

The lack of effect of a water soluble drug like proflavine on glycerogelatin bases probably accounts for the selection of such a base. When less water soluble drugs are included in the bases then the interaction between base and drug can result in alteration of the base properties. The formulation of phenols in glycerogelatin bases would obviously be precluded since the resultant reduction in gel strength results in a decreased release time (Table 2). When substitution of the phenol is carried out to produce molecules with a greater ability to disrupt hydrogen bonds[12] then an even greater gel destruction occurs. The high degree of interaction noted would preclude such formulations.

It is concluded therefore that glycerogelatin base is only of use in the formulation of drugs which do not disrupt hydrogen bonds, unless these are used at low concentrations. Further modification of the base would be necessary if prolonged release products are to be formulated in gelatin based systems.

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