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Formulation of sustained-release products: dissolution and diffusion-controlled release from gelatin films

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Summary

The formulation of gelatin films with a view to producing sustained-release films of lignocaine for application to the buccal cavity is described. Both dissolution and diffusion controls were investigated as possible mechanisms for prolonging drug release. It was found that although the physical properties of the films were markedly affected by changing the formulations, the prolongation in release were insufficient for the proposed clinical applications. Increased cross-linking of the gelatin strands with formaldehyde produced more rigid films than controls but diffusion of lignocaine through them was unaltered. The physicochemical basis for the different physical properties of the gelatins and of the formulations used were investigated.

Introduction

The long history of safe use of glycero-gelatin bases for delivering drugs in the form of suppositories, pessaries and oral strips makes them obvious initial choices when designing soluble polymeric systems. More recent interest has focused on the use of such bases for sustained release of drugs in the oral and vaginal cavities (Paul and Harris, 1976; Spilman et al., 1976; Baker, 1980) and work aimed at designing more prolonged release systems for antibacterial agents (Majkus et al., 1969),

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steroids (Roseman, 1974), prostaglandins (Akkapeddi et al., 1974; Spilman et al., 1976) and narcotic antagonists (Yolles et al., 1975) have been reported.

Painful conditions such as mouth ulcers and toothache are often relieved by application of local anaesthetics. Most of the formulations available are rapidly cleared from the site of action and repeated applications are necessary. This report describes work carried out in attempts to formulate sustained-release gelatin films of local anaesthetics.

Materials and Methods

Materials

Gelatin was kindly provided by Messrs. Alfred Adams (West Bromwich, U.K.). The bloom strength quoted in this report was that quoted by the manufacturers in the products' specifications. No further purification or fractionation was performed on the gelatin samples. All other chemicals used were of analytical grade.

Determination of the isoelectric point of gelatins

The isoelectric point of the gelatin samples were determined by turbidimetry. 1% gelatin solutions were prepared in a series of Britton and Robinson buffers adjusted to an ionic strength of 0.5 M with potassium chloride. The absorbance of the resultant solutions were monitored by spectrophotometry at the non-specific wavelength of 600 nm. The isoelectric point was determined graphically as the point of maximum absorbance.

Preparation of gelatin films

To 60 ml of a 5% w/w aqueous solution of lignocaine hydrochloride were added 20 g of gelatin (200 bloom) and 20 g of distilled water. The mixture was allowed to stand for 1 h at room temperature before being melted at 60 °C. Thin films of approximately 0.5 mm thickness were cast by pouring the molten gel between two flat, stainless steel plates. Wher glycerol or formaldehyde were to be added, they were added to the aqueous solution before the addition of the gelatin. No glycerol was added to formaldehyde cross-linked gels.

Circular films (diameter 7.0 cm) were thus obtained and they were stored at 95% relative humidity at 20 °C for 12 h before release studies were performed.

Release experiments

For drug release studies, the films were clamped underneath a stainless steel wire mesh (40 mesh) between a perspex ring and a perspex plate using light stainless steel spring clamps. The wire mesh was necessary to ensure that the films did not rupture or swell during the experiment. The entire clamped system was then immersed in a Quickfit dissolution vessel containing 500 ml of distilled water as the receiving phase. Stirring was performed using a PTFE blade stirrer driven at 200 rpm, 5 cm above the bottom of the dissolution vessel, using a Heidolph RZR50 stirring motor.

The temperature of the system was maintained at 37 °C for the studies on

dissolution-controlled release and at 25 °C for studies on diffusion-controlled release.

Assay of lignocaine in the receiving phase

Lignocaine was assayed by HPLC chromatography. The Altex Ultrasphere 5 μm silica column was 10 cm long with an internal diameter of 0.5 cm. The mobile phase used consisted of 15% isopropanol, 0.4% strong ammonia solution and 0.2% water by volume in *n*-hexane. The mobile phase was pumped at a rate of 1 ml · min^{-1} using an Altex 100 A double-piston solvent metering pump. Detection was by UV spectroscopy at 235 nm using a Pye-Unicam LC UV detector.

1 ml samples of the aqueous receiving phase were mixed with 1 ml each of: 0.1 N sodium hydroxide, 2.0 μg · ml^{-1} aqueous carbocaine solution as the internal standard, and *n*-hexane. Vigorous shaking on a whirlimixer (Fisons, Loughborough) was followed by centrifugation until two clear layers were obtained. 20 μl of the hexane layer were injected into the column for each assay.

Differential scanning calorimetry

Differential scanning calorimetry was used to determine the melting points, melting ranges and the heat of fusion of the gels under study. The Dupont 910 Differential Scanning Calorimeter (DSC) System used was linked to a Dupont 1090 Thermal Analyzer, programmed to determine melting points and the heat of fusion. The calorimeter was calibrated using naphthol-2-hydroxyl against an empty sample-holder. The samples were heated from 15 to 60 °C at a rate of 5 °C/min.

The gel samples were prepared according to the method outlined above but without including the lignocaine and were stored in airtight glass vials for 3 days. About 20 mg of prepared gel (accurately weighed) were placed on a DSC capsule which was then hermetically sealed to restrict moisture loss and equilibrated at 15 °C for 12 h before the determination of the thermal properties.

Results and Discussion

Gelatin was chosen as a film-forming agent because it is relatively cheap and its safety profile in pharmaceutical formulations is well defined (Maurer, 1954). Likewise, lignocaine was used as the local anaesthetic agent because of its relative lack of toxicity for this purpose (Ritchie and Green, 1980).

Initial work was aimed at producing a slowly dissolving film as both technically and theoretically this should be the simplest formulation to develop. Therefore parameters which could affect the dissolution behaviour of such a formulation were investigated. The basic formulations consisted of gelatin, glycerol as the plasticising agent and water. For this developmental work, preservatives were not incorporated into the system. In altering the formulation, two basic parameters can be changed, the gelatin type and the gelatin–glycerol ratio. Gelatin is available in a range of bloom strengths and in two main types, an acid type and an alkali type, depending on the method of treatment of the collagen precursor. The isoelectric point of the

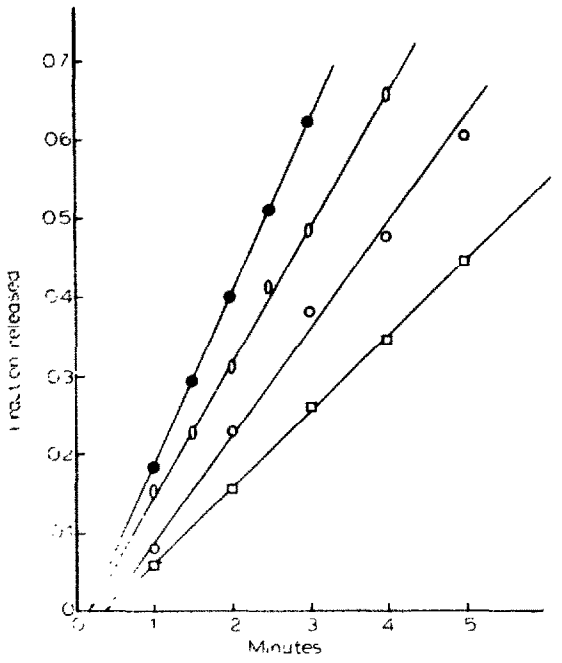

Fig. 1. The influence of bloom strength on the dissolution-controlled release of lignocaine hydrochloride from 20% w/w gelatin gels. Key: ●, 90; O, 150; ○, 200; and □, 230 bloom.

gelatin used in this study was found to be between 8.8 and 9.1.

Fig. 1 shows the effect of bloom strength on the release of lignocaine from the films. Visual observation of the release process quite clearly revealed that dissolution was taking place during release and the data in Fig. 1 showed that dissolution was the release-control mechanism. A plot of the dissolution rate constant against the bloom strength of the gelatin used (Fig. 2) demonstrate a linear relationship between the two parameters. In this study, the slope of the linear part of the plot of fraction of drug released against time was taken as the zero-order rate constant. A similar observation had previously been made by Hom and his colleagues (1973) in their studies of release of FD&C Blue from soft gelatin films.

Because of the constraints placed on the formulation by the requirement that the film must be flexible enough to mold around the application site, it was clear from the data shown in Fig. 1 that bloom strength variation on its own would not be sufficiently effective in prolonging drug release from the gelatin films. A two-fold change in the gelatin bloom strength only decreased the dissolution rate constant by the same magnitude.

It has previously been shown (Hom et al., 1973) that a change in gelatin–glycerol ratio also altered the rate of dye release from gelatin films. As expected, as the gelatin–glycerol ratio increased, the dissolution rate constant decreased. The same trend was observed in lignocaine release in this study (Fig. 3). A theoretical consideration of the dissolution process in an aqueous glycero-gelatin film suggests that if the gelatin were to act as a framework within which an aqueous glycerol solution is entrapped, it is likely then that there would be a mathematical relation-

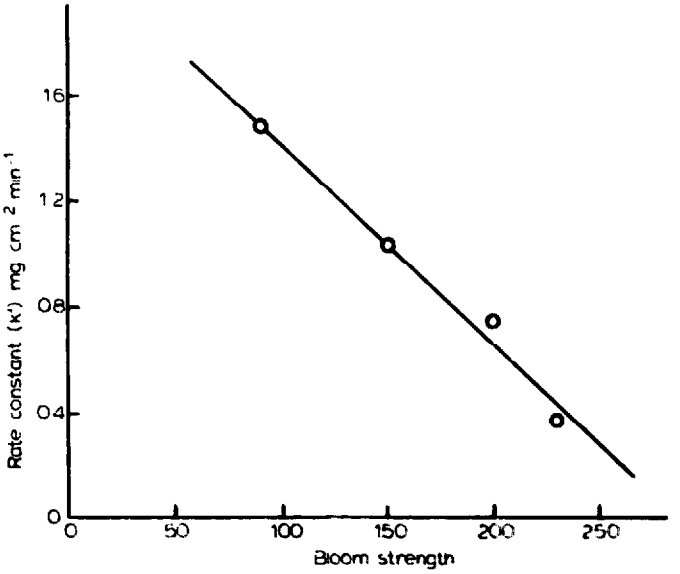

Fig. 2. The influence of bloom strength on the dissolution rate constant of gelatin gels.

ship between the dissolution rate constant of the end product and the viscosity of the aqueous glycerol. A plot of the viscosity of the initial glycerol solution against the dissolution rate constants for the final products in fact reveals a linear relationship between the two (Fig. 4).

Despite the prolongation in the release of lignocaine achieved by increasing the

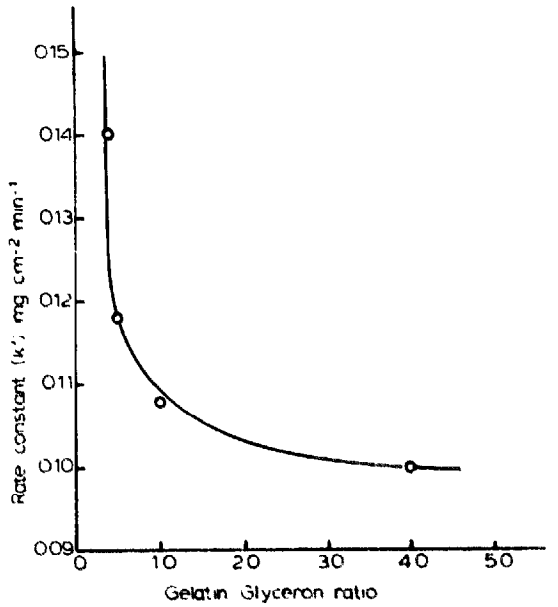

Fig. 3. The influence of glycerol concentration on the dissolution rate constant of 20% gelatin gels at 37 °C.

proportion of glycerol in the formulation, the magnitude of the change was again insufficient to suggest that this approach could on its own lead to a product with the prolonged release characteristics required.

It is well-known that gelatin forms thermally reversible rigid gels (Ferry, 1948; Bradbury and Martin, 1952; Robinson et al., 1975) and it can therefore be expected that the dissolution rates of such gels will be temperature dependent. This has in fact been shown to be so with the most marked changes observed between about 25 and 42°C within the range 25–55°C studied (Hom et al., 1973). The melting point of gelatin gels depends on the gelling history (Ferry and Eldridge, 1949) and composition (Marriot and Kellaway, 1978) of the gels studied. It is therefore unfortunate that in the same studies (Hom et al., 1973) the melting characteristics of the samples were not reported. To investigate whether melting characteristics could be quantitatively related to the dissolution profiles, the melting characteristics of the gelatin gels used in this study were determined. These are summarized in Table 1. Although the automatic procedure used eliminated operator bias, the broad melting range of the gelatin gels makes precise determination of the melting points difficult. It is, however, quite interesting to note that glycerol concentration affects the melting range but not the melting point of the gels (Table 1); whereas the melting point clearly increases with the gelatin bloom strength. This behaviour of glycerol does not appear to have been reported before. Attempts were then made to relate the heat of fusion of the gels to the formulation variables.

Fig. 5 shows the linear relationship found between the heat of fusion and the bloom strength of the gelatin used in the formulation. A further linear relationship between the melting point of 20% gels and the gelatin bloom strength is shown in Fig. 6. Gel rigidity as measured by bloom strength is the result of intermolecular

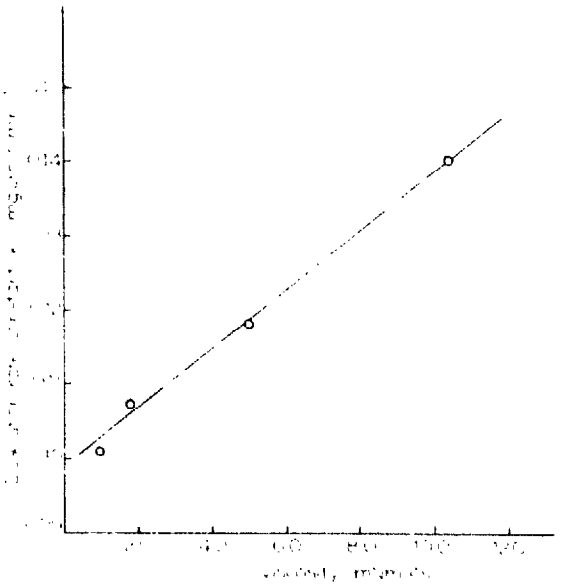

Fig. 4. The relationship between the dissolution rate constant (k) and viscosity of the continuous phase without added gelatin.

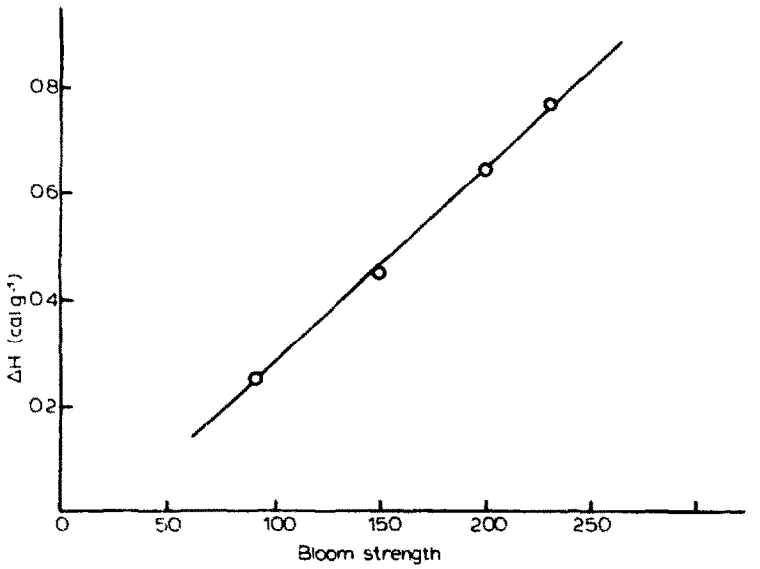

Fig. 5. The relationship between the heat of fusion and bloom strength of 20% w/w gelatin gels.

interactions between the gelatin strands. The relationships observed between bloom strength and these thermal properties of the gel are therefore as expected. Suggestions have been made that the gel network is formed by the establishment of fringed micelles along the chain direction of the gelatin strands via secondary nucleation (Godard et al., 1978). Irrespective of the microscopic structure, it is generally accepted that dilution of the gel will diminish the intermolecular interactions and hence gel strength. The effect of changing the gelatin to glycerol ratio on the heat of fusion of the formulation (Fig. 7) can similarly be rationalized.

The observed relationships between the thermal properties of the gelatins and their dissolution rates leads to more rational explanations for the effect of additives on the physical properties of polymers. Plasticizers, for example, are thought to alter

TABLE I

Bloom strength (g)	Glycerol concentration (% w/w)	Melting range (°C)	Melting point (°C)	Heat of fusion ($cal \cdot g^{-1}$)
90	–	30–39	33.3	0.249
150	–	29–40	35.0	0.445
200	–	29–40	36.9	0.645
230	–	29–40	37.4	0.770
200	5	28–42	38.2	0.660
200	10	26–44	37.9	0.605
200	20	23–47	38.0	0.770
200	40	22–50	38.2	1.286
200	60	22–56	39.0	2.727

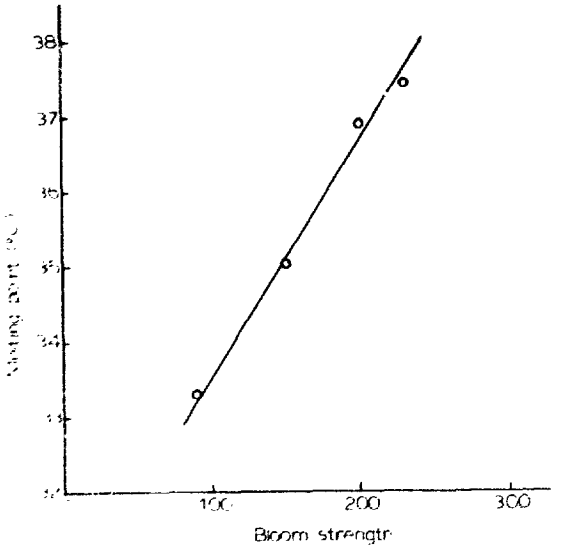

Fig. 6. Relationship between the melting points of 20% w/w gelatin and the bloom strengths of the gelatin used.

the mechanical properties of polymers by decreasing intermolecular interactions (Tager, 1978). Explaining the relationship between bloom strengths of gelatins and their dissolution rates solely on the basis of differences in interfacial diffusion may not be totally adequate (Hom et al., 1973).

Based on these results, the design of a system from which drug release from the matrix was diffusion-controlled rather than dissolution rate-limited was initiated. To do this, initial work was performed by altering the test conditions. It was observed that the gelatin films do not dissolve to any significant extent at 25 °C and any drug release at that temperature should be by diffusion. To obtain maximum information for subsequent work, release of lignocaine from the gelatin films was therefore studied at 25 °C.

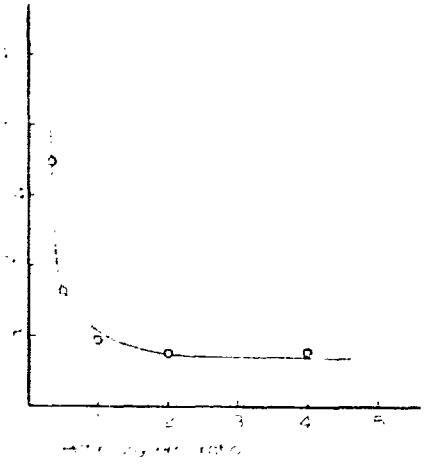

Fig. 7. The relationship between the heat of fusion and the glycerol concentration of gelatin gels.

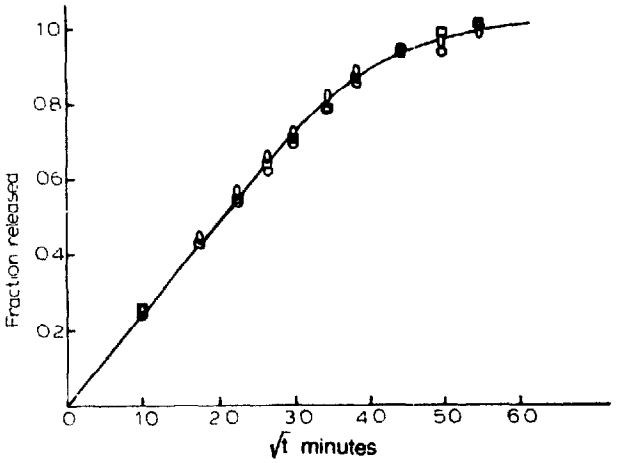

Fig. 8. Absence of effect of bloom strength on diffusive release of lignocaine hydrochloride from 20% w/w gelatin gels at 25 °C. ○, 90 bloom; ●, 200 bloom; and □, 230 bloom gelatins.

Fig. 8 shows the diffusive release of lignocaine from a series of gelatin films of varying bloom strengths. From the linear portions of the plots of the amount of drug released versus the square-root of time the diffusion coefficient can be calculated using the appropriate diffusion equations:

$$\frac{M_t}{M_0} = \left(\frac{4Dt}{\pi \ell^2}\right)^{1/2} \tag{1}$$

where M_t is the cummulative amount of drug released from the film at time t, M_0 is the total amount of drug releasable from the film, D is the diffusion coefficient of the drug in the polymer and ℓ is the thickness of the film.

It is clear from Fig. 8 that the bloom strength does not affect the release of lignocaine from the films. The diffusion coefficient was calculated to be 7.7×10^{-4} $cm^2 \cdot h^{-1}$. The gelatin content of the films also had no effect on the diffusion coefficient over the range of 20–30% w/w studied (Fig. 9).

The lack of effect of gelatin content and bloom strength on lignocaine release from the films is noteworthy since an earlier study using a higher molecular weight diffusant, methylene blue, has shown that these formulation parameters affected release rates (Nixon et al., 1967). The seemingly contradictory results can be rationalized if the molecular volumes of the diffusant are taken into account. Methylene blue also forms molecular aggregates in solution so that the effective molar volume is significantly increased and there is evidence that the size of the aggregates increases with concentration (Nixon et al., 1967).

Further attempts to slow the release of lignocaine from the films were made by hardening them with formaldehyde since slower diffusion in cross-linked gels is anticipated (Johnson, 1965). Results obtained (Fig. 10) indicate that addition of up to 0.05% w/w formaldehyde did not alter the diffusive release of lignocaine from the

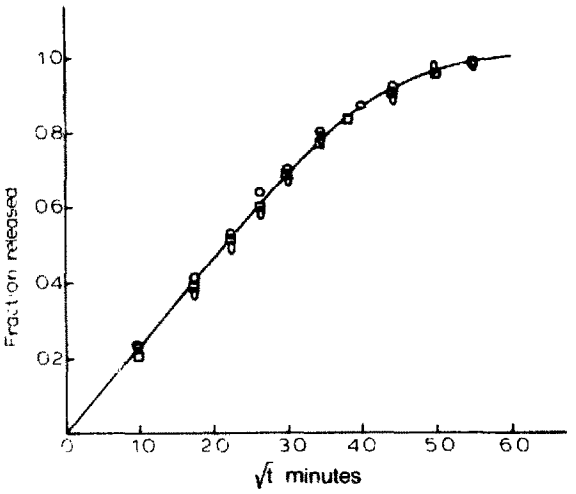

Fig. 9. Absence of effect of gelatin concentration on diffusive release of lignocaine hydrochloride from 200 bloom gelatin gels at 25 °C. ○, 20%; □, 25%; and ◇, 30% w/w gelatin in distilled water.

gels. This suggests that release of lignocaine from the gels is solution diffusion-controlled, that is the diffusion barrier is provided by the liquid in the continous phase and not the cross-linked strands of gelatin forming the gel network.

Conclusions

The data presented demonstrate that formulation parameters such as the bloom strength of the gelatin, the glycerol–gelatin ratio and the concentration of glycerol in the aqueous phase all significantly affect the dissolution-mediated release of drugs dissolved in aqueous glycero-gelatin films. These changes can be rationalized on the basis of molecular interactions within the gel and in particular intermolecular

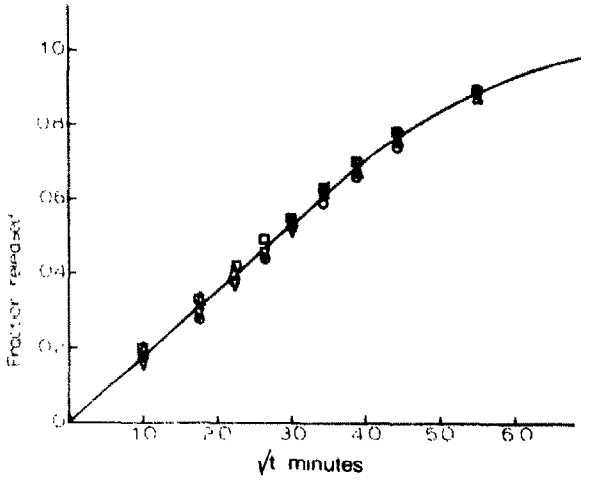

Fig. 10. Absence of effect of formaldehyde concentration on the release lignocaine hydrochloride from gelatin gels. ○, 0.01%; □, 0.02%; △, 0.03%; and ▽, 0.05% w/w formaldehyde in gel.

attractions by the gelatin molecules. Increase in bloom strength is accompanied by an increase in the heat of fusion and dissolution rate constant. These formulation-induced changes in dissolution rate would be crucial in the in vivo performance of glycero-gelatin systems such as gelatin capsules. The present work shows, however, that the magnitude of changes in dissolution rate observed by changing bloom strength, gelatin–glycerol ratio and water content of the films was insufficient for effective use in the design of sustained-release drug formulations without recourse to other approaches.

By lowering the temperature under which drug release was studied, from 37 to 25 °C, the dissolution rate of the film was sufficiently depressed to bring about a change in drug release mechanism from one of dissolution to one of diffusion. This observation has significant implications for the design of sustained release formulations of drugs in polymeric films. It suggests that by chemically altering the gelatin so as to increase its melting point above 37 °C, the polymer can be used for diffusive release of drugs. The use of formaldehyde to produce gels insoluble at 37 °C and from which diffusive release of lignocaine is obtained has been shown. Despite the design of gelatin films from which drugs can be released at 37 °C by diffusion, the system developed did not produce any significant prolongation of drug release relative to the dissolution-controlled films. The present studies, however, contribute to the more rational development of sustained release systems based on glycero-gelatin.

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