Anionic Gels as Vehicles for Electrically-Modulated Drug Delivery. I. Solvent and Drug Transport Phenomena

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Purpose. The purpose of this study was to elucidate the *in vitro* behavior of anionic gels as formulation matrices for electrically-modulated drug delivery. Agarose and combinations of agarose with other anionic polymers (carbomer 934P; xanthan gum) were selected and tested to evaluate their potential for drug delivery.

Methods. Electrical current was applied by an automatic crossover power supply to minimize the current fluctuation. Hydrocortisone was selected as the model drug in order to minimize electrostatic interference with drug transport. Syneresis and drug migration were evaluated as a function of current application time and the intensity of electrical current.

Results. The data show that electrical current strength and gellant content can affect both the syneresis and drug migration. A linear correlation was found between hydrocortisone loss and mass loss *via* the exudate. Moreover, in agarose-carbomer 934P gel systems, cumulative gel mass loss is a linear function of time at low intensities of electrical current (*e.g.*, 0.5 mA and 1 mA). However, hydrocortisone distribution, after electrical application, is relatively asymmetric in those agarose-carbomer 934P gels (and in agarose-xanthan gum gels) in contrast to gel matrices containing only agarose.

Conclusions. In this study, the use of carbomer 934P in conjunction with agarose enables the formulator to achieve zero-order release with electrical application. Increased anisotropicity of a gel system due to the application of electrical current could alter the effectiveness of a drug delivery system.

KEY WORDS: electrotransport; hydrogels; syneresis; agarose; carbomer; xanthan gum.

INTRODUCTION

The development of drug delivery systems which enhance drug transport across biological barriers by electrical means—*e.g.* by iontophoresis or electroporation—has been the subject of much research in recent years (1–7). With few exceptions (8–13), most publications have dealt with the effect of electrical current on the permeability of the biological barrier rather than on the integrity of the drug and the formulation matrix for the drug. Our contention is that electrical current not only affects the barrier to transport but also may affect the drug and the matrix. This research, intended to determine the significance of the latter effects in hydrophilic gels, focuses on gels prepared from anionic polymers.

Interest in hydrophilic gels and hydrogels is a reflection of their (a) low ratio of gellant to solvent; and (b) substantial mechanical (structural) rigidity, both of which facilitate their use as part of a chemomechanical device. Chemomechanical systems undergo shape changes and develop contractile forces in response to external stimuli (14). These external stimulus sensitive gel systems have been widely investigated in recent years. The swelling and shrinking properties of these gel systems can be changed by alterations in temperature, pH, or electrical current (15–18). The sensitivity of these gel systems to external stimuli can be controlled by changing the composition of the gels. Their usefulness as vehicles for drug delivery systems, particularly with the advent of electrically-induced drug transport, is only now being explored. Hydrogel formulations can serve as good electroconductive vehicles which have the additional advantage of ease of application. Although a number of studies on drug release from hydrogels have been published, very little has been reported on solute distribution in the gel prior to its release into the receptor medium. This study focuses on the response of selected anionic gel systems (agarose, agarose-carbomer 934P, and agarose-xanthan gum) to variations in electrical current (mA) and on hydrocortisone migration in these gel systems resulting from exposure to an electrical field. Hydrocortisone release profiles are also examined relative to the electrically induced changes in the gel matrices.

METHODOLOGY

Material and Equipment

Carbomer 934P (Carbopol 934P, B. F. Goodrich), agarose (High EEO electrophoresis grade, Fisher Biotech), xanthan gum (R. T. Vanderbilt Company, Inc.) and hydrocortisone (USP/NF, Spectrum Chemical Mfg. Corp.) were used as supplied. Current and voltage were controlled by an automatic crossover power supply (Model APH 500M, Kepco Corp.) The electrodes used in this study were constructed from platinum wire (diameter: 0.65 mm) and platinum foil (1 cm × 5 cm). A UV spectrophotometer (Model 601, Milton-Roy Co.) was used to detect the hydrocortisone absorbance.

Preparation of Hydrogel Matrices

Three model hydrophilic gel systems were evaluated in these studies: (1) agarose; (2) agarose-carbomer 934P; and (3) agarose-xanthan gum. Agarose was employed at 0.4% w/v and 0.9% w/v concentrations; carbomer 934P was employed at concentrations of 0.5, 1, and 2% w/v, in conjunction with 0.4% w/v agarose; xanthan gum was employed at concentrations of 0.05, 0.1, and 0.2% w/v, in conjunction with 0.4% w/v agarose.

Agarose gel matrices were made by heating aqueous agarose gel dispersions to 80°C in water bath. The agarose-carbomer gel matrices were prepared by mixing aqueous carbomer dispersion with preheated agarose dispersion to form the desired gel composition. The agarose-xanthan gum gel matrices were prepared in the same manner. The gels were cut into 0.6 cm × 1 cm × 4 cm strips for the syneresis studies and 0.6 cm × 2 cm × 4 cm slabs for the drug migration and release studies.

Drug Loading

Hydrocortisone, used as the model drug at a concentration of 0.05% w/v in the drug migration and release studies, was

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loaded into the gel matrices by dissolving in 2 ml alcohol and mixing with 48 ml of the gel dispersion at 50°C during the gel preparation.

Syneresis

Gel syneresis was studied with the aid of an apparatus prepared from polystyrene weighing boats which were modified and assembled as shown in Fig. 1. This apparatus facilitated the separation and weighing of the gel exudate as electrical current was applied: the increased weight of the bottom section represented the weight of the exudate. Syneresis was evaluated as a function of time (0 to 40 min) and electrical current (at 0.5, 1, 2, or 5 mA; voltage $\leq$10V). Parallel platinum wire electrodes were kept in contact with opposite surfaces of the gel strip: the anode was placed on the top of the gel and the cathode on the bottom. At fixed time intervals, the bottom plate of the tared apparatus was disassembled, weighed, cleaned and then reassembled.

Hydrocortisone Analysis

Ten mg hydrocortisone was dissolved in 1 ml alcohol by sonication. This solution was then diluted to 100 ml with purified water and utilized as the stock solution (100 μg hydrocortisone/ml): 5 ml, 2.5 ml, 1 ml, 0.5 ml and 0.1 ml aliquots were subsequently diluted to 10 ml with purified water to provide solutions for calibration. Hydrocortisone concentrations were measured by UV absorbance at 254 nm. The corresponding equation for the Beer-Lambert curve is:

$$y = 0.002519 + 0.040752x \quad (r^2 = (0.9999)$$

where y is UV absorbance at $\lambda = 254$ nm and x is the hydrocortisone concentration (μg/ml).

Drug Migration Study

The gel support and electrification apparatus used in this study is shown in Fig. 2. This design was utilized to maintain the gel at a 45° angle and allow the exudate to be collected by micropipette. Platinum foil strips were used as electrodes. At fixed time intervals, the exudate was collected quantitatively, diluted to 10 ml with purified water, and then analyzed for its hydrocortisone content. In this study, electrical current was set at 1 mA while the maximum voltage was set at 20 V over a 90 minute period. The control gel was equivalent to the test gel except that no electrical current was applied during the experiment.

Drug Distribution After Electrical Current Application

The gel was divided into four fractions from one end (anode) to the other (cathode). Each of the gel fractions was dispersed in 8 ml purified water in a test tube which was then kept in a boiling water bath for 10 minutes. After cooling down to room temperature (~23°C), these diluted gel dispersions were further diluted to 25 ml with purified water and analyzed for hydrocortisone. Drug distribution in the electrically stimulated gel was evaluated by comparing the drug content in each fraction of the gel with that in the corresponding fraction of the control gel. After electrical current application for 90 minutes, the total drug content in this electrically-stimulated gel matrix (E gel) was equal to the sum of the drug content in

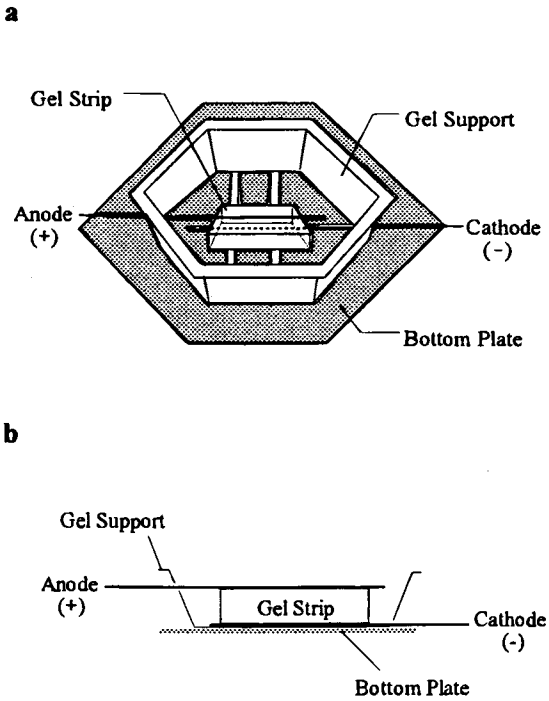

Fig. 1. Modified weighing boat and electrification apparatus utilized in the study of syneresis.

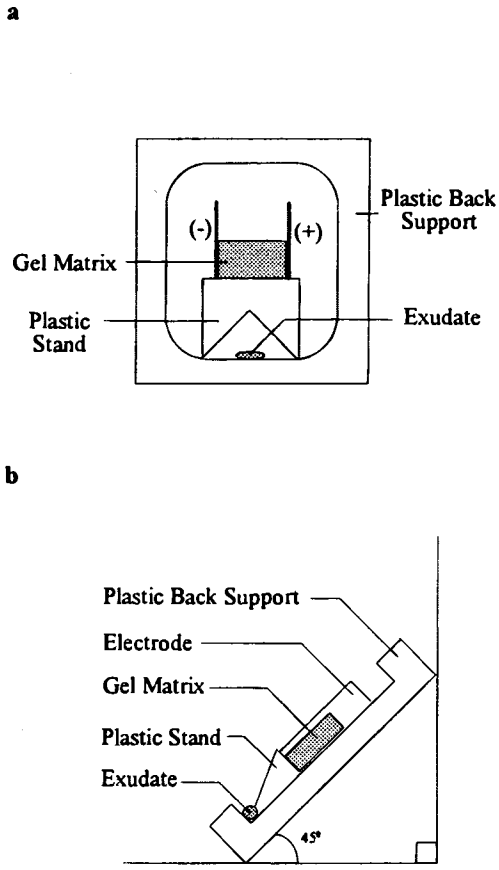

Fig. 2. Gel support and electrification apparatus utilized in the study of drug migration.

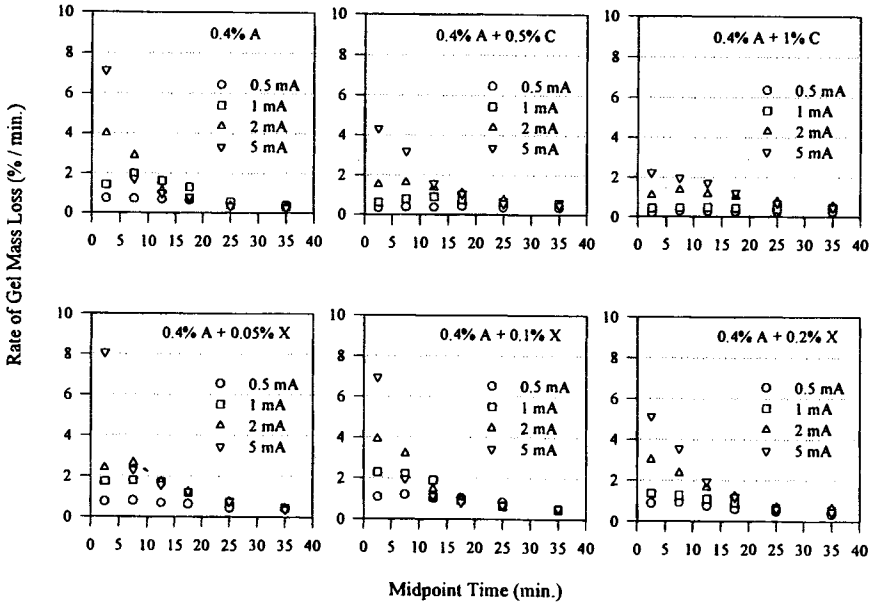

Fig. 3. The correlation between rate of gel mass loss (%/min.) and time (min.) Six gel formulations were studied by applying various electrical current strengths (A: agarose; C: carbomer 934P; X: xanthan gum).

the exudates and the drug content in the gel at 90 minutes. The control gel matrix (C gel) was analyzed in the same manner as the experimental gel matrices. The mean percentage of the hydrocortisone recovered in this study was 99.16% ± 1.43% (mean ± S.D.) of the expected values which showed that the loss of drug during these experimental procedures was minimal.

Degradation Study

A stock solution of hydrocortisone was prepared by dissolving 10 mg of hydrocortisone in 1 ml alcohol via sonication and diluting the resultant solution to 200 ml with purified water to yield a hydrocortisone concentration of 50 μg/ml. Eight-ml aliquots of this stock solution were transferred into test tubes which were then sealed. These test tubes were heated in a boiling water bath for 0 (control), 5, 10, 20, 40, or 60 minutes. Periodically, test tubes were removed from the water bath and cooled down to room temperature. Hydrocortisone concentrations were subsequently determined as described above. No significant quantitative changes were evident in the UV absorbance of hydrocortisone, at λ = 254 nm, from 0 to 60 minutes. This indicates that the hydrocortisone is stable at high temperatures (up to 100°C) for up to 60 minutes and should be stable during the course of the drug distribution study as mentioned above.

RESULTS AND DISCUSSION

Changes in Gel Matrices

The application of electrical current resulted in two changes in the gel matrices in the vicinity of the electrodes in all of the gel matrices examined. First, the gel matrix around the anode was collapsed as expected, although the cause of gel collapse is still not clear. Sawahata et al. (12) and Yuk et al. (13) proposed that the hydrogen ions generated around the anode protonate the anionic groups and cause those groups to become less hydrated or dissociated. Thus, polymer-polymer affinity increases and the gel network collapses. Tanaka (19) suggested that negative charges of anionic groups attached to immobile polymer molecules build "negative pressure" inside the gel network during electrical application. The pressure set up by the electrical current varies continuously along the length of the gel, but the response of the gel is nonetheless discontinuous: once this negative pressure is sufficient to bring on a phase transition, the gel undergoes substantial shrinkage.

Second, the solution exudate appears to have been "squeezed" out from the gel matrix in the vicinity of the cathode. The driving force for this liquid separation or syneresis in these anionic gel systems might be explained by electroosmosis due to solvent movement from anode to cathode (20, 21).

A third change was evident only in agarose-carbomer gel systems: the opacity of the gel matrix around the anode was increased after electrical application. This could be construed as further evidence for the decrease in dissociation of carboxylate groups on the carbomer molecules.

Syneresis

Syneresis can be defined as the separation of fluid from a gel as the gel contracts. It can be evaluated either in terms of the mass of fluid lost from the gel per unit time or the change in mass of the gel phase per unit time. Although the syneresis fluid may contain some gellant in addition to solvent, in these experiments there was little or no evidence of any loss of gellant in the fluid. Figure 3 shows the relationships between the rate of gel mass loss (%/min.) and time. The addition of carbomer to agarose gels results in a suppression of the rate of mass loss which is proportional to the carbomer concentration when the applied current is 5 mA. At lower currents, the rate of mass loss is suppressed but not in proportion to carbomer content.

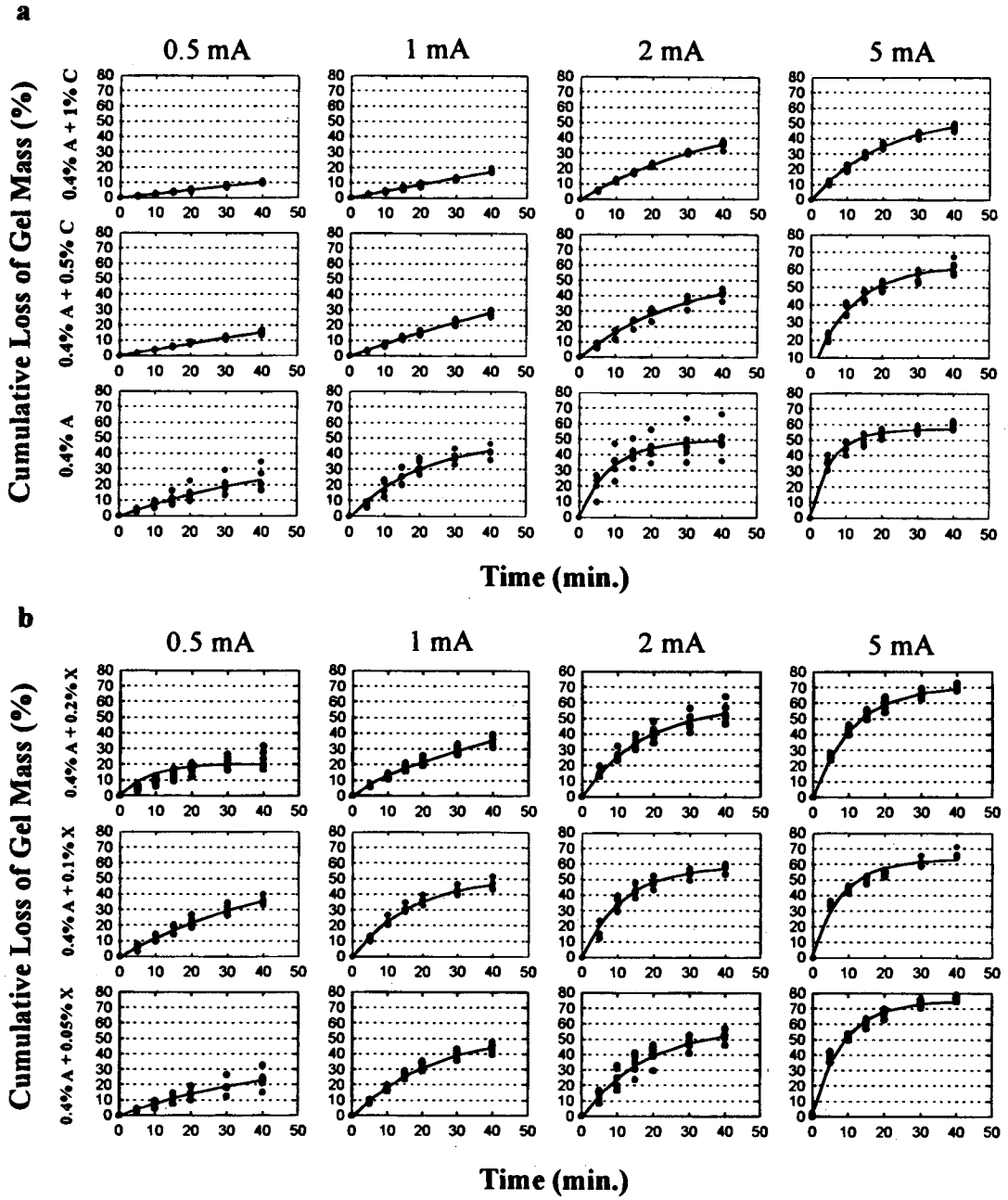

Fig. 4. Cumulative mass loss of the various gel matrices as a function of the percentage of gellant and time. Each separate graph represents 5 replicates and the best fitting line (A: agarose; C: carbomer 934P; X: xanthan gum).

At 0.5 mA, the rate of gel mass loss is minimal. However, when the electrical current is >0.5 mA, the rate of loss becomes higher initially (≤20 min.) In all model gels, the higher the electrical current applied, the higher the total mass lost. Presumably, the effect of electrical current on gel mass loss is the result of liquid phase syneresis which occurs as a result of electroosmosis. Kishi et al. (14) evaluated electroosmosis in different gel systems and demonstrated its adherence to zero-order kinetics. For the agarose gel matrices evaluated in this study, it appears zero-order kinetics for mass loss were involved only when the applied current was 0.5 mA. On the other hand, agarose-carbomer gels displayed zero-order mass loss up to 1 mA. However, at higher milliamperages (≥2 mA), zero-order kinetics were not observed in any of the model gels. This indicates that gel syneresis involved another mechanism in addition to electroosmosis. As mentioned in "*changes in gel matrices*", this additional mechanism, operative at higher electrical currents, apparently involves gel collapse or a gel-phase transition.

Cumulative mass losses of the various gel matrices as a function of the percentage of gellant and time are shown in Fig. 4. In all model gel systems (except agarose-xanthan gum gels), the higher the percentage of gellant in the gel system, the slower and less extensive the mass-loss pattern. Thus, by adjusting the total gellant content of the gel systems, the mass-loss pattern could be controlled. When the maximum electrical

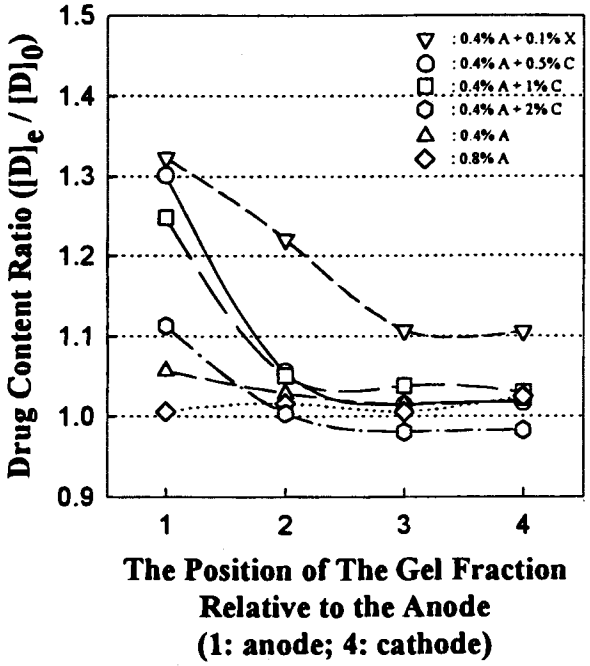

Fig. 5. Hydrocortisone distribution in the gel matrices after 90 min. electrical application (1 mA) (A: agarose; C: carbomer 934P; X: xanthan gum).

current was set to either 0.5 mA or 1 mA, a linear relationship was evident for both 0.4% agarose-1% carbomer gel matrices and 0.4% agarose-0.5% carbomer gel matrices.

However, unlike the agarose-carbomer gel systems, the agarose-xanthan gum gel systems do not show a linear cumulative mass loss vs. time profile, no matter how high or low the intensity of the applied electrical current. Furthermore, the cumulative mass loss-time profiles have steeper slopes for the agarose-xanthan gum gels than for the other gel systems during the first 20 minutes. The effect of gellant concentration in agarose-xanthan gum gel systems was also at variance with the observations for other gel system. The agarose gel containing 0.05% w/v of xanthan gum has lower mass loss than agarose gels containing 0.1% w/v of xanthan gum, whether at 0.5, 1, or 2 mA of applied current. This observations suggest that syneresis in agarose-xanthan gum gels is less likely to occur as a result of electroosmosis than from gel collapse or a gel-phase transition.

Hydrocortisone Distribution and Migration

Distribution of Hydrocortisone

A study of the control gels (*before* electrical application) showed that the distribution of hydrocortisone in the gel matrix was uniform. The hydrocortisone distribution in the gel matrices *after* electrical application is shown in Fig. 5. The ratios of drug content (mg/g) in the electrified gel ($[D]_e$) to that in the non-electrified gel ($[D]_0$) were evaluated for all gel systems and are shown in Fig. 5 as a function of the position of the gel fraction relative to the anode. The ratios ($[D]_e/[D]_0$) were >1 at the anode side for all model gel systems except the agarose gel systems. A comparison of the results for the agarose gels

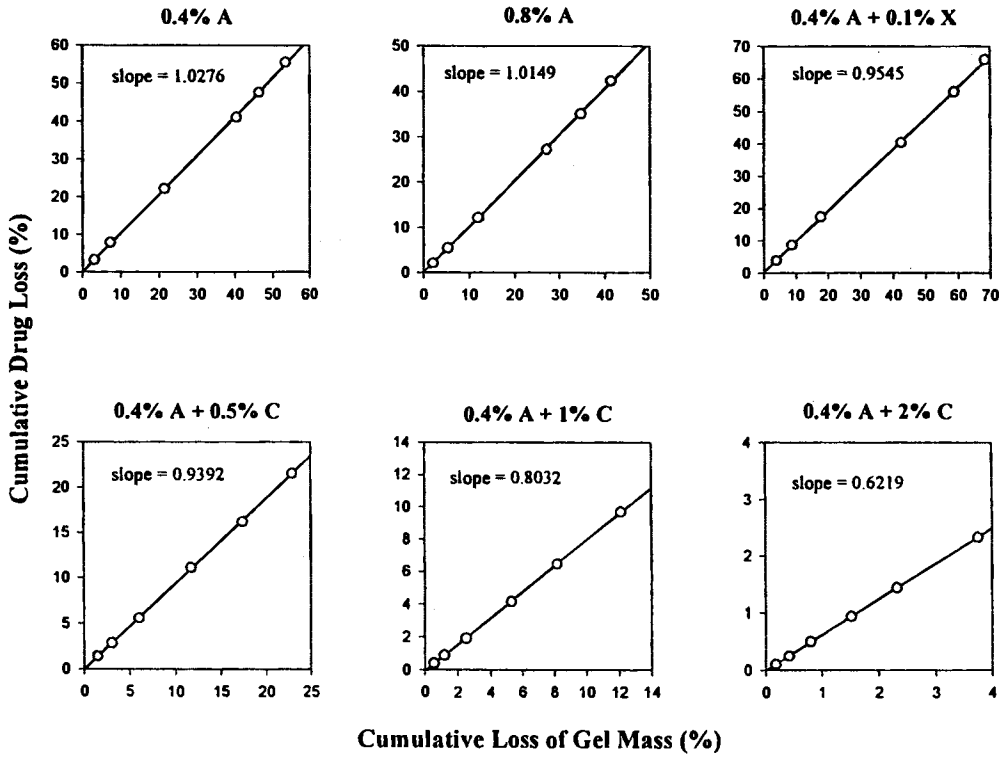

Fig. 6. The linear correlation between cumulative hydrocortisone loss and cumulative gel mass loss *via* syneresis in different gel systems. Each point represents the mean of 4 replicates (A: agarose; C: carbomer 934P; X: xanthan gum).

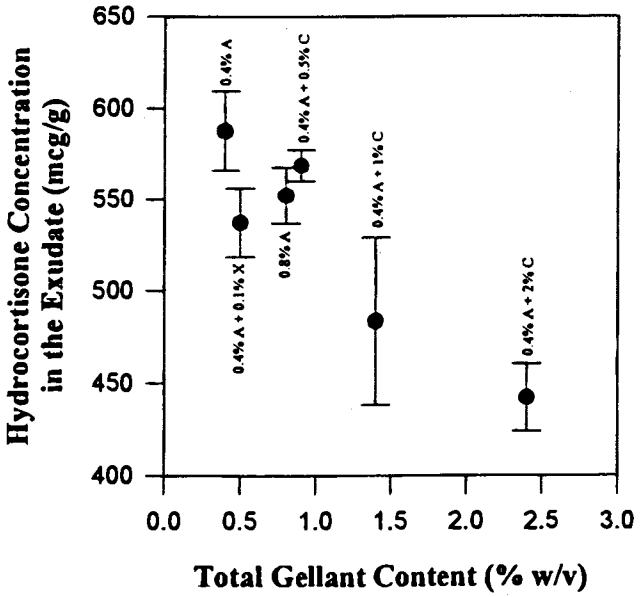

Fig. 7. The inversely dependent correlation between hydrocortisone concentrations in the exudates and the total gellant content (A: agarose; C: carbomer 934P; X: xanthan gum).

with those for the other model gels clearly shows that the disproportionately high drug concentrations in those gel fractions near the anode are a reflection of the entrapment of drug in the partially collapsed gel structure resulting from the loss of bulk solvent and the corresponding decrease in gel mass.

Hydrocortisone Migration

The linear correlation between hydrocortisone loss and mass loss (Fig. 6) is indicative of loss of drug in conjunction with syneresis. However, the slopes for these linear correlations in the different gel systems are not the same: in general, the higher the total gellant concentration, the lower the slope. The hydrocortisone concentrations in the exudates are inversely dependent on the total gellant concentration (Fig. 7): the higher the total gellant concentration, the lower the hydrocortisone concentration in the exudate. Decreased nonionic drug transport in these gel systems, as polymer concentration increases, may be the result of (a) increased microviscosity, (b) increased polymer-drug interaction, or (c) increased diffusion path length.

CONCLUSIONS

These results demonstrate the potential sensitivity of anionic gel matrices to electrical current. It is increasingly more evident that the development of electrically controlled transdermal drug delivery systems for iontophoretic and electroporative applications must consider the influence of the electrical field on subsequent drug and excipient distribution within the gel matrix. Clearly, the increased anisotropicity of a gel system could result in altered delivery system functionality. In effect, drug delivery in these systems could be augmented or diminished by the application of electrical current.

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