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

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\textbf{Purpose.} The purpose of this study was to elucidate the \textit{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.

\textbf{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.

\textbf{Results.} The data show that electrical current strength and gelant 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.

\textbf{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 anisotropy of a gel system due to the application of electrical current could alter the effectiveness of a drug delivery system.

\textbf{KEY WORDS:} electrotransport; hydrogels; syneresis; agarose; carbomer; xanthan gum.

\section*{INTRODUCTION}

The development of drug delivery systems which enhance drug transport across biological barriers by electrical means—\textit{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 gelant 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 now only 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.

\section*{METHODOLOGY}

\textbf{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.

\section*{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.

\section*{Drug Loading}

Hydrocortisone, used as the model drug at a concentration of 0.05% w/v in the drug migration and release studies, was
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 ≤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.](image1)

![Fig. 2. Gel support and electrification apparatus utilized in the study of drug migration.](image2)