Controlled Release of Human Immunoglobulin G. 1. Release Kinetics Studies

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Abstract □ The release of human immunoglobulin G (IgG) using ethylene–vinyl acetate copolymer (EVAc) as a polymer carrier was studied by fabricating them into two commercially available dosage forms: slab and microsphere. A first-order flux decay model and two hierarchical models concerned with the mass transfer coefficient on the slab surface were used to describe the mechanism of release kinetics and the results compared. These models gave insight to some of the important physical parameters of drug release such as the diffusion coefficient, time constant of release, and initial flux. It was found that the release mechanism varies with time, and hence no single model can be used to predict the release profile for the entire period of study. A controlled release study by matrix coating was also done. The results obtained were utilized to examine the suitability of a particular dosage form (matrix geometry) of IgG for clinical applications. The release data compared with the standard methods of IgG therapy proves localized drug delivery to be a major boon for immunodeficient patients.

Introduction

The survival of the human race depends largely on the body's defense mechanism. Better known as humoral immune response, the production of antibodies in response to foreign bodies or "antigens" determines the state of health of any individual. Individuals falling short of this response are said to be immunodeficient and require immune therapy for treatment. This led to the development of γ-globulin therapy about three decades ago.[1] Immunoglobulin G (IgG), a very high molecular weight protein molecule, constitutes the major fraction of the γ-globulin repertoire, and its mean normal serum concentration is of the order 5.4−16.1 g/L. Replacement therapy using IgG is a common feature for patients suffering from hypogammaglobulinemia[2] and for those patients suffering from cancer, burns, and other disorders due to secondary IgG deficiencies. IgG has also been used in the development of efficient immunotherapeutic agents for the treatment of tumors, by the fusion of genetic engineering and hybridoma technology.[3] They function as carriers of drug molecules, which are directed toward a specific antigenic target site located in various parts of the human body.

Classical methods of IgG therapy are done either by intravenous injection or by intramuscular injection.[1] Intramuscular administration of IgG has been in vogue since the early 1950s. However limitations in this therapy, which include the painful method of injection, the persistence of discomfiture, the reduced elevation of serum IgG levels after injection etc. led to the usage of intravenous injection as an alternative in the 1980s. Although the method proved to be effective in certain areas such as an immediate rise in the serum IgG level after infusion, it had its own detrimental effects by introducing certain painful side effects. Further, the dose required for treatment and the frequency of therapy was substantially high, particularly if the treatment is for a tumor. IgG immunotherapy is employed in coordination with the radiation therapy and surgery for extreme cases of tumor. Inspite of these methodologies, the recurrence of malignancies at a site near the original location could not be prevented.[4] This can, however, be avoided if the tumor-bearing region is exposed to increasing doses of radiation and immunotherapy. However, both methodologies have their own defect. Excessive radiation might also affect the normal tissues, and a higher dose of drug might result in systemic toxicity.

A suitable alternative is the use of drug-incorporated polymer matrixes with controlled release applications, which has attracted considerable attention since its practicality was demonstrated.[5] The method is highly attractive due to its reduced dose handling and the drastic reduction in treatment frequency. Controlled delivery of antibody to the mucosal tissue of rats by topical application has been already studied by Kuo et al.[6] Cleek et al.[7] studied the release characteristics of γ-globulin molecules from biodegradable microspheres. Extensive efforts have been put into searching for a suitable polymer carrier and the variety of factors that affect the release kinetics of drug−polymer systems. A nonbiodegradable and hydrophobic polymer, EVAc (ethylene−vinyl acetate copolymer) has been chosen as a drug carrier in many drug−polymer systems because of its proven biocompatibility.[8,9]

In this report, we study the in vitro release kinetics of IgG by using two commercially available dosage forms: the slab and the microsphere. Due to the geometric difference, the release pattern obtained for the two cases will be different, thereby serving as dosage forms for patients with different dose specificities and natures of compliance. Since IgG is naturally present in humans along with other proteins, the in vitro analysis was carried out based on perfusion immunoassay using a high performance liquid chromatography (HPLC) system. We have chosen this method because of its ability to detect specific proteins in a relatively fast and highly automated fashion, as compared to the method of the enzyme-linked immunosorbent assay.[10] The results obtained from the release kinetics were then compared with the conventional methods of therapy and the features discussed.

Materials and Methods

Materials—EVAc polymer (40% vinyl acetate content) (Scientific Polymer Products, Inc. Ontario, NY), IgG crystals (Venoglobulin-I, 2.5 g vial with reconstitution kit, Alpha Therapeutic

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Co., Los Angeles, CA), Protein A/G standard (PerSeptive Biosystems Inc., Framingham, MA).

Methods—*Fabrication of IgG-EVAc Systems*—To prevent the possible denaturation of IgG at high temperatures, which may occur during the classical methods of compression molding and injection molding, a solvent-casting method was chosen for fabrication of drug−polymer systems. The EVAc polymer, which is in the form of pellets, was cleaned as described by Langer et al.[8] It was then dissolved in methylene chloride in a mass ratio of 1:9. IgG crystals were sieved with Endecotts test sieve (250 μm) to obtain the desired size fraction. The amount of IgG powder corresponding to the required drug loading was then weighed out accurately (± 0.0001 g) and added to 10 mL of the resultant EVAc−methylene chloride solution. The drug−polymer suspension was then molded into two geometrical shapes, viz. microsphere and slab as reported in Sefton et al.[11] and Rhine et al.,[12] respectively. Briefly, the drug−polymer suspension was poured into a Petri dish (for slab fabrication) and precooled at −70 °C for 15 min. The dish containing the matrix was initially cooled at −70 °C for 10 min before transferring it to −20 °C. After 2 days, the matrix was kept under mild vacuum for an additional 2 days under room temperature. The resulting matrix was found to be a thin film ~1 mm in thickness. Square slabs with specific dimensions were cut off from the matrix. In the case of microsphere fabrication, the suspension was extruded using a disposable 3 mL syringe fitted with a 16 gauge (BioLaboratories, Singapore) needle into cold absolute ethanol (placed in a container of liquid nitrogen). After leaving for 24 h, the absolute ethanol solution was replaced in order to remove the methylene chloride by liquid−liquid extraction phenomena. The beads that were obtained were finally vacuum-dried for 4 h before using for release study. Microspheres were also prepared using the 19 gauge and 23 gauge sized needles.

Fabrication of Coated IgG−EVAc Matrixes—The slabs that were obtained as per the previous procedure were submerged in 10% EVAc solution for 2 min. Before dipping, one of the 1 × 0.1 cm^2 sides of each slab was covered with a carbon adhesive tape to make it coating free. The slabs were then taken out, and the tape was removed and dried at room temperature for 5 min. Finally, they were dried under mild vacuum at room temperature for 24 h. The same procedure was carried out for slabs coated in 20% and 30% EVAc solution.

In Vitro Release Kinetics Study—Each slice of slab was weighed and submerged in separate beakers containing 2 mL of 0.1 M phosphate buffer, pH 7.4, containing 0.1 M sodium phosphate and 0.15 M sodium chloride (prepared using the PBS pack obtained from Pierce, Rockford, IL) and 4 mg/L gentamicin sulfate (Sigma Diagnostics, St. Louis, MO) which acts as an antibiotic against microbes. A release study was carried out at 37 °C for 1 h. The slices were then removed by forceps, blotted dry by tissue, and then transferred to a fresh buffer solution. Phosphate buffers (2 mL) were analyzed by HPLC to determine the IgG concentration. The same procedure was repeated at specific time intervals. When the releasing was for more than 1 h, the slices were soaked in 10 mL of phosphate buffer to provide the "infinite sink" condition. Buffers (10 mL) were also used to determine the concentrations and to give a clear picture on the percentage of drug that had been released each day. For the case of microspheres, a 50 mg aliquot of microspheres was weighed accurately and subjected to the release study as mentioned above.

HPLC Analysis—The quantification of IgG release was done using the HPLC system (Perkin-Elmer Corporation, Norwalk, CT) and PA Immunodetection sensor cartridge (PerSeptive Biosystems Inc., Framingham, MA). The loading buffer (0.01 M phosphate buffer), pH 7.4, containing 0.12 M sodium chloride and 0.0027 M potassium chloride, was prepared from PBS packs obtained from Sigma Diagnostics while the elution buffer was prepared from 0.15 M sodium chloride, pH adjusted to 2.3 using 6 M HCl. The IgG sample with an injection volume of 50 μL was pumped through the sensor cartridge. The nontarget components of the assay gave the first peak of the chromatography. With the switch of loading buffer to the elution buffer, the IgG−Protein G complexes were dissociated, and IgG was eluted out of the cartridge, which gave the second peak of the chromatography. The sample peak area was obtained by subtracting the chromatogram of the blank from that of the sample. The mass of IgG released was then obtained on comparison with a calibration curve of the peak area plotted against the mass of IgG standard sample taken.

Data Analysis—The decay in the flux of IgG is approximated by a first-order process with a characteristic time constant τ, given by the relation

$$\frac{F}{F_0} = \exp\left(\frac{-t}{\tau}\right) \tag{1}$$

where F is the molar flux as a function of time and F_o is the initial flux. Further, two models of mass transfer were used to analyze the release mechanism of IgG from the polymer matrix. The first one (model I) assumes an infinitely high coefficient of matter transfer on the surface. Hence, making use of the classical Fickian equation for release from slab (thin film):

$$\frac{\partial C_i}{\partial \mathrm{t}} = D_i \frac{\partial^2 C_i}{\partial x^2} \tag{2}$$

where C_i is the IgG concentration in the EVAc matrix as a function of time and position, x is the position within the polymer matrix, and D_i is the diffusion coefficient for IgG transport within the EVAc matrix and assuming that (i) the IgG concentration is uniform throughout the matrix at time $t = 0$ i.e., $C_i = C_i^0$ at $t = 0$, for all x, and (ii) the surface concentration of IgG is maintained at a constant concentration at times $t > 0$, eq 2 can be solved for C_i[13] as a function of x and t. On integrating over the thickness of the film, the amount (mass) of IgG released Q_t from the slab at time t can be obtained. This can be further simplified to obtain the relation for Q_t at short and long times based on the value of Q_t/Q_T

$$\frac{Q_t}{Q_T} = \frac{4}{L}\left(\frac{D_i t}{\pi}\right)^{0.5} \quad \text{for} \quad Q_t/Q_T \le 0.5 \tag{3}$$

$$\frac{Q_T - Q_t}{Q_T} = \frac{8}{\pi^2}\exp\left(-\frac{\pi^2 D_i t}{L^2}\right) \quad \text{for} \quad Q_t/Q_T \ge 0.55 \tag{4}$$

where Q_T is the amount of IgG released at infinite time,[14] and L is the thickness of the slab. The diffusion coefficient D_i for IgG transport in the porous polymer matrix for short and long times were determined by comparing the experimental results to eqs 3 and 4, respectively.

The second model (model II) assumes a finite coefficient of matter transfer on the surface. Starting from eq 2 for a slab of thickness $2L$, the model similar to the previous one, assumes uniform initial concentration of IgG (C_i^0) for all x. The boundary condition representing the loss of IgG at the slab surface is given by eq 5,

$$t > 0 \quad -D_i\left|\frac{\partial C_i}{\partial x}\right| = h(C_s - C_e) \qquad x = \pm L \tag{5}$$

where h is the coefficient of matter (IgG) transfer, C_s is the concentration of IgG at the surface, and C_e is the concentration of IgG required to maintain equilibrium with the medium. Equation 2 can be solved for C_i[13] as a function of x and t making use of the given initial and boundary conditions. On integration over the slab thickness, a relation between the amount (mass) of IgG released Q_t from the slab at time t and the amount released after infinite time Q_T can be obtained.[15]

$$\frac{Q_T - Q_t}{Q_T} = \sum_{n=1}^{\infty} \frac{2N^2}{\beta_n^2(\beta_n^2 + N^2 + N)}\exp\left(-\frac{\beta_n^2 D_i t}{L^2}\right) \tag{6}$$

where N is the dimensionless number given by eq 7

$$N = \frac{Lh}{D_i} \tag{7}$$

and β_n is the positive root of eq 8

$$\beta \times \tan\beta = N \tag{8}$$

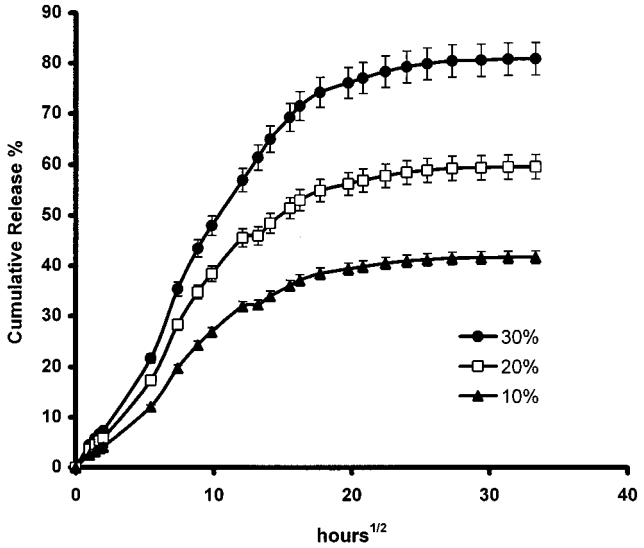

Figure 1—Fraction of IgG released for the 10, 20, and 30% loaded cases, respectively, for the slab geometry. Each point is an average of six data points. Standard error of the mean of release at each time point is 4%.

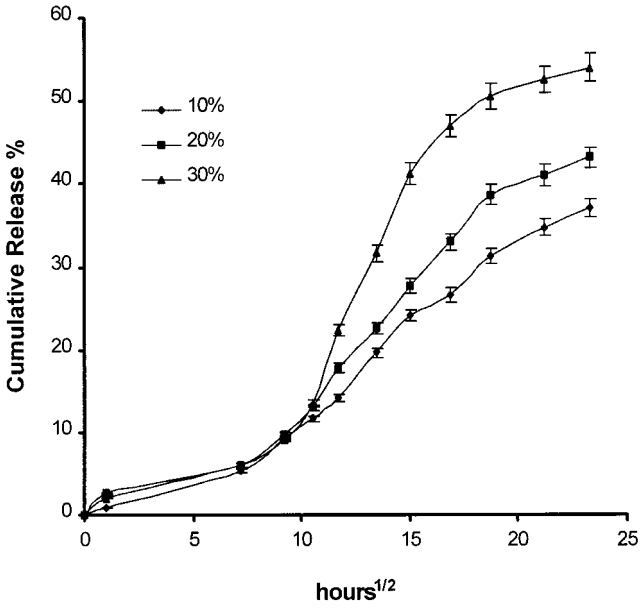

Figure 2—Fraction of IgG released for the 10, 20, and 30% loaded cases, respectively, for the microsphere geometry. Each point is an average of four data points. Standard error of the mean of release at each time point is 3–6%.

The transfer coefficient h and the diffusion coefficient D_i were then determined by fitting the experimental data to eq 6 coupled with eqs 7 and 8.

Results and Discussion

Release Studies—Preliminary studies carried out for different drug loading showed that drug release increased with increased drug loading for both geometries as shown in Figures 1 and 2, respectively. The initial steep slope for the slab geometry is mainly due to the release of drug molecules present on the exterior surface of the matrix that is followed by a stage in which the drug gradually diffuses through the polymer backbone to the exterior of the matrix and therefore a corresponding decrease in the release rate. The possibility of drug dissolution in the buffer followed by diffusion through the solvent-filled pores cannot be completely ignored. Further, since the solubility or the saturation concentration of IgG is less than the drug loading, dissolution in the solvent-filled pores plays a very important role in the initial period of release, whereas the latter period of release is predominated by the diffusion through the pores and channels formed in the matrix.[16]

The very high molecular weight of the IgG molecule restricts its release through the tortuous path within the matrix. Hence, in the presence of the available tortuous path formed by the preceding molecules, the later molecules find their way to the exterior much more easily, and therefore the release rate is gradually maintained but in a decreasing trend because of the increased distance for release. This feature continues until one of the following two limiting cases exist: (1) the path available for the drug to be released becomes more tortuous, and (2) decrease in the available drug content to utilize the existing release path. As a result, the curve tends to be asymptotic at very high time intervals. Thus, the drug release is explained by these two stages, which alternates between each other to give a sustained release. However, this can be avoided by altering the matrix geometry to compensate for the increasing distance for diffusion by increased drug concentration in order to achieve a zero-order release pattern.[17]

On observing the fraction of drug released for slabs from Figure 1, we find that the cumulative drug release rises in proportion with the square root of time for the first 15 days followed by a decline in the release percent. About 81% of the drug was observed to be released after 46 days for the 30% loaded case during which the 10 and 20% loaded cases released approximately 40 and 60% IgG, respectively. It is clearly noted that the drug release follows a square root of time kinetics in the initial period, which might vary for different drug loading and experimental conditions. Since then, the flux deteriorates, following an intermediate transitional order for the next fortnight finally tending toward zero after 45 days. In the case of microspheres, the drug release is initially in the lag period (Figure 2) after which the release gradually improves until an asymptotic behavior exists. The lag period might be due to the role of dissolution playing the rate-limiting step in the release kinetics. An important feature noted in the release profiles is the sigmoidal nature of the curve, and this nature increases for increasing drug loading. Furthermore, the release mechanism of a microsphere approximates that of a slab for smaller drug loading at all times and for higher drug loading at longer times (data not shown). Hence, the geometry of the drug−polymer matrix plays an essential role in deciding the type of release mechanism.

Henceforth, the discussion will be based on the 30% IgG loaded slab and microsphere matrixes (16 gauge size, unless mentioned otherwise) for more rigorous analysis on the release kinetics. In addition, this percentage loading exhibits some agreement with the required dosage levels of drug that has to be maintained in patients suffering from primary immunodeficiency disease.[18] An explanation of this statement is given later in this article.

The decrease in the molar flux of IgG calculated as moles of IgG released perpendicular to a square centimeter of surface area per second from the matrix was found to fit well to the exponential eq 1. F_o and τ were analyzed for slab matrixes with different dimensions (represented by the ratio of surface area to volume [S/V]), with the same thickness using eq 1. The initial flux and time constant for the different cases tabulated in Table 1 agree reasonably well with respect to each other. Further, the release profiles for the slabs with different S/V ratios shown in Figure 3 were in reasonable agreement with each other, thereby confirming the uniformity in drug distribution and the reproducibility of the release kinetics.[12] This is due to the release occurring primarily in the direction perpen-

Table 1—Initial Fluxes and Time Constants Calculated for Slabs of Different Dimensions

S/V (cm^{-1})	initial flux F_0 ($mol/cm^2 \cdot s$) $\times 10^{12}$	time constant (h)
22	1.244 ± 0.03	154.74 ± 1.56
24	1.318 ± 0.025	157.999 ± 2.10
30	1.334 ± 0.026	158.643 ± 1.89

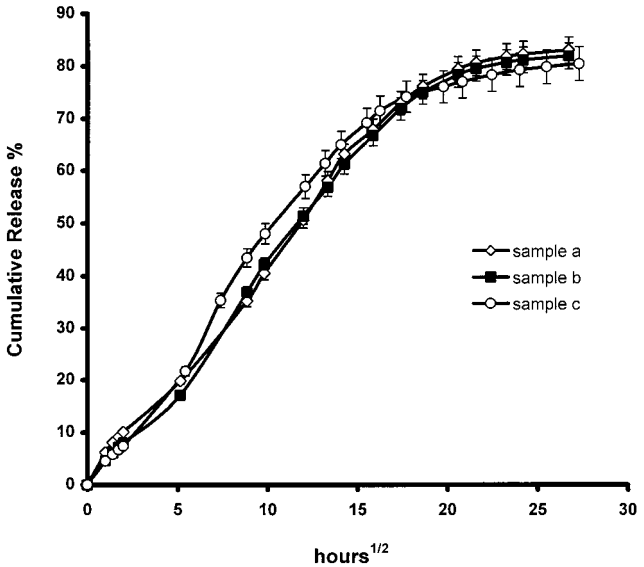

Figure 3—Cumulative percent of IgG release for different sized slab matrixes of 30% IgG loading. (Sample a: 30 cm^{-1}; sample b: 24 cm^{-1}; sample c: 22 cm^{-1}). Each point is an average of four data points, and the error of the mean of the release at each time point is less than 4%.

Table 2—Experimentally Determined Parameter Values for Short and Long Times of Release for the Case of a Slab Using Model One[a]

Q_t/Q_T	D_i (cm^2/s)	tortuosity
≤ 0.50	1.82×10^{-9}	341
≥ 0.55	1.89×10^{-9}	328

[a] $L = 0.1$ cm.

dicular to the thickness of the film. However, this cannot be true for cases in which the thickness is comparable to the other slab dimensions. For example, similar release studies carried out for different sized cubic samples (data not shown) showed variations in their kinetics.

Fitting of the experimental data to model I, i.e., eqs 3−4, show that the diffusion coefficient is almost a constant (see Table 2) with respect to time. The calculated D_i for IgG release through the EVAc backbone agrees reasonably well with the D_{eff} (0.9×10^{-9} cm^2/s) reported by Saltzman et al.[19] for IgG. The slight variation between the two values might be attributed to factors such as the difference in the percentage loading of IgG, the molecular weight of EVAc used, and the matrix geometry. The tortuosity value in the table was obtained on dividing the aqueous diffusion coefficient[20] of IgG (6.2×10^{-7} cm^2/s) by the experimentally determined diffusion coefficient.[21] Hence, it is noted that the path for drug diffusion in the polymer matrix becomes more complicated by an order of ~2 on comparison to unrestricted diffusion in free liquid. This seems to be quite practical on comparison with the tortuosity values obtained in similar experimental runs[22] for other biomolecules. The tortuosity value essentially takes into account all the properties of the polymer−drug and their interactions. In the case of model II, the experimental data was fitted to eq 6 by taking the diffusion coefficient developed in model I as an initial estimate, and refining the values of the

Table 3—Experimentally Determined Parameter Values for Model Two[a]

coefficient of matter transfer (h)	6.89×10^{-5} cm/s
diffusion coefficient (D_i)	2.06×10^{-9} cm^2/s
tortuosity	301

[a] $L = 0.05$ cm.

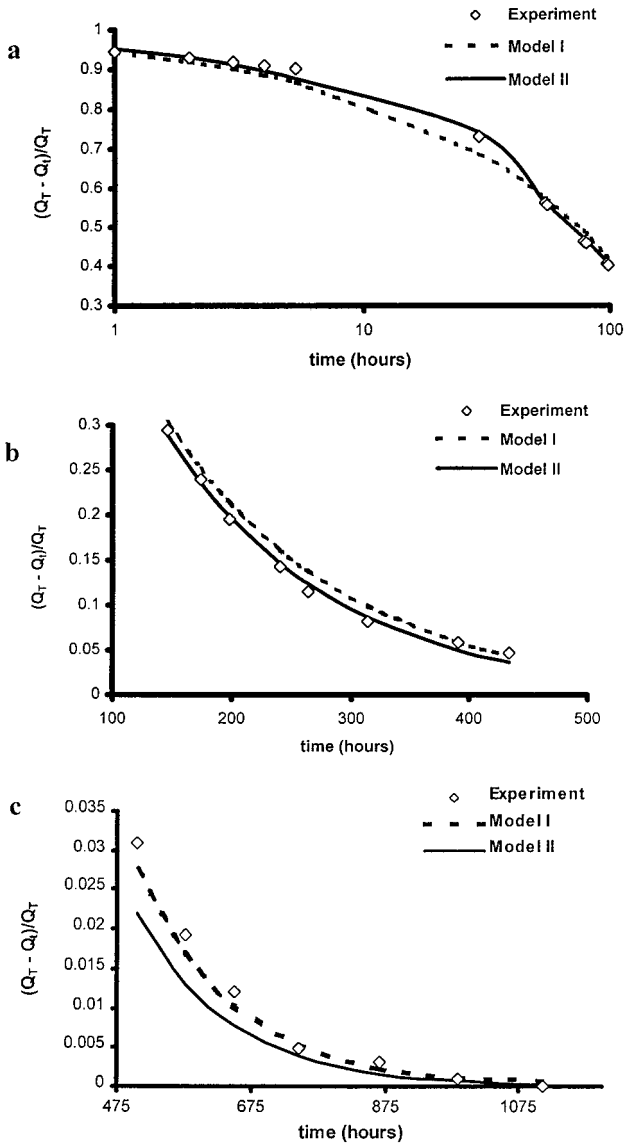

Figure 4—Fraction of IgG released from slab matrixes for (a) time less than 100 hours, (b) between 100 and 500 h, and (c) greater than 500 h.

dimensionless number N and its corresponding β_n by using a standard nonlinear optimization tool. The diffusion coefficient and the matter transfer coefficient that are finally obtained are shown in Table 3. The diffusion coefficient shows a slight deviation from that obtained for model I. Figure 4 gives the variation of the predicted model results from the experimental values. It is clearly seen from Figures 4a and 4b, that model II assuming finite coefficient of matter transfer on the surface is a better model on comparison to model I. Considering the fact that the experiment was conducted under stagnant conditions, the assumption that the rate of matter transfer to the surface by diffusion is equal to the rate at which it leaves the surface proves to be a more realistic model on comparison to model I which assumes all the matter brought to the surface to attain equilibrium with the medium concentration in an infinitesimally short time. Hence, model II approximates itself to model I when we assume an infinite

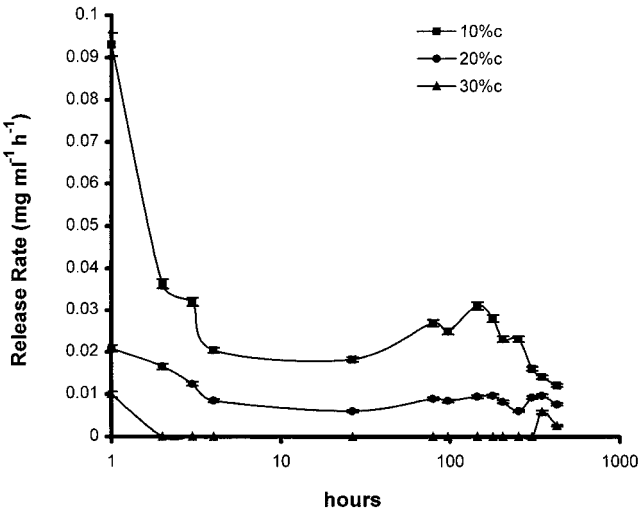

Figure 5—Release rate of IgG from EVAc-coated matrixes. 10, 20 and 30%c refers to 10, 20, and 30% EVAc coating, respectively. Each point is the mean of four data points, and the standard errors of the mean of release at each time point are within 4.5%.

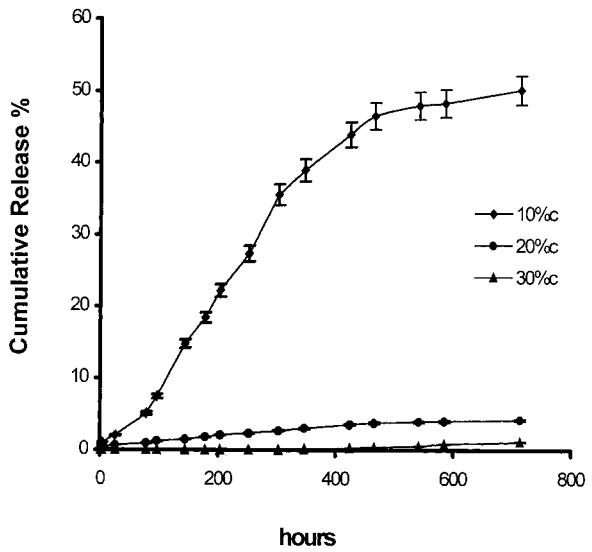

Figure 6—Cumulative percent release of IgG from 10, 20, and 30% coated matrixes. The symbolic representations and the standard errors are the same as those of Figure 5.

matter transfer coefficient ($h \rightarrow \infty$ and $N \rightarrow \infty$) on the surface. However, a slight deviation of the fitting of model II when compared to model I at higher time i.e., $t > 500$ h (Figure 4c) might be due to the experimental conditions involved and the limitations imposed by model II when the surface concentration C_s tends toward the equilibrium concentration C_e. This error observed is practically negligible, considering the fact that more than 76% of IgG has been released at that point of time (Figures 4a and 4b), and the rate of release is so low enough that the fraction of drug released is only 3% during the period greater than 400 h (Figure 4c).

Coating of matrixes (slab) in polymer solution significantly controlled the release rate as seen in Figure 5 which shows the release rate of IgG from matrixes coated in 10%, 20%, and 30% EVAc solution. The profile obtained is not as smooth as that got for uncoated matrixes. The sudden rise and fall in the release rate might be due to the EVAc coating, which, although initially impermeable to the IgG molecules, gradually forms a porous network due to the entry of the buffer solution, thereby bringing about the release of IgG molecules. Hence, a sudden rise in the release rate occurs, which then decreases because of the existence of one of the two limiting cases that have already been mentioned in this paper for uncoated matrixes. From Figure 6, we find that only about 50% and 4% of IgG has been released from the 10 and 20% coated matrixes after 700 h. In fact, the release of IgG from the 20% coated matrix is almost following a time-independent release profile, and this will continue until the coating gives way to porous networks for the IgG molecules to diffuse out. Coating of 30% EVAc polymer solution (or rather a paste because of its highly viscous nature) does not show any measurable release for the first 2 weeks after which the release gradually followed the 20% coating case.

From a clinical viewpoint, one of the primary objectives of sustained release is to maintain the required drug concentration at a reduced dosage level in patients. The usual dose of immunoglobulin for a primary immunodeficiency disease is 200 mg/kg of a patient's body weight[23] normally administered once per month by intravenous infusion (ivi). Although the minimum concentration of IgG necessary for protection has not yet been established, Pirofsky[18] has reported that an ivi of 150 mg/kg to a patient will result in the increase of serum IgG concentration to approximately 300 mg/dL which decays or is used up completely over a span of 28 days. Extrapolating from our experimental data, we find that a slab polymer drug matrix of dose 2.771 mg/kg (assuming an average patient weight as 50 kg) can give the same residual IgG concentration as the 150 mg/kg ivi case and can persist for a period more than one month before resulting in the decrease of concentration for a period of at least 2 months. This dose is found approximately 54 times less than the apparent ivi dose reported by Pirofsky.[18] Therefore a 3.704 mg/kg dose of the polymer–drug matrix can bring about the same effect as the conventional ivi of 200 mg/kg. Since it is a 30% loaded matrix, the total mass of the matrix administered to a 50 kg patient will be 617.5 mg. Hence, approximately six slabs of ~100 mg each will solve the process. Although the comparison above will be valid only if we get the exact relation between the in vitro and in vivo study, this work serves as a preliminary step in identifying the role played by controlled drug delivery to attenuate the problems faced by some of the conventional methods of drug treatment.

The methodology employed in the fabrication of microspheres is a nonaqueous encapsulation protocol in contrast to the commonly used double emulsion encapsulation technique.[24] The nonaqueous methodology is advantageous because it enhances the stability or the structural conformation of IgG, thereby protecting the native structure of the biomolecule as mentioned by Costantino et al.[25] The dehydrated proteins on suspension in organic solvents are conformationally rigid, and the chances of moisture induced aggregation are drastically reduced. Further, the question posed on the deteriorating activity of the protein under such conditions and the ways to overcome them have been discussed by Klibanov.[26] However, the study of IgG stability will be a very interesting topic for future investigations in this field.

All the release kinetics were studied under stagnant conditions (i.e. no shaking), since the implanted materials are localized in a rigid manner as in the case of a drug–polymer matrix being compactly placed and held inside the resection cavity of the pathological site.[27] Studies correlating the in vivo and in vitro release are few, and they greatly depend on the physiological environment in which the wafer has been placed, the presence of fluid remaining around the site, and the type of wafer involved. The initial flux F_o and the time constant of release τ are some of the few in vitro parameters that researchers use in their in

vivo model analysis.[28] The F_o and τ values in the case of slabs are given in Table 1. In the case of microspheres, the 30% loaded case had an initial flux value of 3.13×10^{-13} g·mol/cm^2·s and a time constant of 320.19 h with a deviation of less than 5%. The higher value of time constant and the lower value of F_o are due to the lag period experienced in the initial period of release. Hence, patients who cannot withstand high doses of IgG at the beginning can be recommended for the microsphere dosage form, and the slab dosage form can be recommended for the opposite case.

In general, the exact mechanism by which the IgG molecules are released through the EVAc into the buffer is based on a combination of different factors such as dissolution of the drug in the buffer, the relaxation rate of the polymer chains, the diffusion rate of the drug molecule through the polymer backbone, the experimental conditions involved, and last on the nature of the polymer, drug, and their interactions. This study serves as another step to elucidate the mechanism of release of macromolecules through an EVAc backbone and tries to identify the dosage form suitable for different type of patients.

Conclusions

The in vitro release kinetics of IgG−EVAc system fabricated by a solvent-casting method was studied for slab and microsphere geometry. Mass loading of IgG was found to affect the release rates significantly for both geometries. Release experiments conducted for the 30% loaded slab matrixes showed that the release rate followed a classical Fickian type of diffusion until 75% drug release (or for time $t < 15$ days) and gradually approaches the time-independent release for $t > 30$ days. Experiments conducted with matrixes of different surface areas showed a similar release pattern, and reproducible initial release flux and time constants were obtained. The one-dimensional pattern of drug release was the cause for reproducible results. Coating significantly controls the release rate of IgG from the matrix with the 20% EVAc-coated matrix providing a quasi-zero order drug release. Microsphere geometry gives a release pattern similar to the slab geometry, except for the initial lag time followed by Fickian type of diffusion. A model incorporating the finite matter coefficient of transfer on the surface seems to be more accurate than another model, which has an infinite matter transfer coefficient on the surface. The temporal variation of the diffusion coefficient was not significant. On correlating the experimental results with clinical data, it was worth noting that the polymeric implant dosage form can reduce the dose administration drastically compared with standard dosage forms.

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