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Assessment of diffusion coefficient from mucoadhesive barrier devices using artificial neural networks

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Abstract

This study is aimed to elucidate the physicodynamic phenomena governing diffusion coefficient (D) of the loaded drugs in a female controlled drug delivery system (FcDDS) and to find the most influencing variable on the diffusivity using artificial neural networks (ANN). The release profiles of sodium dodecyl sulphate (SDS), a topical microbicide used as a model drug, from FcDDS were obtained using in vitro apparatus, the Simulant Vaginal System (SVS), under various conditions. The effects of formulation and intrinsic/extrinsic variables on the diffusivity of SDS were assessed using artificial neural networks (ANN). The release profiles of SDS from FcDDS revealed a non-linear relationship between the diffusivity and formulation/physiological variables. Intrinsic variables (vaginal fluid pH, vaginal fluid secretion rate) have a more prominent role in defining the diffusion coefficient of SDS from FcDDS than formulation variables (formulation loading weight and loaded doses in the formulation) or extrinsic variables (inserting position). Among 5 variables, pH of vagina fluids is the most influencing factor in defining the diffusion coefficient (maximum value of 0.95 ± 0.04) of SDS from FcDDS. The external exposure conditions clearly outweighed the effects of the formulation variables on the diffusion coefficient of SDS. A model-based approach can be used to assess the diffusion coefficient of loaded drugs in FcDDS under the given conditions, leading to a parameter-specific prevention strategy against sexually transmitted diseases (STD) with a high degree of confidence. Published by Elsevier B.V.

Keywords: Diffusion coefficient; Mucoadhesive barrier devices; Intrinsic/extrinsic variables; Artificial neural network

1. Introduction

There are a variety of techniques applicable for the discovery of rules, patterns and relationships in a given data set. Artificial neural networks (ANN) are a machine-based computational technique, which was initially introduced to simulate neurological processing ability of the human brain via mathematical modeling of its functional unit (Hopfield and Tank, 1985; Achanta et al., 1995). They are networks of adaptable nodes, which store experimental knowledge through the learning process from the given samples and can be applicable to establishing a nonlinear relationship between the causal factors and pharmacological efficacy (Chen et al., 2002). Therefore, ANN can be considered as an advanced nonlinear regression model to assess the association of variables by means of iterative training of data obtained from a designed experiment. ANN has been successfully applied to solving various problems in pharmaceutical research, such as product development (Hussain et al., 1991), estimating diffusion coefficients (Jha et al., 1995), predicting the mechanism of drug action (Nair et al., 1994), predicting pharmacokinetic parameters (Brier et al., 1995; Smith and Brier, 1996; Weinstein et al., 1992), automated diagnosis of heart disease (Higuchi et al., 2006), evaluation of the direction and dynamics of changes in lipid parameters (Stachowska et al., 2006) and the classification of primary oesophageal dysmotility (Santos et al., 2006). It was also found that ANN predictions are more accurate than those predicted by polynomial equations (Chen et al., 2002).

In this study, ANN was applied to analyzing the quantitative relationships between physiological variables and release profiles of loaded drugs from a female controlled drug delivery system (FcDDS) which has been developed as an intravaginal barrier device in a form of gel to prevent the onset of

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Table 1
Factors affecting drug release profiles and efficacy of the FcDDS

Variables	Conditions	Description	References
SDS concentration	3, 5%	The concentration of SDS at the application site needs to achieve the minimum effective concentration required for HIV inhibition within 2 min of initial application	Howett et al. (1999), Krebs et al. (2000), Krebs et al. (1999)
Loading weight of Gel	1.5, 3.0 g	The loading weight of SDS gel will examine the volume effects on the rate of drug release from SGF	Kim et al. (1992)
Flow rate of VFS	3, 5 ml/h	The flow rate of VFS will reflect the physiological secretion rate (30–60 mg/day) of vaginal mucus at the different phases of the menstrual cycle	Gorodeski et al. (1998), Ruel-Gariepy et al. (2000)
pH of VFS	4.0, 5.5, 7.4	Normal pH range of vaginal secretion is 3.0–5.5. Menstrual and cervical secretions and semen act as alkalizing agents to increase vaginal pH	Hunter and Nicholas (1959), White and Aitken (1989)
Speed of rotation	0, 5 rpm	The dynamic movement was added to the system by shaking and rotating from vertical to horizontal position at various speeds	Hernadez et al. (1998), Sauer et al. (1998)
Site of application	5, 15 cm	The loaded position of SGF will affect the time required to achieve the effective microbicidal concentration at the application site	Ceschel et al. (2001)

The minimum effective SDS concentration: 0.025% (Howett et al., 1999). VFS: vaginal fluid simulant.

sexually transmitted disease (STD) including AIDS (Wang and Lee, 2002, 2004). FcDDS, a gel-type formulation, which was made of a combination of carbopol polymer (934P NF) and hydroxypropyl methylcellulose (HPMC) and loaded with sodium dodecyl sulfate (SDS) as a model microbicidal agent was prepared for this study. FcDDS is intended for a burst release of SDS within a minute of application and gradual release afterwards. As FcDDS is administered inside vaginal cavity where drug release, distribution and pharmacological activity are not easily traceable, a full grasp of the physicodynamic phenomena involved in the drug release and microbicidal activity within the vagina is necessary (Ballagh, 2004). Diffusion coefficient (D), which defines the release profiles of drug from FcDDS, was chosen as a major parameter to assess and predict the kinetics of medical and pharmaceutical applications (Khan et al., 2006). Diffusion of multi-component mixture is usually approximated by defining single diffusion coefficient for each solute, which evaluates the ratio of flux of the solute to its concentration gradient (Fick's law) (Lauffer, 1961; Burke et al., 2005).

To evaluate the effects of various variables on the diffusion coefficient of FcDDS, we used an advanced apparatus called "Simulant Vaginal System" (SVS), which precisely mimics the physicodynamic conditions of the vagina, being equipped with the vaginal fluid whose rate and pH are easily controllable as programmed (Wang and Lee, 2004). The variables were categorized as formulation variables (loading weight and SDS loading doses of FcDDS), intrinsic variables (vaginal fluid pH, vaginal fluid secretion rate, and speed of rotation) and extrinsic variables (inserting position) and evaluated for their prognostic potency on pharmacological activity (Wang and Lee, 2002). Ninety-six sets (i.e., as described in Section 2) of data were generated for this study under various combinations of variables tested in in vitro SVS.

In this study, it was hypothesized that the relationship between the release profile of SDS, a topical microbicide used as a model drug, from FcDDS and the diffusion coefficient can be accurately established using ANN. This relationship can be further transformed into the model-based learning features, which are able to predict the pharmacological efficacy of FcDDS under various intrinsic and extrinsic conditions. The efficacy assessment was based on previous findings that total HIV-1 inactivation was achieved with SDS concentrations as low as 0.025% after topical exposures at body temperatures (Howett et al., 1999).

2. Materials and methods

2.1. Materials

Carbopol 934P NF and HPMC (METHOCEL^{R}) were obtained from BFGoodrich (Cleveland, OH) and Dow Chemical Company (Midland, MI), respectively. SDS, ^{14}C labeled SDS (0.1 mCi/ml) and bovine submaxillary gland mucin (BSM: Sigma, St. Louis, MO) were obtained from Sigma chemical company (St. Louis, MO). All reagents and solvents were of analytical grade.

2.2. Preparation of carbopol-HPMC gel containing SDS

Carbopol-HPMC gel formulation containing SDS was prepared by mixing two solutions: Carbopol (1.5%) and HPMC (1.5%) separately dissolved in the citrate buffer solution (pH 4.0). A proper amount of SDS (the ratio of ^{14}C labeled SDS and SDS was 1:5000) was added into the mixture solution and stirred constantly until the solution was completely homogenized. 100 g each of Carbopol-HPMC gel was prepared under various conditions as described in Table 1. The batch size of the gel was optimized by adjusting concentrations of a gel, condi-

tions of gelation process, viscosity, surface tension and porosity (Wang and Lee, 2002, 2004).

2.3. The drug release profiles

The in vitro simulated vaginal system (SVS) was used to obtain the release profiles of SDS from FcDDS under physiologically simulated conditions. Content of ^{14}C-SDS was analyzed by Liquid Scintillation Counter (a model LS-6500, Beckman Coulter, Fullerton, CA). The modified Higuchi equation:

$$Q = (2ADC_s t)^n \quad (1)$$

was used to examine the release profile of SDS from FcDDS, in which Q is the percentage of drug released from the FcDDS at time t (in hours), n is the diffusion exponent, A the total concentration of drug in the system, D the diffusion coefficient of the drug in the system, and C_s is the solubility of drug in physiological buffer. The modified Higuchi equation has been sensitive to changes in formulation size or loading doses in predicting a linear relationship between drug release and the square root of time (Zimm et al., 1996). Measurements of diffusion coefficient of each solute were followed.

2.4. Data collection for ANN

FcDDS made of carbopol (1.5%) and HPMC (1.5%) gel were incorporated with varying concentrations of sodium dodecyl sulphate (SDS) [3–5% (w/w)]. The major variables that may affect the release profiles of SDS from FcDDS are summarized in Table 1. Vaginal fluid simulant (VFS), which was made of mucin and the other components (NaCl, KCl, sodium acetate, urea, albumin, lactic acid, amino acids and glycerol) (Owen and Katz, 1999) and adjusted to varying pHs, was overflowed on top of FcDDS. The flow rates of VFS (3–5 ml/h) were selected based on the physiological secretion rate as described previously (Hunter and Nicholas, 1959). Among those variables, pH of VFS has 3 conditions and the rest variables have 2 conditions (maximum and minimum values) each. Therefore, 96 cases (the combination of 5 variables (dose, weight, VFS rate, speed of rotation) with 2 conditions, one variable (pH of VFS) with 3 conditions = $2^5 \times 3$) of the release profiles were analyzed to obtain the onset and duration of the effective concentration (EC50) as a function of 6 variables. A large number of release profiles obtained for FcDDS under various conditions made it possible to perform a computational analysis through parameter fitting and data mining approach.

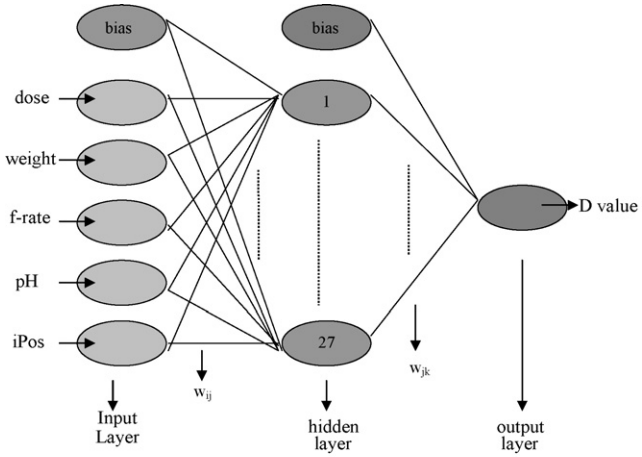
2.5. Development and training of the ANN

ANN has been used to classify, interpret and evaluate the formulation and physiological variables involved with the development of intravaginal delivery systems. In the multivariable system, the quantitative relationship between causal factors and response variables is thought to be complex and nonlinear. In this context, a more precise assessment and new information on the detailed characteristics of such formulations can be obtained by analyzing all, or a sufficient number of the individual subunits through an advanced technique. In addition, the manufacturing of such multiple subunits can be optimized in detail to obtain the best quality product achievable, which has not been possible previously.

ANN was used as an advanced data mining approach to assess the release rate of SDS from FcDDS through machine learning features and to find the prevailing prognostic factors among variables. ANN was built using the forward and backward variable selection process and based on tanh (i.e., the hyperbolic tangent of x, i.e., $\sinh(x)/\cosh(x)$) and linear transfer functions. Commercially available Neural Networks software (STATISTICA, StatSoft Co., Tulsa, OK) with a personal computer was used in modeling and optimization of SDS release from FcDDS.

The schematic diagram of the ANN used in this study is shown in Fig. 1. ANN has three layers: input, a hidden layer of radial centers and an output layer. The number of input layer is same as input variables. The radial layer units represent the centers of clusters of known training data, which is typically large. The number of units in this hidden layer usually cannot be less than the number of training cases without sacrificing performance; the simplest approach is to use the full set of training cases. This layer must be trained by a clustering algorithm such as sub-sampling, K-means or Kohonen training. The output layer performs a specialized function and each unit in the output layer simply divides the output of the associated previous layer.

For network training, the network architecture consists of five neurons in the input layer ($N = 5$) and one neuron in the output layer ($M = 1$) (i.e., six input variables and one output variable D). It is possible to select the number of units (nodes) in the second radial layer, the smoothing factor (which controls the deviation of the Gaussian kernel function located at the radial centers) and clustering algorithm (such as sub-sampling and K-means), as previously described (Jha et al., 1995). The selected structure had four layers: the first layer had two input units;



Network Statistics:

Training Algorithm = BackPropagation of errors
Learning Rate (alpha) = 0.1;
Hidden layer activation function = 1 / (1 + e ** -x) (binary sigmoid function)
Output layer activation function = 1 / (1 + e ** -x) (binary sigmoid function)
Stopping condition of learning = Min Root Mean Square of errors

Fig. 1. The flow chart of ANN.

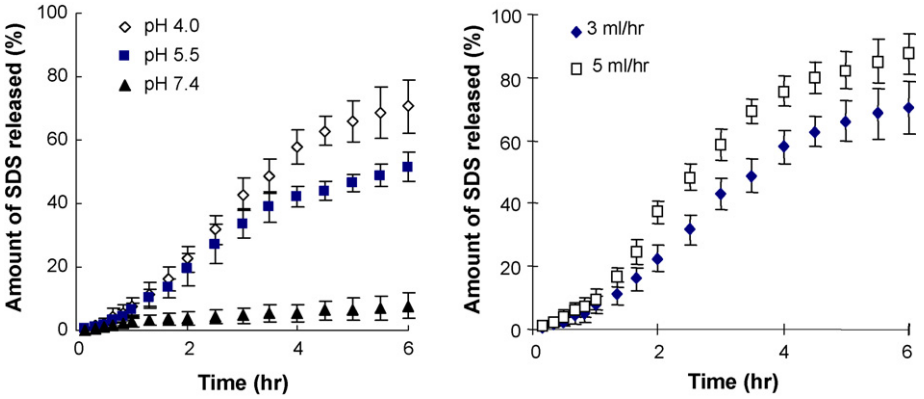


Fig. 2. The effect of fluid pH or fluid rate on the release profile of SDS from FcDDS.

the second layer had 10 hidden units (with negative exponential activation function and radial PSP function). To arrive at the optimum network configuration, 10 network training runs taking 1 to 10 neurons ($L = 1$–10), respectively, in the hidden layer were performed. These units in the hidden layer were assigned using a *K*-means center assignment algorithm. The third layer had seven units (with linear activation and PSP function). The fourth layer had six output units (linear activation and division PSP function).

The network was trained according to the steps previously described (Jha et al., 1995). A single iteration involves as many forward and reverse passes as the number of input patterns in the training set. The learning period was completed when minimum "root mean square" (RMS) was reached:

$$\mathrm{RMS} = \left[\sum \frac{(y_i^p - y_i^m)^2}{n}\right] \quad (2)$$

where RMS is the root mean square, y^p the experimental (observed) response, y^m the calculated (predicted) response and n is the number of experiments. Regression network training sets the weights on the third and fourth layers, which are used to estimate the regression curve. The network weights obtained have been proved useful for estimating diffusion coefficients over a wide range of experimental conditions.

2.6. Data normalization and interpretation for ANN

Since each parameter has a different scale, data in each set are normalized using the weighted mean (1/SE) before combining the effective sizes of each parameter. Different preparations and schedules adapted across the parameters were normalized using the objective categorization process. *D* values in figures (*Y*-axis) shown in Section 3 were rescaled by dividing with 5×10^{-6}, being placed in a range between 0 and 1 for the better comparative demonstration.

3. Results

3.1. Drug release profiles

As previously described, formulation variables (loading weight and SDS loading doses in FcDDS), extrinsic variables (inserting position and speed of rotation) and intrinsic variables (VFS pH, VFS secretion rate) were evaluated for their contribution to the release profiles of SDS from FcDDS. The results of the estimated effects of various variables on drug release profiles of SDS from FcDDS were shown in Fig. 2. There was a wide variation in the release profiles, which were characterized by two stages of the burst release followed by a complete diffusing out towards the final stage. For the entire 6 h span of the release profile, the released amounts at an early stage increased exponentially up to 1 h, and the amount increment became linear, then gradually reaching a plateau at about 5 h. In other words, an initial burst release was followed by the second burst release of up to about 25% of the loading dose and as system hydrolytic erosion continued, the system disintegrated at about 5 h and released the drug into the medium with a higher rate. The cumulative release amount of SDS from FcDDS gradually reached about 80% of the loading dose, as SDS entrapped within the inner region of FcDDS was mostly diffused out.

The release profiles were greatly affected by changes in the levels of the vagina fluid pH and fluid rate. As the pH of FcDDS increased from 4.0 to 7.4, its viscosity increased, further affecting the drug release rates. VFS with pH 7.4 significantly lowered the release rate of SDS from FcDDS, the total released amount of SDS in 5 h achieving only about 8% of the loaded dose in the system. The vaginal fluid secretion rate also has prominent effects on the drug release profiles from FcDDS; the release rate of SDS under a VFS flow rate of 5 ml/h was much faster than that of 3 ml/h.

The gel swelling process under the acidic conditions is classically Fickian, suggesting that drug transport, in most conventional cases, is controlled by the exchange rates of free water and relaxation of polymer chains. However, it was observed that the phenomenon produced by FcDDS did not follow Fick's law, probably owing to the predominant influence of extrinsic/intrinsic parameters. Although the drug loading amount and formulation weight may have distinctive effects on the initial burst release of loaded drugs, no apparent effect on the release behavior of SDS from FcDDS is detected mainly because the polymer hydrolytic erosion caused by extrinsic/intrinsic variables is the prevailing mechanism.

Table 2
Diffusion coefficient values of the samples under various conditions of formulation and intrinsic/extrinsic variables obtained using ANN (Selected from 96 cases)

No.	Loading dose (g/100 ml)	Gel weight (g)	pH of VFS	Flow rate (ml/h)	Insertion Position (cm)	D value ($cm^2\ h^{-1}$)
1	3	1.5	4.0	3	5	0.0586
2	3	1.5	4.0	3	15	0.0455
3	3	1.5	4.0	3	5	0.0359
5	3	1.5	4.0	5	15	0.0769
8	3	1.5	5.5	3	15	0.0258
11	3	1.5	5.5	5	15	0.0408
14	3	1.5	7.4	3	15	0.0020
20	3	3.0	4.0	3	15	0.0243
23	3	3.0	4.0	5	15	0.0590
26	3	3.0	5.5	3	15	0.0345
29	3	3.0	5.5	5	15	0.0342
38	5	1.5	4.0	3	15	0.0264
44	5	1.5	5.5	3	15	0.0166
47	5	1.5	5.5	5	15	0.0312
64	5	3.0	5.5	5	15	0.0257

3.2. Effects of variables on drug diffusion coefficient

The effects of physiological variables on the diffusion coefficients (D) of loaded drug from FcDDS were examined using an ANN model. In this study, the mass transfer profiles of SDS in the polymer gel (fixative polymer composition) were fitted to the experimental data. The information gained by parameter fitting could be useful in understanding and predicting how much formulation and physiological variables influence the release profiles of loaded drugs in FcDDS.

The effects of various variables on the diffusion coefficient assessed using ANN are shown in Table 2. The 15 samples out of 96 cases were retrospectively chosen based on the conditions that properties of all the variables tested in this study were fully represented and outcomes of diffusion coefficient were distinctively comparable. The diffusivity value was calculated as 0.002 $cm^2\ h^{-1}$ under the experimental conditions of pH 7.4 and a flow rate of 3 ml/h (Exp No. 14), while the diffusivity varied to 0.0243 $cm^2\ h^{-1}$, as the pH of VFS was changed from neutral to acidic pH 4.0 (Exp No. 20). The diffusivity significantly increased to 0.059 $cm^2\ h^{-1}$ as the flow rate was changed from 3 to 5 ml/h (Exp No. 23). The root mean square (RMS) value, a statistical measure of the magnitude of a varying quantity, for diffusion coefficient of the network was estimated as 0.9987, which is validated the accuracy of estimated outcomes (Kamuntavicius, 1997).

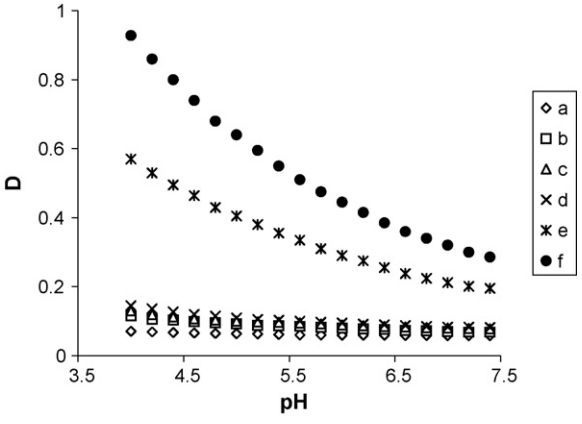


Fig. 3. The effect of the fluid pH on the diffusion coefficient (D; $cm^2\ h^{-1}$) of SDS from FcDDS (flow rate; (a) 2.5, (b) 3.0, (c) 3.5, (d) 4.0, (e) 4.5, (f) 5.0) (D: a scale of 5×10^{-6}).

The release profiles of SDS revealed a non-linear relationship between the diffusion coefficient and formulation/physiological variables. The most distinctive differences in the correlation profiles were observed in Fig. 3, in which diffusivity of SDS from FcDDS were significantly affected by pH, demonstrating that diffusivity values decreased as the fluid pH increased. Six plots in Fig. 3 correspond to the VFS rates, ranging from 2.5 to 5.0 ml/h. Judging from the network estimated outcomes, the diffusion coefficient becomes almost constant irrespective of pH, when the fluid rates were less than a threshold value which was about 4.0 ml/h. When the fluid rates were above the threshold rate, the diffusion coefficient rapidly decreased as the fluid pH increased up to 5.5 and thereafter increased with a slower rate before it eventually became flattening out. It is also demonstrated that the diffusion coefficient at a fixed fluid rate decreased as drug loading amount increased (Fig. 4) or weight of FcDDS increased (Fig. 5). For comparison purposes, the maximum values of diffusion coefficient calculated for each variable were shown in Table 3. The maximum value of diffusion coefficient at a fixed fluid rate was lower than those at fluid pHs (0.85 ± 0.05 vs. 0.95 ± 0.04). An insert position also affected the diffusion coefficient (Fig. 6), but the maximum value of diffusion coefficient was much lower than that of at fluid pHs (0.41 ± 0.03

Table 3
The maximum values of diffusion coefficient for each formulation/intrinsic/extrinsic variable ($N = 6$, D: a scale of 5×10^{-6})

Variables	D value ($cm^2\ h^{-1}$)
SDS concentration	0.58 (±0.04)
Loading weight of gel	0.64 (±0.04)
Flow rate of VFS	0.85 (±0.05)
pH of VFS	0.95 (±0.04)
Site of application	0.41 (±0.03)

$N = 6$.

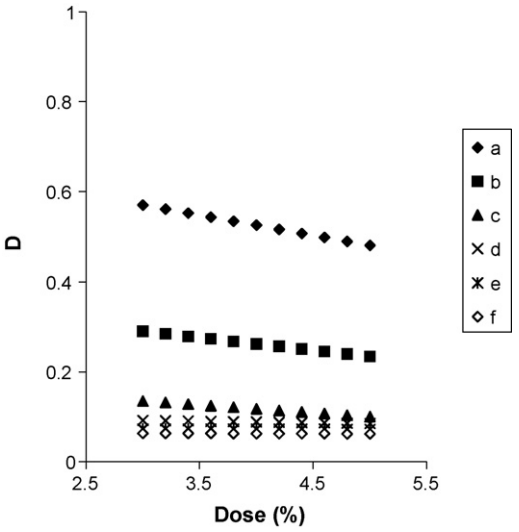


Fig. 4. The effect of the loading dose (%) on the diffusion coefficient (D; $cm^2\ h^{-1}$) of SDS from FcDDS (flow rate; (a) 2.5, (b) 3.0, (c) 3.5, (d) 4.0, (e) 4.5, (f) 5.0) (D: a scale of 5×10^{-6}).

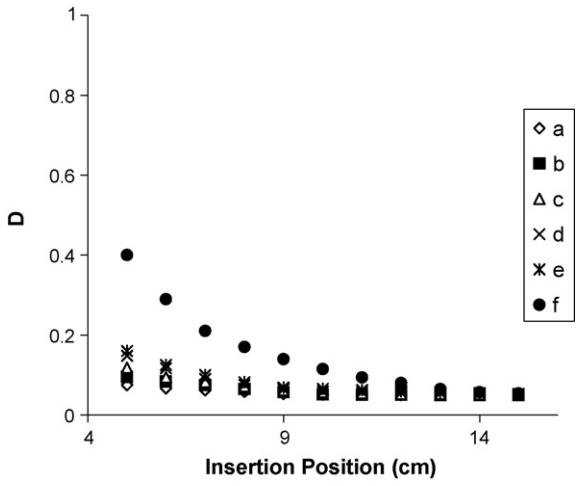


Fig. 6. The effect of the insertion position (cm) on the diffusion coefficient (D; $cm^2\ h^{-1}$) of SDS from FcDDS (flow rate; (a) 2.5, (b) 3.0, (c) 3.5, (d) 4.0, (e) 4.5, (f) 5.0) (D: a scale of 5×10^{-6}).

vs. 0.95 ± 0.04). These results confirmed that fluid pH is one of the most influencing parameters for defining diffusivity of FcDDS.

The distinctive deviation of the SDS release rates estimated by ANN from those by linear-regression on the Higuchi equation indicated that the erosion of the polymer matrix driven by externally-added vaginal fluid on the gel was the major force that defined the release profiles of SDS from FcDDS. Especially, the speed of rotation significantly affected the diffusivity when the fluid rate was greater than 4.0, as shown in Fig. 7. The obtained results indicated that the prevalent release mechanism of SDS from FcDDS seemed to be the combined action of erosion and diffusion (anomalous, non-Fickian mechanism).

4. Discussion

When a matrix system is implanted into the organs, a cumulative drug concentration to the target site is hardly assessable. The most common procedure for identifying an optimized release behavior of polymer-based systems at the implantation site has been to analyze the formulation on the dose level, i.e., one or more dose units (Moriguchi et al., 2006). However, with extrinsic/intrinsic hydrodynamic conditions, factors other than those involved with formulation (i.e., dose or weight) also significantly affect the release profiles of loaded drugs. Different from other topical delivery routes, vagina is unique in that it has hormone regulated reproductive organ (Chien and Lee, 2002). Most mucosal sites, such as nasal or rectal, have relatively perpetual physiological regulation, whereas vagina has more dynamically active and fluid rich organs. Owing to that, even though it has a huge potential to serve as a route for the topical/systemic deliv-

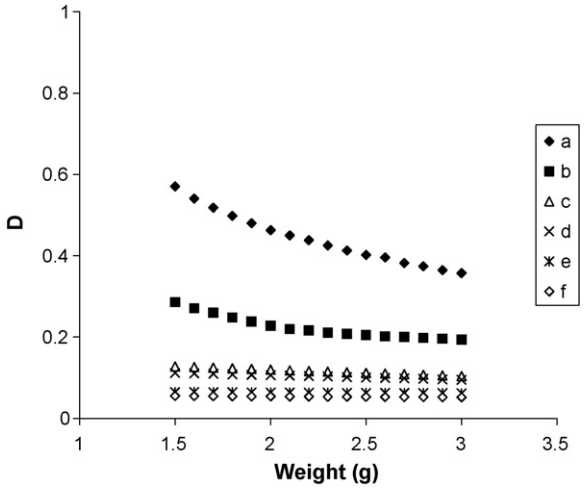


Fig. 5. The effect of the loading weight (g) on the diffusion coefficient (D; $cm^2\ h^{-1}$) of SDS from FcDDS (flow rate; (a) 2.5, (b) 3.0, (c) 3.5, (d) 4.0, (e) 4.5, (f) 5.0) (D: a scale of 5×10^{-6}).

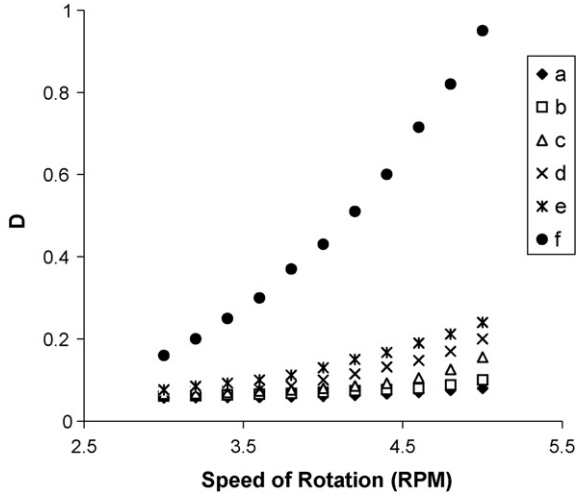


Fig. 7. The effect of the speed of rotation (rpm) on the diffusion coefficient (D; $cm^2\ h^{-1}$) of SDS from FcDDS (flow rate; (a) 2.5, (b) 3.0, (c) 3.5, (d) 4.0, (e) 4.5, (f) 5.0) (D: a scale of 5×10^{-6}).

ery of exogenous compounds, its actual usage is very limited. Through this study, we have attempted to elucidate physicodynamic phenomena involved with intrinsic/extrinsic variables of vagina and set a proper guide in application of these variables to the intravaginal delivery of exogenous compounds.

Since vaginal secretion rate and pH have an integral role in regulating polymer hydrolytic erosion and drug release rates from the intravaginal formulation, the statistic tool which can accurately generate and precisely interpret the experimental data seems to be essential in evaluating efficacy of FcDDS. The nonlinear dependence of diffusion coefficient on concentrations of surfactant and electrolyte, together with the complex nature of the interactions between them, makes it difficult to describe the diffusion phenomenon by computationally simple and unique phenomenological or empirical models (Schliecker et al., 2004). Excellent correlations for predicting the effects of nonionic surfactant partitioning on the dissolution kinetics of residual drug in a model porous medium were previously reported (Sharmin et al., 2006). However, these processes needed to define several experimentally determined parameters and prediction of release profiles based on the polynomial equation was often limited to low levels, resulting in poor estimation of the optimal formulations. Moreover, extrinsic/intrinsic variables make it more complicate to analyze given data set. On the other hand, a data mining approach that posses the ability to learn and generalize nonlinear functional relationship(s) can be very effectively employed to arrive at a correlation for estimating diffusion coefficients based on a set of limited data and easily measurable experimental conditions.

In order to overcome the shortcomings in multiple regression analysis, a multi-objective simultaneous optimization technique incorporated with artificial neural network (ANN) has been developed (Glass et al., 2005). ANN is a flexible, nonlinear modeling tool that is an extension of traditional statistical techniques. ANN is a hierarchical architecture wherein neurons in the neighboring layers are fully interconnected and the strength of a connection is known as weight. The main advantage of ANN is very rapid training in data acquisition, which makes regression networks more effective than polynomial equations in situations where approximations of such relationships are required (Chen et al., 2002). The neural networks are applicable to most data mining fields and various parameters on the target outcome. Due to its linearity, neural networks can closely approximate most functions, thus highly accurate prediction of the relationships between diffusion coefficient and involved variables is made possible. One of the negative aspects of ANN is that the outcomes are sometimes difficult to interpret. Besides since there are no predefined rules about the topology of the network, one must work through trial and error before deciding the best topology suitable for the given problem domain. Nevertheless, many researchers are currently opting for the interpretability of the neural networks.

To support aforementioned claim, the diffusion coefficient of the loaded drug in FcDDS was analyzed using an ANN model. The computational model makes it possible to maintain complexity regarding phenomena, such as dissolution of the solid drug and boundary conditions at the formulation surfaces (Zhang et al., 2003), providing further insight into the mechanisms governing the release process from FcDDS. Moreover, the information obtained can be used to simplify or change the model so as to concentrate on the most important phenomena influencing the release profile. The simulation results illustrated that, for the entire span of release, the concentrations at all zones continue to increase exponentially until after 1 h of application, when the concentration increment becomes linear. These profiles were verified by the simulation process under various drug loading or loading weight conditions as shown in Figs. 4 and 5. This finding departs from the conventional drug release profile, which is mostly regulated by formulation factors as supported by the claim on the constant release mechanism in the polymer system (Ishihara et al., 1982; Zimm et al., 1996). The rationales behind the apparent departure is that although the polymer carriers deliver a constant drug flux, intrinsic variables including VFS secretion rate and its pH, outweigh a traditional drug release profiles derived from the drug elimination kinetics and the process of convection and diffusions from FcDDS. Especially, influence of weight of FcDDS on the released amount of SDS was much lower than that of intrinsic/extrinsic variables, denoting the maximal values of diffusion coefficient of 0.64 ± 0.04 and 0.95 ± 0.04 (Table 3) for FcDDS loading weight and fluid pH, respectively. The results of this study clearly indicated that in-depth studies on the roles of extrinsic and intrinsic variables in the kinetics of topically delivered pharmaceuticals are needed for the evaluation of intravaginal drug delivery systems.

The ANN approach presented in this paper handles the influence of phenomena, such as polymer film diffusion, external mass transfer, dissolution of the solid drug and geometric parameters including gel weight and size. This model helps to establish the in vitro–in vivo correlation based on in vitro properties of a dosage form and relevant environmental conditions. In vivo studies using the rabbit model is currently undergoing. A computer-based model established on ANN approach enables us to properly predict the effects of the intrinsic variables (i.e., pH and vaginal secretion rate) on the drug release profiles in each customer. The results of this study will further help us to understand the role of parameter-specific physiological conditions in the in vivo drug profiles from intravaginal drug delivery systems.

5. Conclusion

This study elucidated physicodynamic phenomena governing the diffusion coefficient of the loaded compounds in FcDDS and was intended to find the most influencing parameters on their release rates. ANN retrospectively assessed the implication of formulation and physiological variables and identified prognostic factors for the diffusion coefficient of SDS from FcDDS. Even though formulation variables (loading weight and SDS loading doses in FcDDS) and extrinsic variables (inserting position) apparently influence the diffusivity of SDS from FcDDS, intrinsic variables (vaginal fluid pH, vaginal fluid secretion rate) more significantly affected the drug release rate of SDS from FcDDS. The external exposure conditions, which were added to simulate organ-specific drug delivery conditions, outweighed

the effects of dose related variables on the diffusivity of SDS from FcDDS. Among 5 variables, pH of vagina fluids is the most influencing factor in determining the release profiles of SDS from FcDDS.

An ANN-based assessment is explicitly able to predict the drug release profiles as a function the given physiological conditions. Subsequently, an ANN-based assessment of FcDDS will lead to a parameter-specific prevention strategy against sexually transmitted diseases including AIDS with a high degree of confidence and at a high level of functional integration.

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