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Determination of residence-time distribution in i.v. tubing of in-line drug delivery system using deconvolution technique

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Summary

The axial dispersion model was used in this work to describe the residence-time distribution (RTD) of solute molecules traveling along the i.v. tubing of an in-line drug delivery system. The degree of dispersion in this model was assessed by the magnitude of the dispersion coefficient, D. In order to determine D, a dilute sodium chloride solution was used as the tracer and infused at the beginning of the tubing for a short period of time. This method is termed the finite-pulse change. The elution profiles of sodium chloride at various flow rates were assayed at the entrance and the outlet of the tubing A numerical deconvolution technique incorporated with Powell's nonlinear least-squares algorithm was then employed as the mathematical tool to search for the values of D that give a best fit to these profiles The results of modeling showed that the axial dispersion model gave an excellent fit to the experimental data. It was also observed that the plot of the obtained dispersion coefficient D vs U, the mean fluid velocity in the tubing, was linear with a high degree of correlation. The results obtained in this work provide important information for optimization of in-line drug delivery kinetics.

Introduction

Drug delivery systems, in general, can be categorized as the nonflow and flow systems (Kuu et al., 1992). The nonflow system is representative of the situation where the drug is eluted into a relatively stagnant milieu. A typical example of the flow system is the in-line drug delivery system, in which a large-volume parenteral solution continuously flows through a device containing the formulated drug. The mode of delivery of this device can be controlled release, sustained release, or pulsed depending on the needs. Numerous advantages associated with this system have been described (Kuu et al., 1992). One of these systems is depicted in Fig. 1 where the device with formulated medication is placed between the large volume parenteral (LVP) and the patient. Drug is released into this flowing stream and is delivered intravenously in solution phase via the administration set.

In the system depicted in Fig. 1, the concentration of the drug reaching the patient depends not

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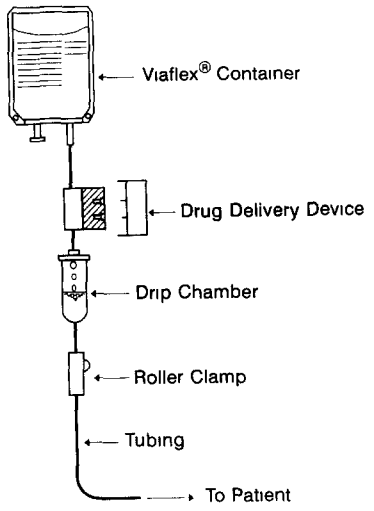

Fig 1 An intravenous in-line drug delivery system

only on the release rate from the device but also on the flow rate, the volume of the fluid, and the geometric configuration of the system. This phenomenon is termed the 'dispersion effect,' and can be described by the residence-time distribution (RTD) of drug molecules in the entire system.

The scientific background of RTD is well established in the area of chemical reaction engineering (Himmelblau and Bischoff, 1968; Levenspiel, 1972; Wen and Fan, 1975; Froment and Bischoff, 1979). This theory states that the traveling time of each drug molecule in the fluid path is, in general, not equal. Instead, a statistical distribution, such as normal or Gaussian distribution, is usually observed. The quantitative notation used in this work for expressing the RTD is $E(t)$. The physical implication of $E(t)$ is that it characterizes the 'degree of mixing' of drug molecules in the fluid path. The general concept of dispersion in the tubing can be elucidated by Fig. 2, where a diluent is flowing through the tubing at a certain flow rate. For simplicity, it is assumed that an impulse injection of a small amount of concentrated drug solution is given at the entrance of the tubing. The drug molecules start to travel along the tubing with the diluent immediately after the injection. In order to understand the progress of this profile, it is assumed

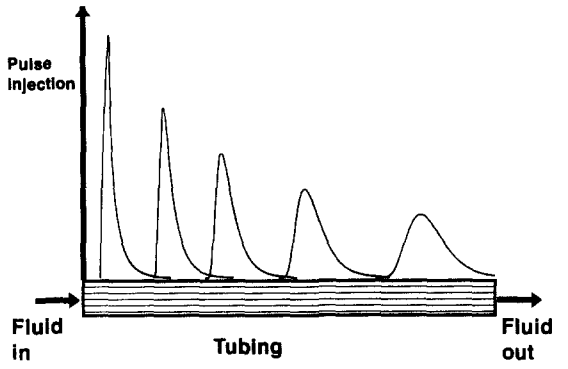

Fig 2. Variation of RTD along the tubing following an impulse injection of the drug solution

that the drug molecular distribution in the tubing can be assayed instantaneously. As Fig. 2 shows, the distribution at the location close to the entrance can be portrayed by a sharp peak. The peak broadens as it moves away from the entrance until it reaches the outlet. It is noted that the total area under the curve of the peak is constant, since there is no loss of drug molecules along the tubing.

This peak-broadening effect is also true for other types of input function. In general, the aforementioned dispersion effect of a system can be illustrated by the schematic diagram depicted in Fig. 3, where the i.v. tubing is symbolized by a black box. The input rate profile is regarded as the input function to the black box, denoted as $R_{in}(t)$, whereas the broadened profile at the outlet is regarded as the output function, represented as $R_{out}(t)$. The RTD in the entire tubing is regarded as the system function, denoted as

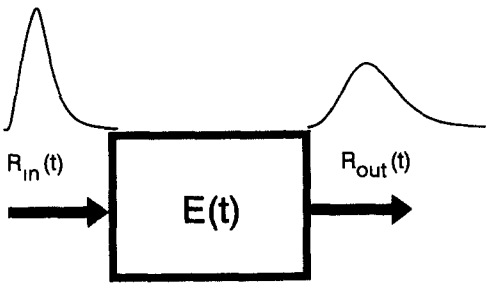

Fig. 3. Schematic illustration of the relationship among $E(t)$, $R_{in}(t)$ and $R_{out}(t)$.

$E(t)$. Provided that the system is linear, i.e., the system follows the principle of superposition, theoretically the output function can be predicted for any type of input function (Levenspiel, 1972; Froment and Bischoff, 1979) using a convolution integral.

Impulse and step-change are the two commonly used methods for determining the RTD of a vessel by experiment (Himmelblau and Bischoff, 1968; Levenspiel, 1972; Wen and Fan, 1975; Froment and Bischoff, 1979), giving an impulse injection or a step-change infusion of a tracer at the entrance of the vessel and assaying the tracer concentration profile at the outlet of the vessel. These methods minimize the effort of data analysis from which the RTD can be deduced. In the tubing of an in-line drug delivery system, however, the use of the impulse method appears to be problematic since the volume of the fluid in the tubing is relatively small. The movement of tracer molecules along the tubing, especially at a high flow rate, is very rapid, resulting in a sharp peak. In order to accurately determine the elution profile of the tracer it would be necessary to collect samples at very small time intervals. In addition, the amount of fluid collected in each sample may not be sufficient to perform significant assays. For the step-change method, a constant rate of tracer solution is infused and sustained for a very long period of time until all samples are collected in the effluent for assay. Thus, only the data points in the rising phase of the elution rate profile are useful for analysis, which may result in bias estimate of the dispersion coefficient.

To overcome the drawbacks associated with the impulse and step-change methods, the finite-pulse change (Wen and Fan (1975), p. 77) was chosen in this work, where the tracer solution was infused only for a short period of time, ranging from 1 to 4 min. The tracer concentrations in the effluent-collecting reservoir were monitored from the beginning of infusion until a point where the tracer is nearly depleted in the tubing. In other words, the tracer concentration was monitored for both the rising and falling phases of the elution rate profile. With the finite-pulse method, the advantages of impulse and step-change methods can be retained. Although the mathematical procedures are much more complex, the shortcomings of using the impulse or step-change method can be avoided.

Theory

Axial dispersion model for RTD in tubing

Various models have been developed to quantitatively describe the dispersion effect of a flow system, namely, the velocity profile model, dispersion model, tank-in-series model, etc. (Himmelblau and Bischoff, 1968; Levenspiel, 1972; Wen and Fan, 1975). For drug release from a tubing, if the degree of dispersion is relatively low and the radial dispersion is negligible, the RTD function, $E(t)$, for a small degree of dispersion may be expressed by (Levenspiel, 1972; Wen and Fan, 1975)

$$E(t) = \frac{1}{2\bar{t}(\pi D/UL)^{0.5}} \exp\left(-\frac{(1-\tau)^2}{4D/UL}\right) \quad (1)$$

For a large degree of dispersion, it becomes (Levenspiel, 1972)

$$E(t) = \frac{1}{2\bar{t}(\pi\tau D/UL)^{0.5}} \exp\left(-\frac{(1-\tau)^2}{4\tau D/UL}\right) \quad (2)$$

In Eqns 1 and 2, D is the dispersion coefficient of the tracer, $\bar{t}$ denotes the mean holding time of the fluid in tubing ($= V/Q$), τ is the dimensionless time ($t/\bar{t}$), U represents the mean velocity of the fluid in tubing (in cm/s) and L is the length of tubing (in cm).

Convolution integrals

Once the RTD and the input rate profile of the tracer to the tubing are given, the elution profile of the tracer at the outlet of the tubing can be computed through the following convolution integrals (Himmelblau and Bischoff, 1968; Levenspiel, 1972; Froment and Bischoff, 1979):

$$R_{out}(t) = \int_0^t R_{in}(t')E(t-t')\,dt' \quad (3)$$

where $E(t)$ is the RTD function expressed by either Eqn 1 or Eqn 2, $R_{in}(t)$ denotes the input rate profile of the tracer (in percent released per min), $R_{out}(t)$ is the output rate profile of the tracer at the outlet of the tubing, and t' represents a dummy variable. As stated earlier, Eqn 3 is virtually applicable to any type of input function, provided that the elution profile follows the principle of superposition, as termed the linear kinetics (Levenspiel, 1972; Froment and Bischoff, 1979). A list of FORTRAN source programs for computing the convolution integral of Eqn 3, using the trapezoidal rule for numerical integration, has been developed (Kuu et al., 1992).

Deconvolution

In this work, the input and output rate profiles of a tracer, $R_{in}(t)$ and $R_{out}(t)$, respectively, were obtained by experiment. The primary purpose of this work is to deduce $E(t)$ from $R_{in}(t)$ and $R_{out}(t)$. Logically, this is feasible to perform via a mathematical procedure, since there is only one variable $\bar{D}$ in Eqn 3. This procedure, however, is a complex trial-and-error approach. For instance, a value of $\bar{D}$ in either Eqn 1 or 2 is first tried, depending on which equation gives a better fit to the experimental data, followed by integrating Eqn 3 to obtain a set of $R_{out}(t)$ vs t. The theoretical values of $R_{out}(t)$ obtained are then compared with those determined experimentally. If the discrepancy is large, the value of the initial guess of $\bar{D}$ is adjusted, and the integration of Eqn 4 is repeated until no further improvement is observed. The foregoing procedure is equivalent to the nonlinear least-squares algorithm, where the best-fit value of $\bar{D}$ is obtained by minimizing the following sum of squares, SSQ

$$\mathrm{SSQ} = \sum_{i=1}^{M} \left(R_{out}(t) - R_{outi}(t)\right)^2 \qquad (4)$$

where $R_{out}(t)$ and $R_{outi}(t)$ are, respectively, the theoretically and experimentally determined elution rates of the tracer particles or drug molecules at the outlet of the tubing at time t, and M is the number of data points. The technique described above is essentially the same as the deconvolution integral (Press et al., 1987), since the unknown to be determined, $\bar{D}$, is embedded in the convolution integral, Eqn 3. In order to determine $\bar{D}$, it needs to 'undo' the convolution integrals.

Powell's nonlinear least-squares algorithm

There are several nonlinear least-squares algorithms that are available for parameter estimation purposes (Himmelblau, 1972). Some of them require that the first derivative of Eqn 4 is given. Others, such as Powell's algorithm, require only functional values of Eqn 4. In fact, Powell's algorithm can be used for very complicated computations, such as numerical deconvolution integrals with a complex objective function. The speed of convergence of Powell's algorithm has been found to be much more rapid than that of other algorithms of the same category (Himmelblau, 1972). The overall computational scheme used for the deconvolution integrals in this work is presented in Fig. 4.

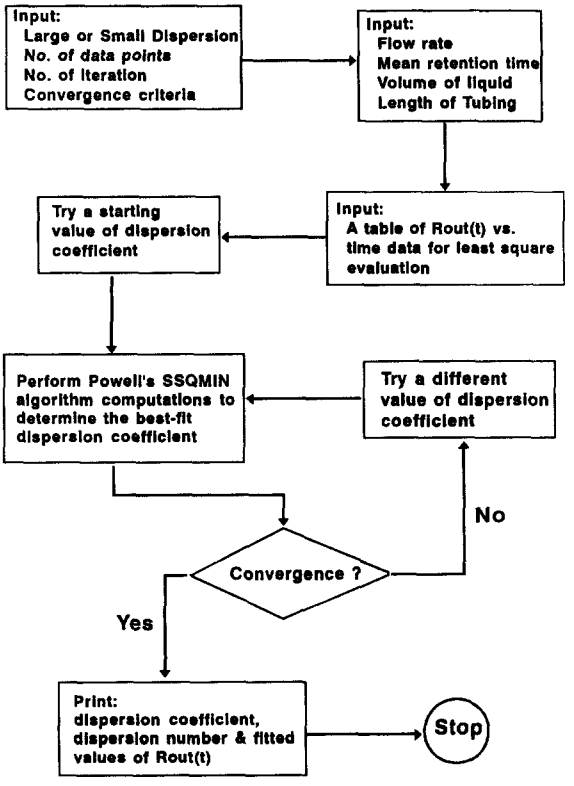

Fig 4 The computational scheme of convolution-deconvolution integrals

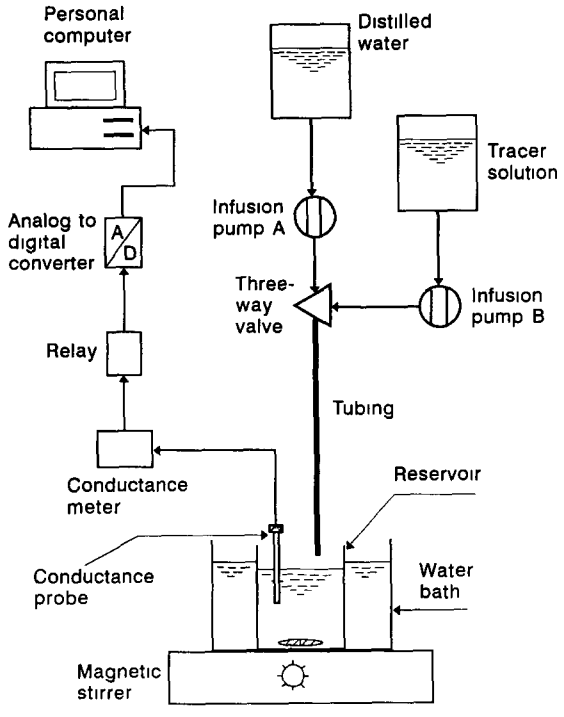

Fig 5 Schematic diagram of the experimental setup for RTD determination. The tubing was 0.1 inch i.d and 173 cm in length

Materials and Methods

The schematic diagram of the experimental setup for determination of tracer elution profiles is depicted in Fig. 5, where two infusion pumps (Baxter Flo-Gard™ 6100) were used for maintaining a constant flow rate of the fluid in the tubing during the experiment. Infusion pump A was used to deliver distilled water, whereas infusion pump B was used for a constant rate infusion of tracer solution. The tubing used was 0.1 inch inside diameter PVC intravenous infusion tubing, 173 cm in length. The three-way valve (Baxter part no. 2-4-19-577, lot no. MH 7-17-87) was used to switch between the tracer solution and distilled water. Dilute sodium chloride solution (1 g/l), was used as the tracer. Sodium chloride has been proven as an ideal tracer for RTD studies, and has been used by a number of investigators (Wen and Fan, 1975). The tracer ions, after elution from the tubing, were collected by a constant temperature reservoir with stirring. The assay of sodium chloride ions was performed by an automatic computer-controlled data acquisition system. As shown in Fig. 5, the conductivity

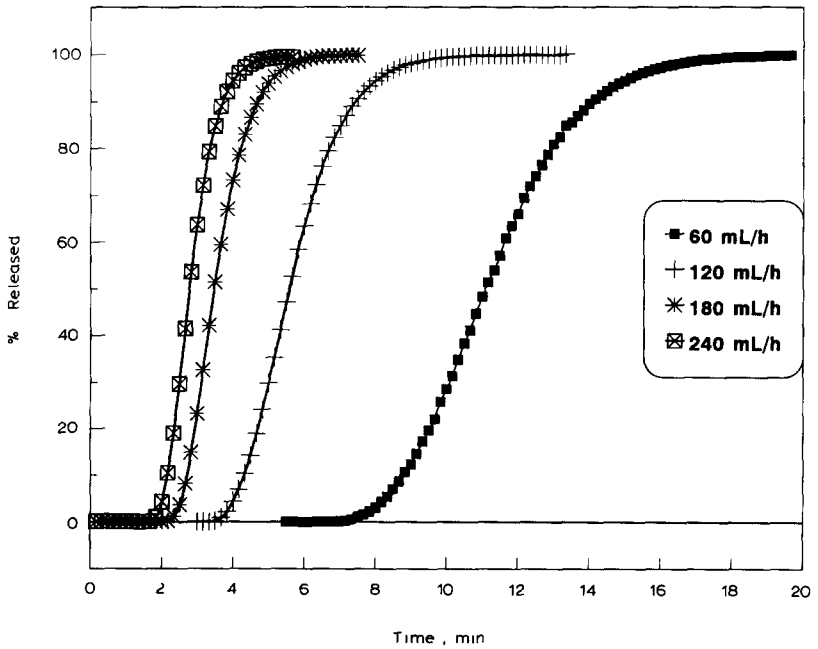

Fig 6. Elution profiles of sodium chloride from an i v. tubing at flow rates of 60, 120, 180, and 240 ml/h The symbols and the solid curves indicate the experimental and fitted profiles, respectively. Each symbol represents a mean of three replicates.

of the reservoir was measured by a conductance meter (YSI Model 32, Yellow Springs Instrument Co., Inc., Yellow Springs, OH) and a conductance probe (YSI Model 3417, $K = 1\ cm^{-1}$). The signals were transmitted through an analog-to-digital converter (Product no. DT2801, Data Translation, Inc., Marlborough, MA), a relay (Product no. DASCON-1, MetraByte Corp., Taunton, MA) and finally captured by an IBM personal computer.

For each run, pumps A and B were calibrated to a desired flow rate, and the three-way valve was switched to the distilled water flow path. Pump A was first started for a sufficient time to fill the tubing and to wash out any residual tracer ions. Pump A was then stopped, and the three-way valve was switched from the distilled water flow path to the tracer flow path. Pump B was immediately started to deliver tracer solution to the entrance of the tubing. Tracer infusion times used in this work at the flow rates of 60, 120, 180 and 240 ml/h were 4, 2, 1, and 1 min, respectively. Pump B was then stopped, followed by switching the three-way valve back to the distilled water flow path, and pump A was turned on to resume delivery of distilled water. The conductivity of the reservoir was detected by the conductance probe for every 10 s interval and displayed on the screen of the personal computer. The experiment was considered completed when the conductivity of the reservoir declined for a few minutes, implying that all the residual tracer ions in the tubing had been washed out.

Results and Discussion

Fit of elution profiles by Weibull distribution

The elution profiles of sodium chloride determined at various flow rates are presented in Fig. 6. Each S-shaped profile represents the mean of three replicates. These sigmoidal curves can be

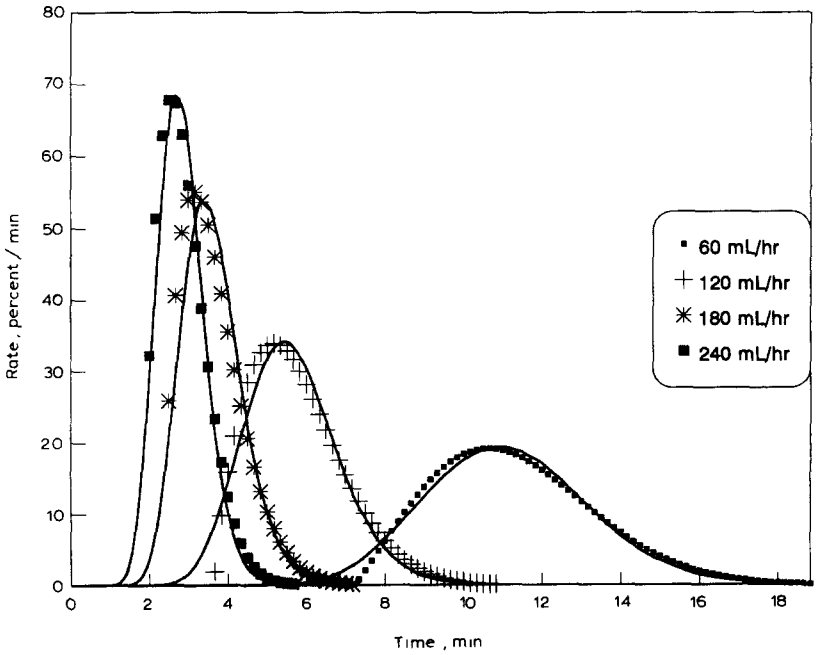

Fig. 7. Comparison of the fitted and experimental delivery rate profiles of sodium chloride from the I.V. tubing. The symbols and the solid curves indicate the experimental and fitted profiles, respectively.

closely fitted by the Weibull distribution (Ratkowsky, 1983; Kececioglu, 1991), as given by the following equations

$$M_t = 100\left(1 - \exp\left(-f_2(t - t_{lag})^{f_1}\right)\right) \quad \text{for } t > t_{lag} \tag{5a}$$

and

$$M_t = 0.0 \quad \text{for } t \leq t_{lag} \tag{5b}$$

where M_t is the accumulated amount of elution of sodium chloride from the tubing (in percent), f_1 and f_2 represent parameters; and t_{lag} denotes the lag time. In Eqn 5a, the final accumulated amount of elution is assumed to be 100%, which is true for the profiles presented in Fig. 6. These parameters can be obtained by a nonlinear least-squares method, such as Powell's algorithm (Powell, 1965; Kuester, 1973) as described earlier. The resulting values of the parameters for these profiles are listed in Table 1. The fitted profiles can then be obtained by plotting Eqn 5a, using the parameters in Table 1 for each flow rate. As shown in Fig. 6, the fitted profiles give excellent fits to the experimental data, indicating the validity of using Eqn 5a to model these profiles.

The elution rate profiles for the curves in Fig. 6 are simply equal to the first derivative of Eqn 5a, as given by

$$R_{outi} = 100 f_1 f_2 (t - t_{lag})^{f_1 - 1} \exp\left(-f_2(t - t_{lag})^{f_1}\right) \tag{6}$$

for $t > t_{lag}$. In Eqn 6, R_{outi} is the elution rate (in percent per min), the same as the second term in Eqn 4. Since the values f_1, f_2, and t_{lag} of all profiles have been determined in Table 1, the rate profiles can be readily plotted through Eqn 6, as presented in Fig. 7.

TABLE 1

Weibull parameters of sodium chloride elution profiles

Flow rate (ml/h)	Weibull parameters		
	f_1	f_2	t_{lag} (min)
60	2.109	0.03972	7 22
120	1.808	0.2090	3 64
180	1.644	0.5774	2.36
240	1 770	0 759	1.84

TABLE 2

The obtained dispersion coefficients and dispersion numbers of the dispersion model, using the large dispersion model

Flow rate (ml/h)	Dispersion coefficient $Đ$ (cm^2/s)	Dispersion number $Đ/UL$ (dimensionless)
60	0 9695	0.01704
120	2 901	0.02549
180	4 567	0 02675
240	5 691	0 02500

Determination of dispersion coefficient Đ

It was observed that the RTD equation for the large dispersion, Eqn 2, gave a better fit to the elution profiles of all flow rates. Thus, this equation was used to determine the dispersion coefficient for all the flow rates investigated. The dispersion coefficients and dispersion numbers determined using the computation scheme displayed in Fig. 4 are listed in Table 2. The computed rate profiles, $R_{out}(t)$, are plotted in Fig. 7, which indicates that the axial dispersion model gives an excellent fit to the experimental data at the four flow rates studied. The resulting dispersion coefficients are plotted vs the square of the flow rate in Fig. 8. It is interesting to note that an excellent straight line is observed with R^2 of 0.9869. The regression equation obtained is given by

$$Đ = -0.4255 + 4.813U \tag{7}$$

where $Đ$ is in cm^2/s, and U in cm/s. Eqn 7 indicates that $Đ$ is proportional to the velocity of the fluid in the tubing. With this very useful relationship, the dispersion coefficient at other flow rates can be readily calculated.

Simulations using convolution integral

Once the functional relationship between the dispersion coefficient and the flow rate (Eqn 7) is

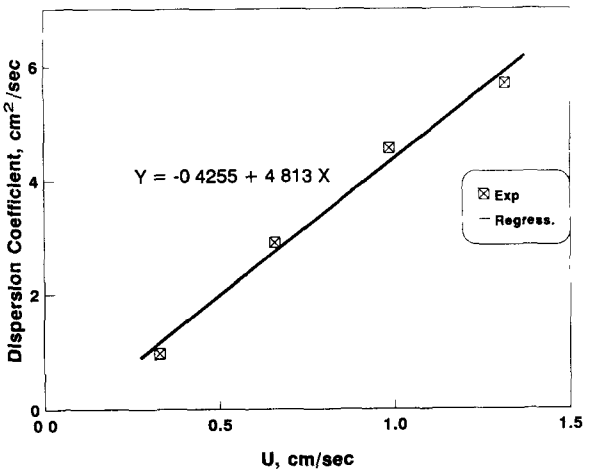

Fig 8 Plot of dispersion coefficient vs the mean velocity, U

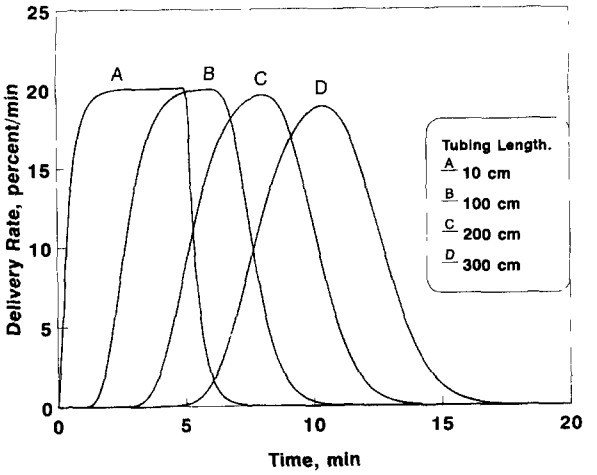

Fig 9 Effect of tubing length on $R_{out}(t)$ at a flow rate of 120 ml/h, simulated using Eqn 1

established, the output rate profile $R_{out}(t)$ can be determined through the convolution integral (Eqn 3) for various conditions, such as the effect of flow rate, tubing length, etc. In order to determine the effect of flow rate (or velocity) on $R_{out}(t)$, Eqn 7 is inserted into Eqn 2 to give an equation which is only a function of the mean velocity U. The resulting equation is now ready to be used for the integration of the convolution integral (Eqn 3) for a given input function $R_{in}(t)$.

On the other hand, in order to determine the effect of tubing length on $R_{out}(t)$, the dispersion coefficient D is obtained directly from Eqn 7 since the flow rate is fixed. The resulting value of D is then inserted into Eqn 2 to define $E(t)$ which is then inserted into Eqn 3. The resulting convolution integral equation is ready to be performed for any input function $R_{in}(t)$. For example, the delivery rate profiles $R_{out}(t)$ as a function of the tubing length, following a 5 min constant rate infusion, are obtained using this procedure and presented in Fig. 9. As seen, increasing the length of tubing not only broadens the delivery rate profiles but also reduces the maximum rates. The areas under the curves in Fig. 9 are the cumulative release profiles, which can be evaluated numerically, such as with the trapezoidal rule. The results are depicted in Fig. 10. It can be seen from Fig. 10 that one of the consequences of the peak broadening observed in Fig. 9 is the tailing effect of the delivery profile which will prolong the delivery of the drug.

Effect of RTD on therapeutic assessment and optimization

Dispersion of drug molecules in the tubing of an in-line drug delivery system is a very important issue, since it affects the actual delivery rate profile that is to be received by the patient. Traditionally, in an i.v. delivery system, such as a piggyback system (Plumer, 1982), the delivery of

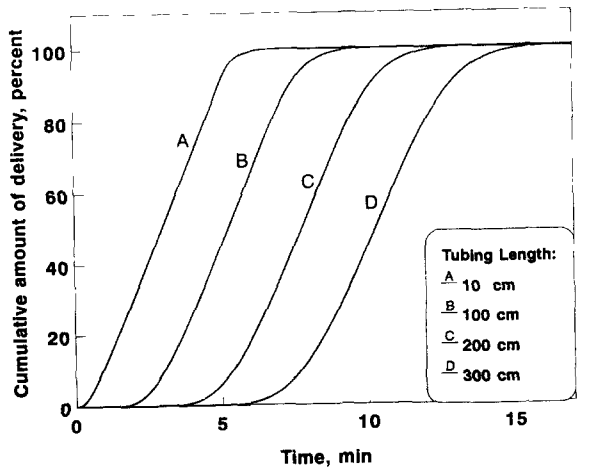

Fig 10 Effect of tubing length on delivery profiles at a flow rate of 120 ml/h, simulated using Eqn 1

drug is regarded to be completed when the drug is released out of the secondary line. In the in-line delivery system, as depicted in Fig. 1, the device is designed as a cartridge form, so that after the delivery is completed and the device is subsequently removed from the i.v. set, all the remaining drug in the set will still be delivered to the patient by the continuous flow system. Thus, the in-vitro delivery rate profile is usually assessed at the interface between the device and the set, or more conservatively, at the end of the drip chamber. On the other hand, in order to assess the in-vivo therapeutic effect, the delivery rate profile just prior to entering the patient should be used. Thus, in order to fulfill both the in-vitro and in-vivo assessment requirements, there is a need to determine the release profiles both at the beginning of the tubing and at the end of the set. Unfortunately, it is almost impossible to determine these profiles at both locations simultaneously. With the contributions of this paper, one can easily convert the profile determined at one location of the i.v. set to that at the other location, using the convolution integral (Eqn 3). The procedure for the conversion is briefly described below. When the release profile, $M_t(t)$, at the beginning of the tubing, is given, the release rate profile, $R_{in}(t)$, can be readily evaluated using Eqn 6 by replacing the notation R_{out} by $R_{in}(t)$. Since the RTD function, $E(t)$ has been determined in this work, the combination of $R_{in}(t)$ and $E(t)$, using Eqn 3, allows one to evaluate $R_{out}(t)$ using Eqn 3. The desired release profile, $M_t(t)$, at the end of the set is simply the integration of $R_{out}(t)$ over the time, t. This type of studies for delivery of various drugs in the in-line system will be described in a forthcoming paper.

Figs 7, 9 and 10 show that the dispersion effect reduces the maximum delivery rate and prolongs the tailing of the profile. The former effect is desired, but the latter should be avoided. The optimum design of the set depends on a compromise between the two effects. The optimization should be performed by combining the in-vitro delivery kinetics, evaluated just prior to entering the patient, and the pharmacokinetics of the drug of interest to give the in-vitro response.

Conclusions

The axial dispersion model, along with the convolution-deconvolution algorithm, has been successfully used to characterize the dispersion phenomenon of solute molecules in the tubing of an intravenous administration set. The advantage of using the dispersion model for RTD in tubing is that the dispersion coefficient D is the only parameter that is needed to characterize this phenomenon. Once the dispersion coefficient is determined, the model can be applied to the systems with various experimental conditions. It should be emphasized that the numerical convolution-deconvolution FORTRAN codes developed in this work are also applicable to any types of input function, $R_{in}(t)$. The results generated in this work provide very useful information for the design of administration sets and optimization of drug delivery kinetics. For instance, the dispersion coefficient obtained can be used for predictions of release kinetics of drug molecules in the tubing. Verification of the model using the release profiles of model drugs is in progress.

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