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Correlation of the intravenous in-line drug delivery kinetics with the diluent flow rate, angle of internal flow, wettability, solubility and particle surface area

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Abstract

The primary objectives of this work were to investigate various parameters that would potentially affect the delivery kinetics of drugs via an in-line intravenous (IV) delivery system and to establish a mathematical model to correlate the drug delivery kinetics with these parameters. The in-line delivery system contains a drug containing device which is placed between a parenteral solution (which is also termed as the diluent) container and a patient. The solid drug in the device is automatically dissolved by the diluent and administered to the patient as the diluent solution flows through the system via an administration set at a controlled flow rate. This system comprises numerous advantages over the conventional infusion systems, including labor-saving, convenient to use and minimizing human error. The delivery kinetics of this system was assessed using T_{Net95} which is defined as the time to deliver 95% of drug, excluding the lag time, via this system. The values of T_{Net95} for various drugs were experimentally determined in this study. A semi-empirical regression equation was used to fit the experimental data. In this equation, T_{Net95} is expressed in terms of the five parameters, the diluent flow rate (FR), angle of internal flow Θ, contact angle θ, solubility C_s, and the particle surface area (SA). The regression analysis was performed using the statistical package (SAS) and the results indicated that the most important parameters affecting T_{Net95} are FR, Θ and θ for the drugs investigated. A close fit of the regression equation to the experimental data was observed, with R^2 equal to 0.99. The resulting equation is expressed as $T_{Net95} = -60.88 + 1980.7/FR + 330.88/\Theta^{1/2} + 15.34/\cos\theta$. Using this equation, the delivery kinetics of other drugs in this in-line system may be predicted, provided that the angle of internal flow Θ and the contact angle θ of the drugs are available or determined. In order to give a close prediction, the solubility of the drug of interest should be similar to the range of solubility investigated in this paper.

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1. Introduction

An in-line delivery system for intravenous (IV) drug administration consists of a drug containing device which is placed between a parenteral solution (which is also termed as the diluent) container and a patient (Kuu et al., 1992; Zdeb and Jepson, 1989). The schematic diagrams of the particular system investigated in this study are depicted in Fig. 1(a, b). The device is primarily designed to deliver powder drugs, although liquid drug may also be delivered. This in-line system comprises numerous advantages over the conventional infusion systems including labor-saving, convenient to use and minimizing human error. It can be used with either a large volume parenteral (LVP) solution or a minibag. When used with a LVP solution, it eliminates the secondary infusion set and the minibag used in a typical IV piggyback drug delivery system. One important delivery feature of this system is that the dissolution and reconstitution of the drug in the device is automatically taking place as soon as the diluent enters the device. In addition, the system minimizes drug waste because the device is activated just prior to IV administration. This system is particularly useful for administering unstable drugs which degrade rapidly in the liquid phase, since these drugs are maintained in powder form in the device during the shelf-life storage.

The criterion for assessing the in-line delivery kinetics in this study is T_{Net95} which is defined as the time to deliver 95% of drug, excluding the lag time, denoted as T_{Lag}. A previous study (Wong et al., 1995) shows that the lag time of the IV in-line delivery profile does not affect the in-vivo response of the drug in the plasma. T_{Net95} is a complex function of the variables contributed by the drug and the delivery system. So far, there is no theoretical approach which can be utilized to predict T_{Net95}. Rather, it has to be determined experimentally at various diluent flow rates. In order to obtain a complete delivery profile, which is needed to assess the delivery kinetics, numerous data points have to be generated. This requires frequent sampling and assay, and this time consuming work needs to be repeated for every drug of interest. In order to reduce this experimental effort, a mathematical model is established to correlate T_{Net95} with the physical properties of the drugs and the flow rate of the diluent. The resulting model can be utilized for prediction purposes. The physical properties of the drugs may be readily available from literature or can be independently determined.

The objectives of this work were to investigate various parameters that would affect the in-line delivery kinetics and to establish a mathematical model to correlate T_{Net95} with various factors. The resulting equation can then be utilized to perform screening of drug candidates that are feasible to be delivered via this IV in-line system.

2. Theoretical

The factors influencing the delivery kinetics of solid drug from an in-line systems may be summarized in terms of two areas: (1) the dissolution rate of the drug in the device; and (2) the residence-time distribution of the dissolved drug molecules in the entire flow stream (Kuu et al., 1992). The dissolution rate is a function of the solubility of the drug, the wettability of the drug and the rate of the liquid penetration into the powder bed. On the other hand, the residence time distribution is primarily governed by the geometrical configuration of the flow path and the flow rate of the diluent. The detailed quantitative effects of these factors on the delivery kinetics are discussed below.

The effect of solubility on the dissolution rate is well understood and is described by the Noyes–Whitney equation (Martin et al., 1983), as given by:

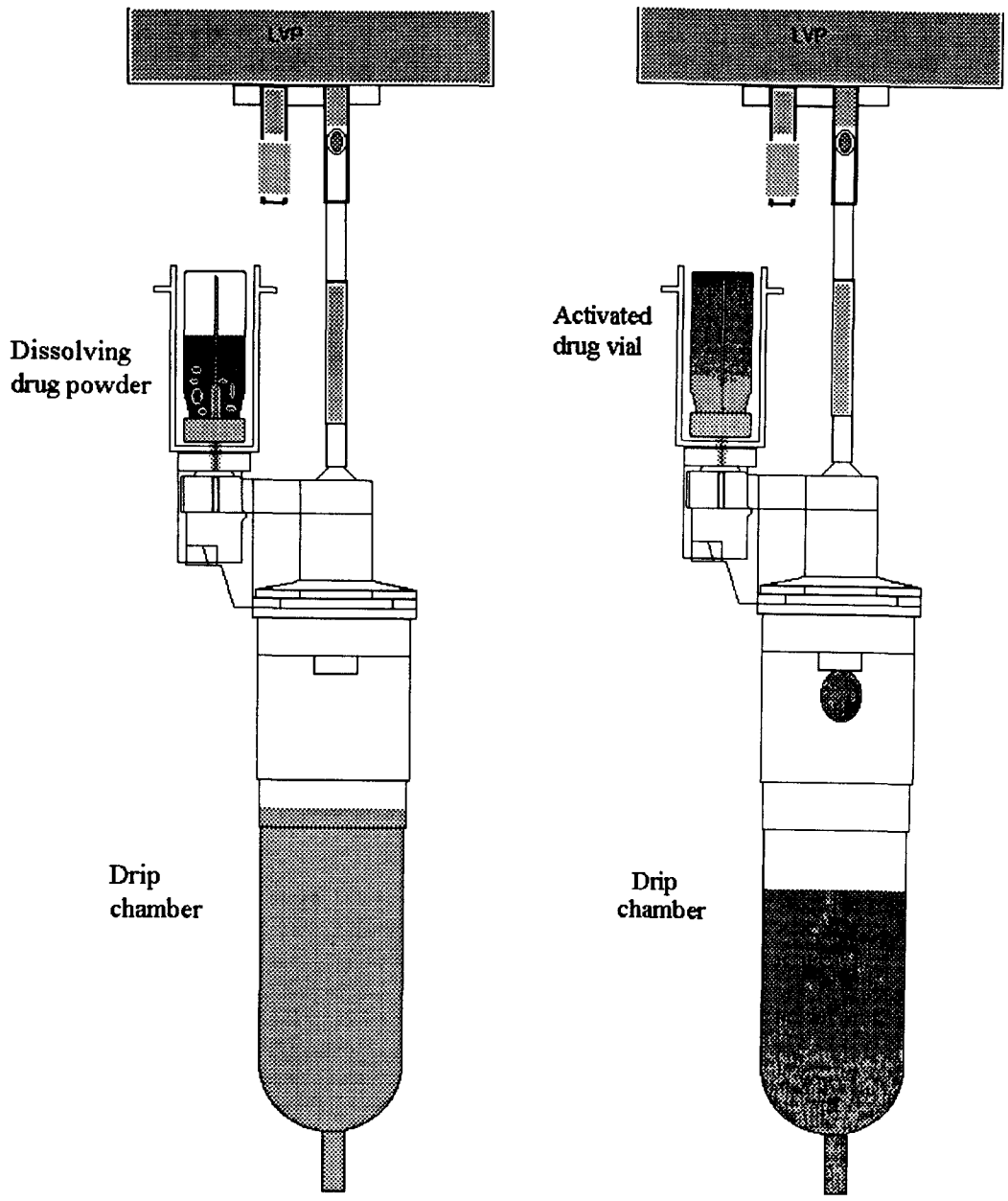

Fig. 1. (a) In-line drug delivery system investigated in this study. The diluent starts to enter the drug vial from the LVP (large volume parenteral) container and dissolves the drug powder.(b) In-line drug delivery system investigated in this study. The device is filled with the diluent and the dissolved drug is started to release from the drug vial.

$$\frac{dM}{dt} = \frac{DSA(C_s - C)}{h} \quad (1)$$

where dM/dt is the rate of dissolution, D is the diffusion coefficient of drug, SA is the surface area of exposed solid, h is the thickness of the diffusion layer, C_s is the solubility of drug and C is the concentration of the drug at time t. Eq. (1)

shows that the dissolution rate is proportional to the solubility of the drug C_s at the liquid–solid interface for otherwise fixed conditions.

In the in-line delivery system, the device is filled with drug powder. The effect of powder compression, primarily due to transportation and storage of the device, on the delivery kinetics needs to be investigated. Powder is known to compact following the agitation of the powder bed by mechanical means (Woodhead et al., 1983; Woodhead and Newton, 1984). The extent of powder bed compaction was found to be significantly higher following vertical vibration than following horizontal vibration (Woodhead et al., 1983). The extent of liquid penetration of a powder bed can be quantitatively expressed in terms of the powder bed compaction, as reported by several researchers (De Beukelaer and Van Ooteghem, 1985; Yamashiro et al., 1983; Groves and Alkan, 1979; Buckton and Newton, 1985). In this paper, the Washburn equation (De Beukelaer and Van Ooteghem, 1985) was used to determine the length of liquid penetration as shown by the following equation:

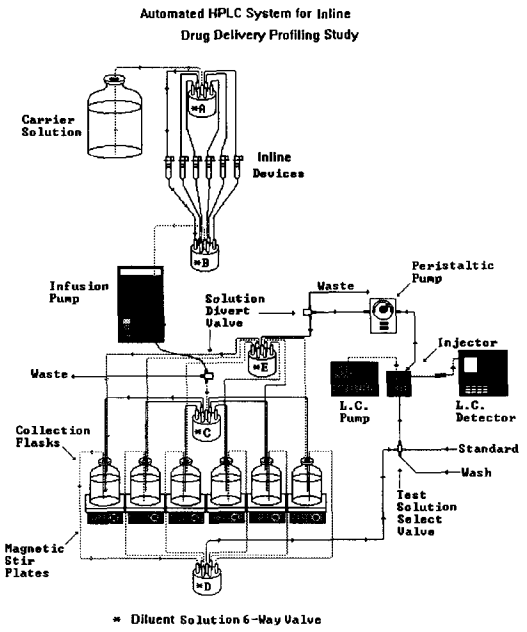

Fig. 2. Six-unit in-line drug delivery system, equipped with an HPLC which is connected to the Hewlett-Packard 3357 Laboratory Automation System (LAS) to perform data acquisition.

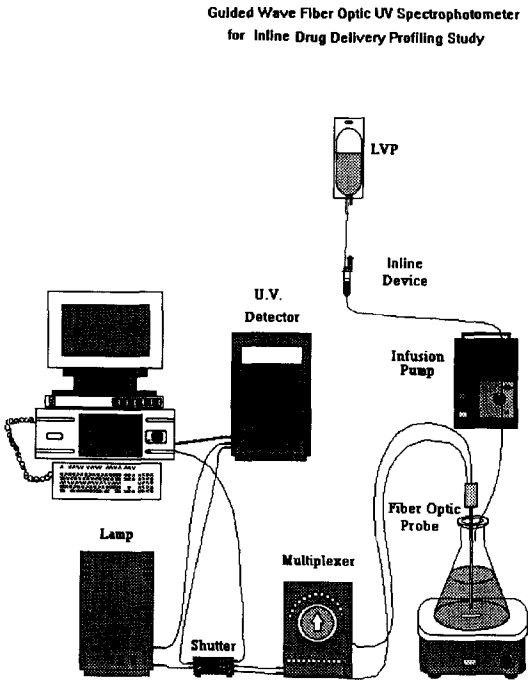

Fig. 3. Twelve-unit in-line drug delivery system, equipped with a Guided-Wave fiber optic spectrophotometer which is connected to a stand-alone PC (personal computer)-based data acquisition system.

$$L^2 = \frac{dr\cos\theta t}{4\mu} \tag{2}$$

where L is the length of penetration, d is the mean pore diameter, θ is the solid/liquid contact angle, t is the time, r is the surface tension of the penetrating liquid and μ is the viscosity of the liquid. Eq. (2) indicates that the length of penetration is proportional to $(\cos\theta)^{1/2}$.

Although the mean pore diameter d in Eq. (2) is an indicator of powder bed compression, it may not accurately reflect the true extent of powder compaction. This is because Eq. (2) was originally developed for describing liquid penetration in a highly compressed powder bed or tablet. Subsequently, investigation (Newton and Bader, 1987; Varthalis and Pipel, 1976) revealed that powder packing could be described in terms of the 'angle of internal flow'. This angle of internal flow is an empirically derived parameter calculated from the rate of change of bulk density with tapping by these investigators. It is clear that this

Table 1
HPLC analytical methods

Drug	Detector Wavelength (nm)	Mobile Phase
Nafcillin Sodium	280	33% ACN 67% pH 3, 50 mM NH_4Ac
Cefazolin Sodium	254	17% ACN 83% pH 2.5 citrate/phosphate buffer
Ampicillin Sodium	220	7% ACN 93% pH 7, 0.1 M MOPS

- HPLC systems:
Injector: Model 235 (Scientific Systems, Inc., State College, PA)
HPLC Pump: Model 590 (Waters, Milford, MA)
Detector: Spectroflow 783 (Kratos, Applied Biosystems Inc., Foster City, CA)
Column: C18 '3 × 3', 3 × 0.46 cm, 3 μm particles (Alltech, Deerfield, IL)
- HPLC conditions:
Flow rate: 2 ml/min
Temperature: Ambient
Injection volume: 1 μl

angle of internal flow is an appropriate indicator of powder bed compaction in in-line drug delivery device. It relates the number of tapping n of a powder bed, ranging from 25 to 150 taps, to its porosity ϵ. The relationship is expressed by the following equation:

$$n\epsilon^2/(1-\epsilon) = \tan \Theta n + \text{Intercept} \quad (3)$$

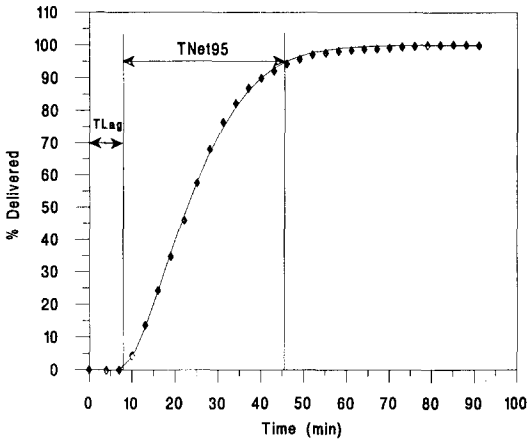

Fig. 4. Typical in-line drug delivery profile of sodium cefazolin, using normal saline as the diluent at the flow rate of 50 ml/h.

where Θ is the angle of internal flow in degrees.

As described in Section 1, T_{Net95} is a convenient term for assessing the delivery kinetics of an in-line drug delivery system. The value of T_{Net95} decreases with increasing rate of drug dissolution or delivery. It is very difficult, however, to derive a theoretical equation to express T_{Net95} in terms of the factors described above, due to the complexity of the mechanisms involved. A semi-empirical equation is used in this paper. Considering the factors mentioned earlier, T_{Net95} may be expressed as a linear function in terms of 1/FR, 1/SA, $1/C_s$, $1/\Theta^{1/2}$ and $1/\cos\theta$, as expressed by:

$$T_{Net95} = \beta_0 + \beta_1/\text{FR} + \beta_2/\text{SA} + \beta_3/C_s + \beta_4/\Theta^{1/2} + \beta_5/\cos\theta \quad (4)$$

where FR is the flow rate of the diluent, in ml/h; SA is the powder surface area, in m^2/g; Θ is the angle of internal flow in degrees; θ is the contact angle in radian. The term β_0 is the intercept of the linear equation, and β_1, β_2, β_3, β_4, and β_5 are the coefficients. The values of these coefficients and the significance of each term will be investigated using the statistical package SAS.

3. Materials and methods

3.1. Analytical methods for determining in-line drug delivery profiles

Two analytical systems were used to obtain the in-line drug delivery profiles for five drugs (as sodium salt) as depicted in Figs. 2 and 3. The analytical methods were developed at Baxter, capable of performing rapid sampling and assay, with a run time of less than 3 min for a data point. Among the five drugs studied, two were proprietary or experimental drugs. They were assigned the code names of Drug Code BR and Drug Code BC. The delivery profiles of nafcillin sodium, cefazolin sodium and ampicillin sodium were obtained using a high performance liquid chromatography (HPLC) system which was connected to the Hewlett-Packard 3357 Laboratory Automation System (LAS) to perform data acquisition, as depicted in Fig. 2. This system is capable

Table 2
The values of T_{Net95} at various flow rates for drugs investigated

Drug	FR (ml/h)	T^{a}_{Net95} (min)	C_s (g/l)	Θ (°)	θ (rad)	SA (m^2/gm)
Nafcillin sodium	50	53.9 ± 7.9	489.4	37.44	0.7679	2.00
	120	29.9 ± 3.5	489.4	37.44	0.7679	2.00
	180	26.0 ± 4.2	489.4	37.44	0.7679	2.00
	250	24.7 ± 2.1	489.4	37.44	0.7679	2.00
Drug code BR	50	41.5 ± 2.7	485.2	64.96	0.7714	6.80
	120	18.7 ± 1.8	485.2	64.96	0.7714	6.80
	180	11.3 ± 1.1	485.2	64.96	0.7714	6.80
	250	8.7 ± 0.9	485.2	64.96	0.7714	6.80
Drug code BC	50	45.5 ± 6.8	419.8	46.22	0.4102	8.93
	120	18.9 ± 0.8	419.8	46.22	0.4102	8.93
	180	14.6 ± 0.6	419.8	46.22	0.4102	8.93
	250	14.4 ± 3.7	419.8	46.22	0.4102	8.93
Cefazolin sodium	50	37.8 ± 1.5	481.8	56.87	0.2025	1.12
	120	16.2 ± 1.0	481.8	56.87	0.2025	1.12
	180	10.5 ± 0.8	481.8	56.87	0.2025	1.12
	250	7.6 ± 0.9	481.8	56.87	0.2025	1.12
Ampicillin sodium	150	15.7 ± 2.5	634.4	43.62	0.3491	3.17

[a] The values of T_{Net95} are the mean values ($n > 6$) at each flow rate.

of performing six delivery experiments sequentially without attendance of laboratory personnel. The analytical conditions for these three drugs are listed in Table 1.

The delivery profiles of Drugs BC and BR were obtained using a fiber optic system which was connected to a stand-alone PC (personal computer)-based data acquisition system. The system was equipped with a Guided Wave fiber optic (UV) spectrophotometer, as depicted in Fig. 3. This system gives a high speed data acquisition, capable of performing 12 delivery experiments simultaneously. Fig. 3 only shows one of the 12 probes used (Guided Wave, El Dorado Hills, CA).

3.2. Typical in-line drug delivery profile

The typical drug delivery profile obtained from the delivery experiments described above is shown in Fig. 4. The drug vial of the in-line device (see Fig. 1) contains 1 g of cefazolin as sodium cefazolin. The volume and the length of this drug vial are approximately 4.5 ml and 4 cm, respectively. This S-shaped curve can be divided into three phases: the lag-time phase, the active-dissolution phase and the tailing phase. For this particular profile, the lag-time phase starts from time 0 to approximately 7 min, denoted as T_{Lag} in the figure. The diluent flow rate was 50 ml/h. In this period, the diluent needs to prime (expel the air in the void space in the drug vial) the drug container, to penetrate the powder bed, and to wet the powder. The dissolved drug is then released from the delivery system and detected by the analytical instrument. The active-dissolution phase starts from approximately 7 min and sustained to 30 min, which occurs after the powder bed is wetted and the drug is being 'actively' dissolved by the in-coming diluent. In this region, an approximate straight line is observed which indicates a pseudo-constant delivery rate. The tailing phase starts from 30 to 60 min, which indicates the releasing kinetics of the residual drug molecules out of the flow path of the delivery system. The performance of this delivery system is assessed by the 'net amount' of time to deliver 95% of recoverable drug (or dose) to the drip chamber, denoted as T_{Net95}. T_{Net95} is therefore equal to the T_{95}, time to deliver 95% of drug, minus T_{Lag}.

Table 3
The resulting parameters in Eq. (4), obtained using SAS, with multiple linear regression and stepwise option, in the order of importance

Number of parameter P	β_0	β_1	β_4	β_5	β_3	β_2
2	4.88	1977.7				
3	−45.62	1991.8	353.8			
4	−60.88	1980.7	330.88	15.34		
5	−67.20	1973.9	2714.8	330.18	15.96	
6	−73.97	1967.1	325.93	18.204	4451.15	2.584

3.3. Drug characterization

3.3.1. Angle of internal flow (powder cohesion)

The procedure for measuring the angle of internal flow outlined by Varthalis and Pipel (1976) was used in this study. Briefly, drug powder was removed from a sealed container. Powder of known weight in a 10 ml graduated cylinder was then tapped using a Quantachrome Dual Autotap (Quantachrome, Syosset, NY). As the cylinder was being tapped, drug particles settled between the voids and the powder void volume decreased. One measurement of the tapped powder volume was recorded for every 25 taps. The angle of internal flow was computed from the reduction in powder volume by plotting $n\epsilon^2/(1-\epsilon)$ versus n, as indicated in Eq. (3), where ϵ is the porosity and n is the number of taps, and a linear relationship was observed for each drug between 25 and 150 taps (R^2 between 0.98 and 1.00). The whole experimental process for one powder tapping run was estimated to be completed in less than 10 min. The resulting slope of the line is $\tan\Theta$ and Θ is the angle of internal flow.

Porosity in Eq. (3) is defined as (1 − [bulk density/true density]). The true density of a powder was measured using a Quantachrome Stereopycnometer (helium gas penetration of a powder bed; Quantachrome, Syosset, NY). Briefly, helium gas penetrates powder pores, cracks or crevices even as small as 1 Å. The Stereopycnometer was first pressurized to 15–20 psi above ambient (P_1). The helium gas was then allowed to flow into a known and calibrated reference volume (V_A). The larger the volume of sample in the sample cell, the greater was the pressure drop (P_2) when V_A was added to the circuit. From the relationship between P_1 and P_2, the sample volume V_P can be calculated by:

$$V_P = V_C + \frac{V_A}{1 - P_1/P_2} \tag{5}$$

where V_C was the sample cell volume. Once V_P is obtained, the true density is calculated by dividing the powder sample weight by V_P.

3.3.2. BET particle surface area

The particle surface area measurements using the BET method (Hiemenz, 1986) were conducted using Quantachrome Quantasorb (Model OS-17, Quantachrome, Syosset, NY). In this method, nitrogen gas was used as adsorbate on particle surfaces. Briefly, the measurements were carried out using a single point BET surface area method. The equation for the calculation of weight of gas in a single molecular layer X_m is given by:

$$X_m = X[1 - (P/P_0)] \tag{6}$$

where X is the weight of gas adsorbed at a particular relative pressure (P/P_0), P is the adsorbate gas pressure, P_0 is the saturated equilibrium vapor pressure of the adsorbate at ambient temperature. The procedures for the determination of X, P and P_0 are described in the Quantachrome Quantasorb operation manual. The surface area, of a powder sample can then be calculated using the following equation:

$$SA = \frac{X_m N A}{M} \tag{7}$$

where N is Avogaddro's number, M is nitrogen molecular weight, and A is the cross-sectional area of nitrogen molecule (16.2×10^{-20} m^2).

Table 4
The analysis of the variance of parameters

Parameters	P	df	RSS_p	MSE_p	C_p	R^2
β_0, β_1	2	15	604.099	40.273	302.4	0.805
$\beta_0, \beta_1, \beta_4$	3	14	145.399	10.386	64.9	0.953
$\beta_0, \beta_1, \beta_4, \beta_5$	4	13	32.712	2.516	8.1	0.989
$\beta_0, \beta_1, \beta_4, \beta_5, \beta_3$	5	12	28.40	2.367	7.8	0.991
$\beta_0, \beta_1, \beta_4, \beta_5, \beta_3, \beta_2$	6	11	21.07	1.916	6.0	0.993

P, number of parameters; df, degree of freedom; RSS_p: sum of squares; MSE_p, mean squares.

3.3.3. Solubility

In order to determine the drug solubility, a drug powder sample of known weight was transferred to a predetermined volume of deionized water at 25°C. This slurry was continuously stirred during the experiment (Gennaro, 1990). Since the slurry density exceeded the solubility of the drug, undissolved drug particles were visible in the saturated solution. The effect of dissolution time on drug solubility was also studied to ensure that solubility had been reached at the time of sampling. The slurry was subsequently filtered through a 0.5 μm filter in order to obtain a saturated solution (filtrate). The drug content in a known volume filtrate as well as the corresponding drug reference standards were assayed spectrophotometrically. The resulting concentration was the solubility of a drug in water at 25°C.

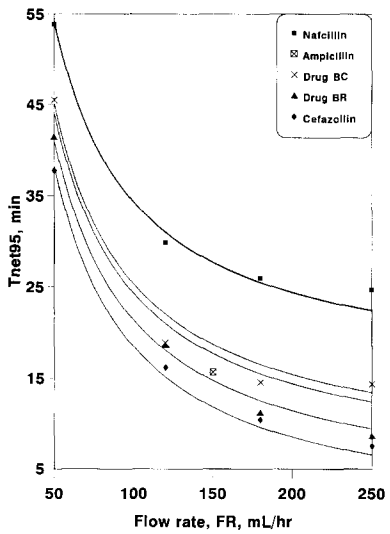

Fig. 5. Plots of T_{Net95} versus flow rate FR, comparison of experimental and simulated data. The curves (from the top to the bottom) are: sodium nafcillin, sodium ampicillin, Drug BC, Drug BR and sodium cefazolin.

3.3.4. Contact angle

In order to determine the contact angle, approximately 250 mg of a drug powder was compressed in a 0.5 in. diameter die at a 2000 lb force (Model C Carver Press, Menomonee Falls, WI) for 5 min. A drop of saturated drug solution was then placed on the compressed pellet of the same drug. The contact angle was measured using a goniometer (Rame-Hart, Mountain Lakes, NJ). The goniometer was calibrated by measuring contact angles of water, glycerine, and dodecane on parafilm (Osol, 1980).

4. Results and discussion

4.1. In-line drug delivery profiles

The diluent used was sodium chloride for injection and the flow rates were controlled using infusion pumps (Flo-Gard 6100, Travenol, Deerfield, IL). The value of T_{Net95} for each experiment was determined directly from the delivery profile as illustrated in Fig. 4. The resulting T_{Net95} values for the drugs investigated are presented in Table 2, where each value is the mean of at least six replicates. The range of the flow rate studied, 50–250 ml/h, is typically used in the hospital. The value of T_{Net95} for sodium nafcillin, at each flow rate appears to be much greater than other drugs.

4.2. Drug characterizations

The solubility of each drug was measured at 25°C, and the other parameters, the angle of internal flow Θ, contact angle θ and powder surface area, were measured at room temperature. The resulting values of these parameters are presented in Table 2, where each data point represents the mean of at least two replicates. In Table 2, it can be seen that the solubility of the drugs investigated is relatively high, ranging from 419 to 634 g/l.

4.3. Determination of regression coefficients

The coefficients in Eq. (4), β_0, β_1, β_2, β_3, β_4, β_5, were determined using the statistical package SAS (SAS User's Guide, 1985) executing in the IBM Mainframe using the multiple linear regression in terms of the five independent variables 1/FR, 1/SA, $1/C_s$, $1/\Theta^{1/2}$, and 1/Cos θ, with the stepwise option. The resulting best parameter sets and their statistical information are listed in Table 3. It can be seen that several models closely fit the data listed in Table 2. In order to determine the most appropriate model, the Mallows C_p statistic is used, which was proposed by Mallows (Drapper and Smith, 1981; SAS User's Guide, 1985) as a criterion for selecting a model. C_p is a measure of total squared error defined as:

$$C_p = \frac{\mathrm{SSE}_p}{s^2} - (n - 2p) \tag{8}$$

where SSE_p is the residual sum-of-squares error for a model containing p parameters plus the intercept; p is the number of parameters in the model including β_0, n is the number of data points, s^2 is the residual mean square from the largest equation postulated containing all the parameters, and is presumed to be a reliable and unbias estimate of the error variance σ^2. The values of C_p are presented in Table 4. The following criteria were used to determine the most appropriate model (Drapper and Smith, 1981): (1) large value of R^2; (2) small value of s^2; and (3) small value of C_p. It should also be noted that when several equations fit 'equally well' to the experimental data, the one with minimum parameters should be used. Thus, if C_p is graphed with p, Mallows recommends the model where C_p first approaches p. Table 4 shows that the value of R^2 becomes large when the number of parameters is greater than 3. As can be seen in Table 4, the value of C_p decreases rapidly from the two-parameter equation to a four-parameter equation and is 'stabilized' with further increasing of the parameters. Considering the above criteria, the following three-parameter equation was chosen for the drugs investigated in this work.

$$T_{\mathrm{Net95}} = -60.88 + 1980.7/\mathrm{FR} + 330.88/\Theta^{1/2} + 15.34/\cos\theta \tag{9}$$

It is noted from Eq. (9) that it does not contain the drug solubility C_s as one of the key factors. This may be attributed to the fact that the values of C_s investigated, as indicated in Table 2, only range from 420 to 634 mg/ml. Most of IV drugs, however, are highly soluble electrolytes. The experimental data and simulated data, using Eq. (9), are plotted in Fig. 5. It can be seen that Eq. (9) gives a close fit to the experimental data of all drugs investigated, with R^2 equal to 0.989 as indicated in Table 4. The resulting regression equation indicates that in order to determine the values of T_{Net95} for a particular drug of interest, only the angle of internal flow Θ and the contact angle θ need to be determined. Eq. (9) provides a rapid screening of drugs that can be delivered in the in-line delivery system.

5. Conclusion

The results in this study support that T_{Net95} of an in-line drug delivery profile is closely correlated to the three parameters as shown in the semi-empirical equation, Eq. (9). The successful development of this mathematical model by simply knowing the angle of internal flow Θ and the contact angle θ in the prediction the IV in-line drug delivery performance of a drug will substantially reduce product development time in the future. This equation will mainly be used to minimize experimental effort in the determining T_{Net95} for a particular drug at a particular diluent flow rate.

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