DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(20), 2145-2161 (1992)

SIGNIFICANCE OF INTERACTIONS OF A NOVEL ANTI-EMETIC DRUG AND PACKAGING COMPONENTS DURING CLINICAL STUDIES

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ABSTRACT

RG-12915 is a new drug currently being evaluated in clinical trials for the management of emesis. In this study, the sorption of RG-12915 to intravenous packaging materials was investigated. It was determined that the sorption of RG-12915 by intravenous infusion bags composed of polyvinyl chloride was temperature dependent, greater sorption occuring as the temperature was increased. Linear and nonlinear regression models were used to derive the parameters of percent initial concentration at equilibrium, rate of sorption, and the time when the rate of sorption becomes zero. Polypropylene syringes were demonstrated to be compatible with RG-12915 solutions under the conditions of the investigation.

INTRODUCTION

RG-12915 is an investigational new drug currently being evaluated in clinical trials for the management of emesis. It is supplied as a sterile, buffered, isotonic solution in a concentration of 1 mg/mL. For the purpose of clinical studies, the formulation is intended for administration by intravenous infusion after dilution by the hospital pharmacist with common diluents such as 0.9% Sodium Chloride Injection, USP. In the process of evaluating the clinical efficacy of a new intravenous formulation, significant consideration must be given to properly transfer the preparation and administration methods from the industrial laboratory to the hospital pharmacy. This is particularly critical during the initial clinical studies which may require non-routine preparatory procedures by the hospital pharmacist. Failure to anticipate this technology transfer from the laboratory to the hospital pharmacy may compromise the results of the clinical study. Risks during pharmacy preparation and manipulation include light degradation of the drug, loss of drug by sorption to the bag material, and loss of drug by adsorption to the filter during filtration of the sterile solution following withdrawal of the drug solution from a newly opened glass ampule.

The manufacture of intravenous solutions for clinical studies is performed by the industrial pharmacist according to current Good Manufacturing Practices (cGMPs). It was recently documented that additional compounding steps and further manipulations of sterile products pose significant opportunities for inaccuracies and microbial contamination by the hospital pharmacist[1]. It is the goal of the industrial pharmacist to minimize manipulations by the hospital pharmacist in order to reduce the risk of inaccuracies or infections caused by microbial contamination of pharmacy-prepared products in the absence of adequate quality assurance procedures[1]. Therefore, the method of preparation and storage conditions for the RG-12915 dilutions in the clinical setting was investigated in order to ensure that the new drug substance is available at the intended dose as required in the clinical protocol, and the clinical study is not compromised.

An important source for potential drug loss from solution may be the packaging components, including the plastic (e.g., polyvinyl chloride, PVC) flexible infusion bags, during manipulation of intravenous solutions in the hospital pharmacy. The use of PVC bags may be contraindicated in these cases, and the hospital pharmacist who is charged with preparing the experimental dose at the site of the clinical study must be alerted to this fact. Drug loss from solution may occur through adsorption to the surface of the plastic (e.g. insulin), absorption into the plastic matrix (e.g., un-ionized forms of various drugs), or penetration through the plastic (e.g., nitroglycerin)[2-7]. The potential hazard of drug loss by sorption to the infusion sets or intravenous infusion bags has been evaluated for many marketed products, including warfarin sodium and various benzodiazepines[8]. The authors determined that the rate and extent of sorption of warfarin and diazepam into the plastic matrix of PVC infusion bags were influenced by the pH of the solution containing the drug; only the un-ionized form was sorbed[8]. A comprehensive understanding of the compound and its compatibility with various packaging materials which may be used at the clinic is normally not available during the early phases of formulation development and clinical evaluation. It is necessary for the industrial pharmacist to understand and anticipate the potential hazards which may arise during the preparation of the clinical material by the hospital pharmacist during the formulation development of new chemical entities. Recommendation of appropriate procedures and materials which may be safely employed in the clinical study is the ultimate goal.

Infusion bags composed of PVC are commonly used in the preparation of intravenous solutions. PVC infusion bags are collapsible, impact resistant, easy to transport and handle, and flexible enough to allow easy administration without air intake. Significant disadvantages of PVC infusion bags include the fact that they remain hazy several weeks after steam sterilization, exhibit high moisture permeation that may limit storage of a solution, and sorb many drugs from solution during storage[9]. The factor most potentially detrimental in compromising a clinical study is loss of drug from solution by sorption to the PVC bag. In this case, the use of infusion bags composed of PVC would be unacceptable.

The purpose of this study was to evaluate the sorption propensity of RG-12915 from aqueous solution to PVC infusion bags commonly used in hospitals. The concentration of RG-12915 in solution was determined at various storage temperatures in order to evaluate the effect of temperature on sorption of the drug to the excised PVC strip. In addition, the stability of RG-12915 solutions during storage in polypropylene syringes was also evaluated.

METHODS

Materials. The new chemical entity, RG-12915, supplied as a 1 mg/mL solution, was examined in this study. The RG-12915 formulation, composed of a buffered, isotonic, aqueous solution, was found to be stable (i.e. no drug degradation observed) at each of the storage conditions employed in this study, therefore any drug loss from solution was attributed to sorption to the PVC or polypropylene.

A sample of PVC film was excised from a single-use evacuated PVC container (Empty Container, 250 mL, Abbott Laboratories, North Chicago, IL, 60064, Lot No. 36-091-NG01) for the PVC compatibility study. The excised rectangular strip measured approximately 45.8 cm^2 in surface area and weighed about one gram. The excised PVC strip was placed in a 100 mL Type I glass volumetric flask containing 100 mL of the

RG-12915 1 mg/mL solution, and the flask was closed with a glass stopper. The samples were stored at 5°C, 30°C, and 50°C, and 1.0 mL aliquots were withdrawn and assayed initially, and at 4, 6, 24, 48, 72, 144, 168, 216, and 264 hours. The pH of all solutions was determined (Model 245, Corning Science Products, Corning, NY, 14831) at the beginning and end of each study, and found to remain unchanged during the study time period. Each data point represents the mean of three samples. All samples were protected from light during the study.

The 1 mg/mL RG-12915 solution was diluted to either 0.04 mg/mL or 0.20 mg/mL concentration with 0.9% Sodium Chloride Injection, USP (50 mL, Abbott Laboratories, North Chicago, IL, 60064, Lot No. 45-957-JT) using aseptic techniques for the polypropylene syringe compatibility study. 60 Milliliter aliquots of each dilution were withdrawn into 60 mL empty polypropylene syringes (B-D 60 cc Syringe, Becton Dickinson & Company, Rutherford, NJ, 07070, Lot No. 1C662), and stored at room temperature. All samples were protected from light. Samples were assayed for potency initially, and at 2, 4, 8, 12, 24, 36, and 48 hours. All determinations were conducted in duplicate.

Sample Analysis. All samples were assayed for drug content using an HPLC system that typically consisted of a solvent delivery system (Model 6000A, Waters Associates, Milford, MA, 01757), an autosampler (WISP 710, Waters Associates, Milford, MA, 01757), and a variable wavelength detector (Model 450, Waters Associates, Milford, MA, 01757). The chromatograms were processed using an integrator (Model 3390A, Hewlett Packard, Palo Alto, CA, 94303). A μBondapak C18 column (4.6 cm X 25 cm, Waters Associates, Milford, MA) or equivalent was used for RG-12915 analysis. Chemicals and solvents were reagent grade and HPLC grade or the equivalent, respectively. Characterized standards were used for quantification.

RESULTS AND DISCUSSION

The results of the PVC infusion bag sorption study are displayed graphically in Figures 1, 2, and 3. The concentration of RG-12915 initially decreased at an approximately zero-order rate as the compound was sorbed to the PVC strip at each temperature. The decrease in drug concentration eventually reaches an equilibrium plateau at a time and concentration dependent upon the temperature of the sample. The time to reach this plateau at each temperature is of interest, as well as the rates of sorption and equilibrium concentrations. Two different equations were investigated to model the RG-12915 sorption.

An ad hoc procedure was used to estimate the initial rate of sorption (% of initial concentration/hour), start of equilibrium (hours), and % of initial concentration at

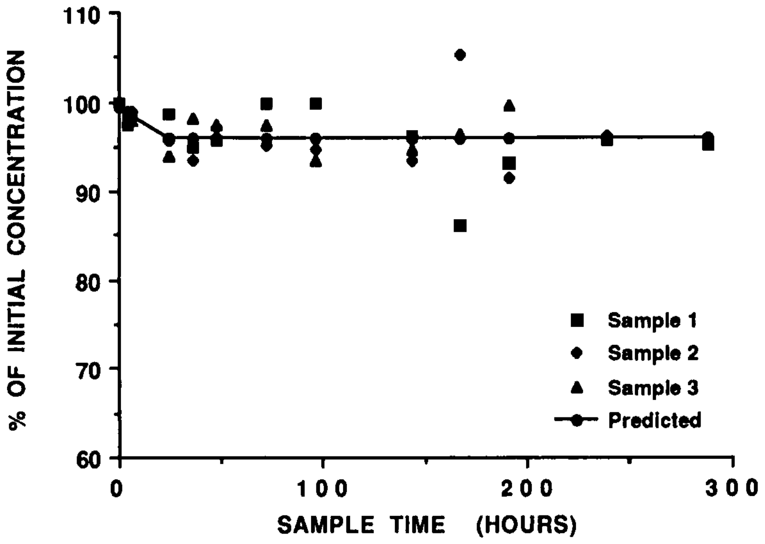

Figure 1

Plot of data according to Equation 1 at 5°C.

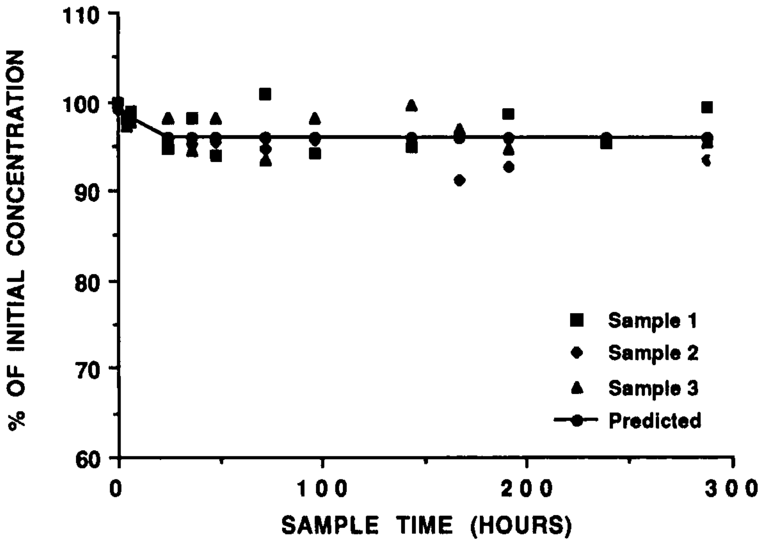

Figure 2

Plot of data according to Equation 2 at 30°C.

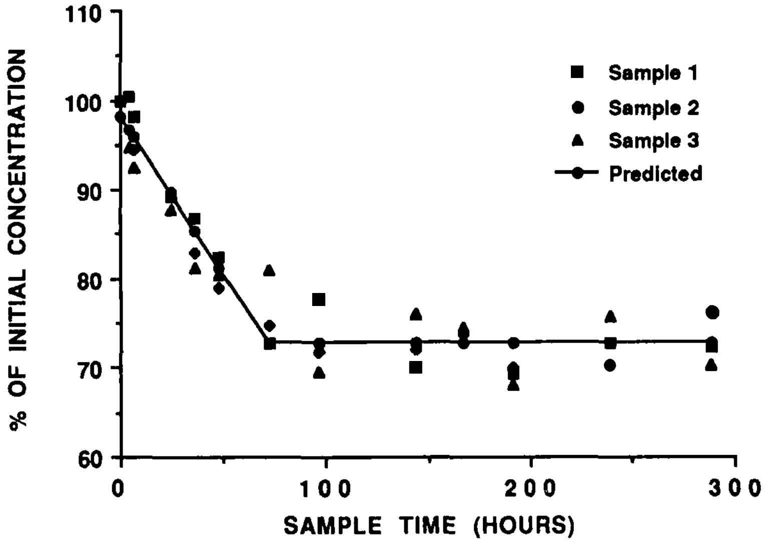

Figure 3

Plot of data according to Equation 1 at 50°C.

equilibrium. Linear regressions were fit to the equilibrium model given by Equation 1.

$$C_T = C_{eq} + KX_T \qquad \text{Equation 1}$$

where:

C_T = concentration at time T

C_{eq} = % of initial concentration at equilibrium

K = rate of sorption

X_T = 0 if T > E_S or (T - E_S) otherwise

E_S = time when rate of sorption becomes zero

T = sample time

For each temperature examined, the regression was fit to data collected from three samples for E_S set equal to each sample time T. The root mean squared error, an estimate of the standard deviation of C_T (SD(C_T)) is noted in each model. This is a measure of the model goodness of fit. The value of E_S where SD(C_T) is minimum is the best estimate of the start of equilibrium or the time when the rate of sorption becomes zero. At a fixed E_S, the regression slope and y-intercept estimate the initial rate of sorption and the % of initial concentration at equilibrium.

In Figures 1, 2, and 3, the results for the plots of % of initial RG-12915 concentration versus time measured in the sorption experiments, as well as the results of the regression fitting procedure, are shown. The parameter estimates are given in Table I. The regression fitting method does not provide an estimate of the standard error or statistical significance of the E_S estimate, since the slope and y-intercept estimates are conditional on the selected value of E_S. The results indicate that the samples stored at 5°C and 30°C showed only slight sorption of RG-12915 by the PVC strip. The predicted rates of sorption over 24 hours were significantly different from zero ($p = 0.01$ and $p = 0.007$) but the proportions of variability about the mean explained by the model (R^2) were 0.17 and 0.27. The regression model fit sorption at 50°C, with the start of equilibrium predicted at 72 hours and an equilibrium concentration of 72.7% of initial concentration.

TABLE 1

Estimates of Parameters Derived from Equation 1.

Temperature °C	E_S Hours	K (SE)[a] % Init/hour	C_{eq} (SE) % Init	SD(C_T)[b] % Init	R^2
5	24	-0.15(0.05)	95.9(0.5)	2.9	0.17
30	24	-0.13(0.04)	95.8(0.4)	2.0	0.27
50	72	-0.35(0.02)	72.7(0.6)	2.8	0.93

[a] Standard error of the mean.

[b] Root mean squared error as an estimate of the standard deviation of C_T.

A smooth equation for a curve with an initial, approximately linear, decrease followed by a stable phase is the hyperbolic 'Vmax' curve defined by Equation 2.

$$C_T = 100 - C_\delta T / (H + T) \qquad \text{Equation 2}$$

where:

C_T = % of initial concentration remaining at time T

C_δ = C_{eq} as a difference from C_o (approximately 100%)

T = sample time

H = time when $C_T = 0.5(C_o + C_{eq})$

The parameters of this curve, estimated by nonlinear regression from the 5°C, 30°C, and 50°C samples, are listed in Table II.

The data and predicted curve for the 50°C samples are shown graphically in Figure 4. In this nonlinear model

TABLE 2

Estimates of Parameters Derived from Equation 2.

Temperature (^oC)	9 H (SE)[a] Hours (approx. E_S)	C_δ (SE) % Init (approx. C_{eq})	SD (C_T)[b] % Init
5	66(80)	95.5(0.8)	3.0
30	45(37)	95.6(0.5)	2.1
50	311(52)	66.0(1.5)	3.0

[a] Standard error of the mean.

[b] Root mean squared error as an estimate of the standard deviation of C_T.

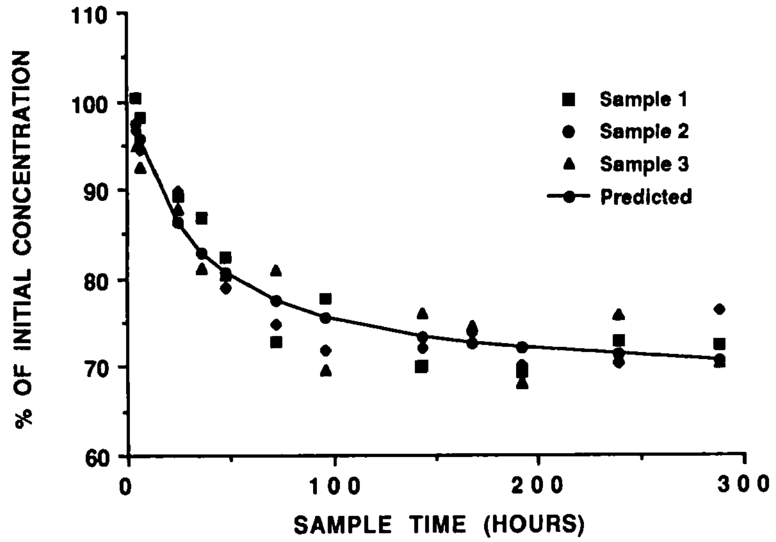

Figure 4

Plot of data according to Equation 2 at 50^oC.

approximately 90% of the total loss has occured after 9 half-lives (e.g., 0.9 H / 0.1 hours), and 95% by 19 H (e.g., 0.95 H / 0.05) hours. The estimates of the equilibrium concentration (E_S) by the 'Vmax' model are consistent with estimates from linear regressions. The estimated 9 half-life values are later than the E_S estimates from the linear regression model. This difference may be seen in a comparison between Figures 3 and 4. The 'Vmax" model does not predict a stable concentration within the range of the data. Comparison of the SD(C_T) estimates between Tables I and II show that Equation 1 fits the data slightly better than Equation 2.

Equation 1 may be re-written to allow simultaneous estimation of E_S, K, and C_{eq} by fitting Equation 3 to the samples.

$$C_T = C_{eq} + K\delta(T - E_S) \qquad \text{Equation 3}$$

where:

C_T = % of initial concentration at time T

C_{eq} = % of initial concentration at equilibrium

K = rate of sorption

$\delta(X)$ = 0 if X is positive or X otherwise

E_S = time when rate of sorption becomes zero

T = sample time

Although this is not a linear model or a smooth nonlinear model, it can be optimized by nonlinear regression methods. The estimates for these parameters are given in Table III. The

TABLE 3

Estimates of Parameters Derived from Equation 3.

Temperature ^{o}C	E_S(SE)[a] Hours	K (SE) % Init/hour	C_{eq} % Init	SD(C_T)[b] % Init
5	12(13)	-0.32(0.42)	95.8(0.5)	2.9
30	11(6)	-0.35(0.27)	95.8(0.4)	2.0
50	73(1)	-0.39(0.04)	72.8(0.6)	2.8

[a] Standard error of the mean.

[b] Root mean squared error as an estimate of the standard deviation of C_T.

estimated standard errors show that E_S estimates for the 5°C and 30°C samples are imprecise, possibly because they are not close to any observed sample times. Only the 50°C samples had an E_S estimate significantly different from zero. Comparison of the residual error estimates, SD(C_T), between Tables I and II shows that estimates from the simple regression procedure fit the data almost as well as estimates from the nonlinear optimization.

Syringes composed of polypropylene were investigated as an alternative to preparing the RG-12915 dilutions in PVC infusion bags. The data displayed graphically in Figure 5 show the variation of RG-12915 concentration from dilutions stored in 60 mL polypropylene syringes at 23° C for up to 48 hours. The results indicated that the concentration of RG-12915 at both 0.04 mg/mL and 0.2 mg/mL dilutions did not change

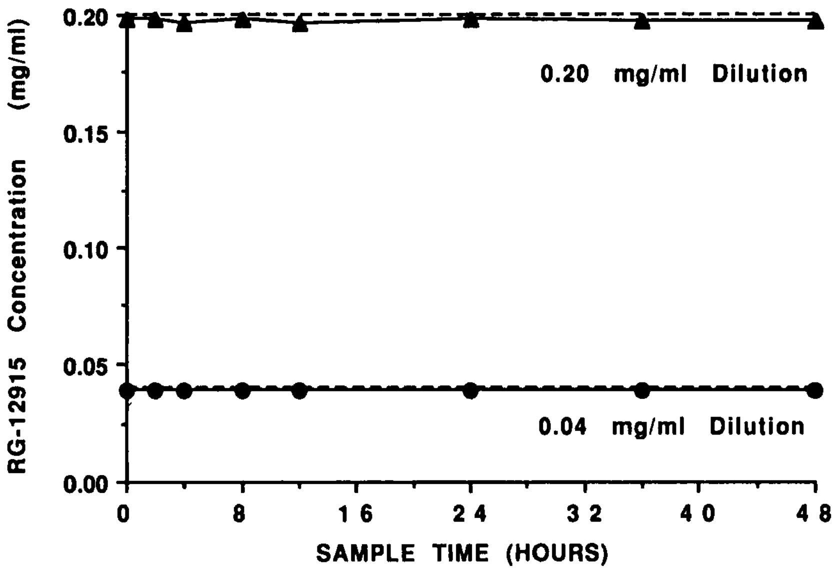

Figure 5

Concentration of RG-12915 as a function of time for samples from polypropylene syringes. Dotted lines represent theoretical concentration.

significantly over 48 hours. Each point on the graph represents the mean of two determinations. The relative standard deviations were less than 0.90% in all cases. Therefore, the polypropylene syringes are compatible with RG-12915 solutions since the data indicated no drug loss by sorption to the polymer material. Polypropylene has been characterized as possessing very good solution and drug compatibility as has been demonstrated in this study[9].

The results of this study demonstrate that intravenous infusion sets composed of PVC, sorbed RG-12915 slightly at

5°C and 30°C, and significantly at 50°C. Linear and nonlinear regression models were used to derive the parameters of initial percent concentration at equilibrium, rate of sorption, and time when the rate of sorption becomes zero. Polypropylene syringes were shown to be compatible with RG-12915 solutions at 23°C for up to 48 hours.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Ms. Patricia Logue for her excellent technical assistance, and Dr. Janet Walkow and Dr. Howard Levin for their help in reviewing this manuscript.

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