Studies on a Novel Doughnut-Shaped Minitablet for Intraocular Drug Delivery

Received: March 1, 2007; Final Revision Received: August 1, 2007; Accepted: August 1, 2007; Published: December 28, 2007

Yahya E. Choonara,[1] Viness Pillay,[1] Trevor Carmichael,[2] and Michael P. Danckwerts[1]

[1]University of the Witwatersrand, Department of Pharmacy and Pharmacology, Medical School, Johannesburg, Gauteng, South Africa

[2]University of the Witwatersrand, Department of Ophthalmology, Medical School, Johannesburg, Gauteng, South Africa

ABSTRACT

The objective of this study was to evaluate the effect of 2 independent formulation variables on the drug release from a novel doughnut-shaped minitablet (DSMT) in order to optimize formulations for intraocular drug delivery. Formulations were based on a 3^2 full-factorial design. The 2 independent variables were the concentration of Resomer (% wt/wt) and the type of Resomer grade (RG502, RG503, and RG504), respectively. The evaluated response was the drug release rate constant computed from a referenced marketed product and in vitro drug release data obtained at pH 7.4 in simulated vitreous humor. DSMT devices were prepared containing either of 2 model drugs, ganciclovir or foscarnet, using a Manesty F3 tableting press fitted with a novel central-rod, punch, and die setup. Dissolution data revealed biphasic drug release behavior with 55% to 60% drug released over 120 days. The inherent viscosity of the various Resomer grades and the concentration were significant to achieve optimum release rate constants. Using the resultant statistical relationships with the release rate constant as a response, the optimum formulation predicted for devices formulated with foscarnet was 70% wt/wt of Resomer RG504, while 92% wt/wt of Resomer RG503 was ideal for devices formulated with ganciclovir. The results of this study revealed that the full-factorial design was a suitable tool to predict an optimized formulation for prolonged intraocular drug delivery.

KEYWORDS: PLGA, kinetic modeling, controlled release, factorial design.

INTRODUCTION

Response surface methodology (RSM) is a rapid technique used to empirically derive a functional relationship between an experimental response and a set of input variables. It reduces the number of experimental runs necessary to establish a mathematical trend in the experimental design allowing for determination of the optimum level of experimental factors required for a given response.[1] Reducing the number of experiments by optimizing a formulation during development of a drug delivery device may also lead to significant reductions in production costs. RSM is widely used to optimize process parameters, especially in determining optimum conditions for investigations in large-scale drug design and delivery.[2] It has been applied to pharmaceutical systems such as the preparation of particulate carriers like gelisphere matrices[3] and microspheres.[4] It is necessary to have a clear understanding of how preparation conditions and inherent characteristics of excipients employed in pharmaceutical formulations are influenced by potential interactions between various factors in order to optimize a formulation.

Intravitreal implants have been investigated for the controlled release of antiviral bioactives to treat posterior segment eye disease. They can be fabricated from poly(lactide-co-glycolide) (PLGA), a biodegradable and biocompatible polymer, and implanted into the vitreous cavity of the eye with the advantage of being degraded and eliminated from the body once its drug load has been depleted. This polymer has been used for the preparation of various implants, sustained-release preparations, and inserts for their administration through parenteral, oral, dermatological, pulmonary, nasal, and ocular routes.[4-7]

Intravitreal implants of ganciclovir have also been demonstrated to be more effective than intravenous and intravitreal injections for the treatment of ocular pathologies such as cytomegalovirus retinitis (CMV-R), which can lead to irreversible blindness. Successive intraocular injections are poorly tolerated with risks such as endophthalmitis, cataract, retinal detachment, and vitreous hemorrhage. These inconveniences have been overcome by the use of drug delivery systems that are able to promote prolonged release of the bioactive into the vitreous cavity such as biodegradable implants. Implants, however, could constitute a poor delivery device if control of the release of the bioactive material was poor. By modifying the implants' formulation parameters, such as the type and concentration of polymer employed, it is possible to exert control on the in vitro release profile.

In a previous study by Sanborn and coworkers,[8] developed a nonbiodegradable intraocular implant, namely, the Vitrasert device, which was approved by the United States Food and Drug Administration (FDA) in March 1996. The device

Corresponding Author: Viness Pillay, University of the Witwatersrand, Department of Pharmacy and Pharmacology, Medical School, 7 York Road, Parktown, 2193, Johannesburg, Gauteng, South Africa. Tel: +2711 717-2274; Fax: +2711 642-4355; E-mail: viness.pillay@wits.ac.za

is able to provide controlled drug release kinetics over a 12-month period but has the distinct disadvantage of having to be removed from the eye once its drug load has been depleted as it is formulated from nonbiodegradable polymeric materials. The release of ganciclovir from the Vitrasert device was reported to be constant in the region of 2 μg/h.[9-13] When implants are prepared for the administration of bioactives in a practically isolated zone such as the vitreous humor, release must be able to reach therapeutic levels with the minimum dose. Moreover, if the implant is simple to manufacture and biodegradable, it may significantly reduce cost of production.

The objective of this study was to optimize a novel drug-loaded doughnut-shaped minitablet (DSMT) formulated from various concentrations of biodegradable polymers. The novelty of the DSMT is that the central hole makes suturing much easier, and the device is bioerodible making removal of the device once its drug-load is depleted unnecessary. The DSMT is also easy to manufacture and is reproducible as it is produced on a tableting press. To achieve optimization, a 3^2 full-factorial experimental design with center point replication was employed. The 2 input variables were the type and concentration of polymer, and their effect on the release kinetics of 2 model drugs, ganciclovir and foscarnet, was evaluated.

Materials and Methods

Materials

Resomer grades RG502, RG503, and RG504 consisting of poly(lactide-co-glycolide) (PLGA) with a 50% lactide content were purchased from Boehringer Ingelheim (Ingelheim, Germany). These polymers are all biodegradable and have inherent viscosities ranging from 0.16 to 8.2 dL/g. All polymers were ground in a mortar, and the fraction passing through a sieve with an aperture size of 125 μm (Endcotts Test Sieves, Ltd, London, UK) was used. Foscarnet was obtained from Sigma-Aldrich Co (Steinheim, Germany) and ganciclovir was obtained from Roche Products (Pty) Ltd, (Isando, South Africa). Disodium hydrogen orthophosphate, sodium chloride and potassium dihydrogen phosphate were obtained from Saarchem (Pty) Ltd, (Krugersdorp, South Africa). All other reagents used were standard laboratory grade substances of the highest purity.

Preparation of the Doughnut-Shaped Minitablet Device

A specially designed punch set engineered by Holland Tableting Science (London, UK) was used for manufacturing the doughnut-shaped minitablet device (DSMT). The punch set consisted of a lower and upper punch, die, and central rod. Both the upper and lower punches contained a longitudinal central hole for the insertion of the rod, which enabled a doughnut-shaped tablet to be compressed around it with a diameter of 5 mm and a 2-mm central hole (Figure 1). The press was set to compress DSMT devices to a thickness of 2 mm. Powder blends containing 50% wt/wt, 60% wt/wt, and 70% wt/wt polymer with foscarnet and 80% wt/wt, 85% wt/wt, and 90% wt/wt polymer with ganciclovir were prepared. All blending was performed using an Erweka AR 400 cube blender (Erweka, Heusenstamm, Germany), and a Manesty F3 eccentric (single punch) tableting press (Manesty Machines, Liverpool, UK) was used for directly compressing the powder blends into the DSMT.

Experimental Design

The study followed a 3^2 full-factorial experimental design using 2 factors on 3 levels for the DSMTs tested. The concentration of polymer employed in manufacturing the DSMTs (c) and the type of polymer (t) were used as the independent formulation variables. The normalized upper and lower factor levels of the independent variables for DSMTs containing foscarnet and ganciclovir are presented in Table 1. The various polymer types have been coded as −1 to +1 relevant to the inherent viscosity of each polymer grade. The number of experimental runs that relates to the tautness of the factorial matrix had to be maximized to ensure that all possible statistical combinations of concentration (c) and type (t) of polymer were included. The release rate constant (k_1) computed from the in vitro release data of foscarnet and ganciclovir from the DSMT was selected as the dependent variable. The factorial matrix was built using compiled Windows XP Microsoft Excel Macros (Add-Ins); namely, Essential Regression and Experimental Design Version 2.2 (Microsoft, Redmond, WA).

In Vitro Drug Release Studies

A modified closed-compartment United States Pharmacopeia (USP) 25 dissolution testing apparatus was used in performing all the release studies. At time zero, the DSMTs were immersed in 4 mL of simulated vitreous humor (SVH) pH 7.4 in closed vials. Thereafter they were centrally placed in a laboratory incubator equipped with an oscillating platform (Labcon FSIE-SPO 8-35, Petaluma, CA) equilibrated at 37°C ± 0.5°C. The platform was set to oscillate at 50 rpm. At predetermined intervals, 2 mL of the release medium was

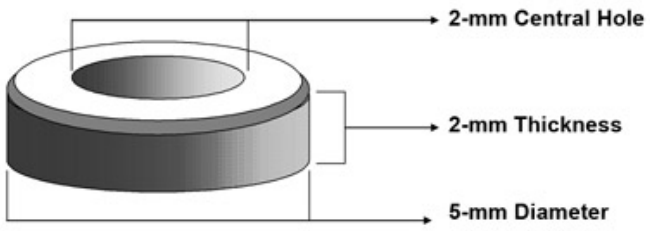

Figure 1. Schematic of the doughnut-shaped minitablet (DSMT).

Table 1. Levels of Independent Formulation Variables for Drug-Loaded DSMT Devices*

Variable	Factor Level −1	0	1	Units
Foscarnet Formulations				
Concentration of polymer (*c*)	50	60	70	% wt/wt
Type of polymer employed (*t*)†	RG502	RG503	RG504	dL/g
Ganciclovir Formulations				
Concentration of polymer (*c*)	80	85	90	% wt/wt
Type of polymer employed (*t*)†	RG502	RG503	RG504	dL/g

*DSMT indicates doughnut-shaped minitablet.

†Resomer grades differ with regard to their inherent viscosity ranges.

sampled and 2 mL of fresh SVH was replaced to the sampled vial to maintain sink conditions. Drug release computations were performed accordingly by considering a correction factor to account for sample volume displacement as a result of the previous time point sampling. All sampling was performed using a calibrated micropipette to ensure maximum accuracy.

Kinetic Modeling of Drug Release Data

Release data was analyzed on WinNonlin Version 4.2 (Pharsight Corp, Mountain View, CA). Data was represented by means of the Gaussian-Newton algorithm for the diffusional release model with an initial release exponent of 0.5. The method uses the estimated variance-covariance matrix of the parameters, and therefore it was chosen as a suitable method for the kinetic modeling of the in vitro release data obtained in this study. Equation 1 was the diffusional model used for obtaining a release constant for the Vitrasert implant, which releases ganciclovir at a constant rate of 2 μg/h:

$$A = k_1 t^n, \tag{1}$$

where A is the quantity of drug released; k^1 is the release rate constant; n is the release exponent; and t is the time period over which drug is released.

During statistical analysis it was found that 1000 iterations were sufficient to converge release data to a minimum mean square error for all formulations with a convergence criteria setting of 0.0001. The release rates were further analyzed by the strong parametrical support from statistical descriptors such as the Akaike Information Criterion (AIC), Schwartz Bayesian Criteria (SBC), and the Condition Number (CN). The CN value refers to the matrix of partial derivatives. It is the square root of the ratio of the largest to smallest eigenvalue of the matrix of partial derivatives. Eigenvalues and their associated eigenvectors can be thought of as building blocks for models (variance-covariance matrices). Very large CN values may be indicative of instability in the model fitting process. Similarly, the AIC and SBC values are a measure of goodness of fit based on maximum likelihood. When comparing several models for a given set of data, the model associated with the smallest value of AIC or SBC is regarded as giving the best fit.

Regression Analysis

Analysis of variance (ANOVA) was performed on the data presented in Table 2, using Essential Regression and Experimental Design for Excel (ERED) software (Microsoft Excel Macros Add-Ins). The independent variables were the concentration of polymer (*c*) in the DSMT and the type of polymer (*t*) employed in manufacturing the DSMT, while the dependent variable was the release rate constant (k_1) of foscarnet or ganciclovir from the DSMTs.

The significant difference between the types of polymers employed was the viscosity grade, which served as a hidden continuous independent formulation variable. Thus, a mixed-effects ANOVA model during regression analysis was not selected.

Response-surface plots were constructed for the above variables in order to determine their optimal combination. Response-surface methods are based on the fundamental

Table 2. Summary of Regression Analysis of Release Kinetics From DSMT Devices*

Statistical Parameter	Result
Foscarnet Release	
R^2	0.954
Standard error	0.009
Coefficient of variation	10.887
Ganciclovir Release	
R^2	0.891
Standard error	0.194
Coefficient of variation	43.563

*DSMT indicates doughnut-shaped minitablet.

assumption that the influence of the independent variables on the dependent parameters can be approximated by a mathematical function. Hence, response surface methods locate the sample points in the space of random independent variables such that an appropriate regression model can be found most efficiently. This study employed a full-factorial design, with 2 factors, 2 center points, and a quadratic model with 6 terms for the formulations tested. Equation 2 displays the regression model used:

$$k_1 = a_0 + a_1(t) + a_2(c) + a_3(t^2) + a_4(c^2) + a_5(tc), \quad (2)$$

where $a_0 \ldots a_5$ are coefficients of the system; c is the concentration of polymer in the DSMT; t is the type of polymer employed in manufacturing the DSMT; and k_1 is the release rate constant of foscarnet or ganciclovir from the DSMT.

Regression was conducted by employing a series of backward elimination and forward selection steps using all possible model terms as a starting point. This process eventually led to the best model for the various formulations. The critical significance levels were preset to a value of 0.05. Terms with a higher value than the critical significance were removed in the backward elimination step. These terms refer to either the concentration of polymer (*c*), type of polymer (*t*), or a combination of any independent variables (*cc, tt, ct*). Main effects and significant interactions were also calculated, and simple regression models for the 2 independent variables were developed. Each term in the final regression equation for the release constant was only included if the Student *t* test *P* value was less than .05 from the original regression model estimated. The regression coefficients for those effects that were considered insignificant were eliminated and the model was reestimated (Table 3).

The model with constraints of a minimum of 10% wt/wt polymer and a maximum of 100% wt/wt polymer could not find a suitable solution that provided an ideal release rate constant of 0.0431 as determined by the release data during preliminary studies, when a polymer loading of 30% to 50% wt/wt for the foscarnet formulations was employed. In order to produce a DSMT that may release foscarnet for ~3 to 4 months, the concentration of polymer (*c*) needed to be adjusted. Therefore, the experiment was repeated and concentrations of 50%, 60%, and 70% wt/wt polymer were used for the release of foscarnet.

Table 3. Relevant Regression Parameters for DSMT Release Kinetics*

Drug-Loading	Coefficients	*P* Value	Standard Error	*t* Value Statistic
Foscarnet Release	Constant	0.0001	0.0235	10.550
	c	0.0002	0.0004	–6.892
	t	0.0021	0.0039	–4.751
Ganciclovir Release	Constant	0.0092	1.3490	3.783
	c	0.0135	0.0150	–3.456
	t	0.0603	1.6530	–2.309
	tc	0.0709	0.0190	2.191

*DSMT indicates doughnut-shaped minitablet.

Results and Discussion

In Vitro Drug Release Studies

Figures 2 and 3 display the influence of polymer viscosity and drug loading on various drug release profiles obtained from un-optimized DSMT devices. Release profiles displayed a typical initial burst phase followed by a second phase derived from diffusional release. The initial burst may have resulted from the release of drug deposited on the surface of the matrices. During the diffusional phase, drug release was possibly controlled by the degradation rate of the polymer, as the release tended to be more prolonged in a device prepared with a higher molecular mass polymer (Figure 2). Release kinetics during the second phase was fairly consistent at the various drug-loading concentrations. The devices had a biphasic pattern, and with the higher viscosity polymer (Resomer RG504), the duration of drug release tended to be more prolonged (Figure 3).

Kinetic Modeling of In Vitro Release Data

Table 4 lists the results obtained following kinetic modeling of release data from ganciclovir and foscarnet DSMTs on WinNonlin Version 4.2 (Pharsight) pharmacokinetic software. Results indicated that the in vitro release data conformed well to the diffusional model with a release exponent of 0.5. The release rate constants represented in Table 4 are the results acquired after kinetic modeling of the raw data from the in vitro release studies. The AIC, SBC, and CN values were found to be sufficiently low. Therefore this indicated a good fitting as well as stability of the kinetic model to the release data.

The ideal release rate constant (k_1) that would permit a release of bioactives from the DSMT over a 3- to 4-month period was calculated in a manner that would allow the DSMT to be analogous to the Vitrasert implant. The diffusional release model (Equation 1) was solved to attain the ideal release rate constant of $k_1 = 0.0430$. This value was subsequently used as the ideal k_1 value for determining the release kinetics of foscarnet and ganciclovir from the DSMT device. The value of 2 μg/h for the quantity of drug release over a time period t (A) was determined from data previously published on the Vitrasert device (Smith et al, 1992; Sanborn et al, 1992; Avery, 1999). The first 2 digits of the formulation code in Table 4 represent the percentage wt/wt of polymer. The

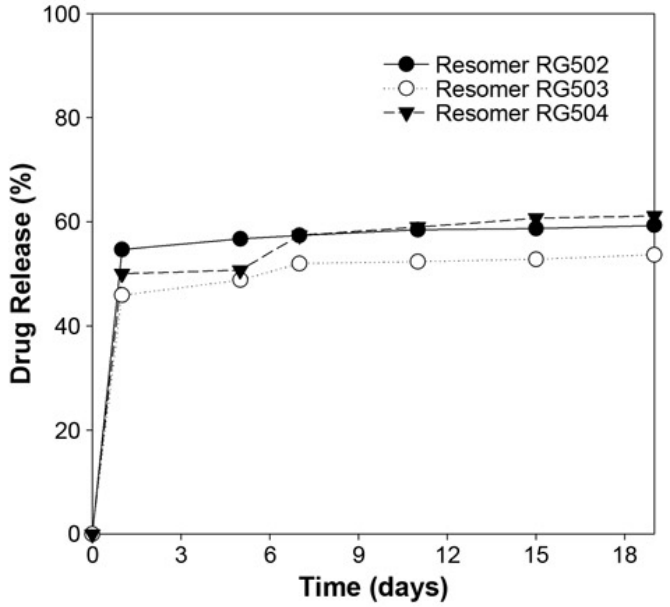

Figure 2. Effect of PLGA grade on the in vitro release from the DSMT at a constant drug load. PLGA indicates poly(lactide-co-glycolide); DSMT, doughnut-shaped minitablet.

RG502, RG503, and RG504 represent the Resomer grades, whereas "F" indicates foscarnet and "G," ganciclovir.

Foscarnet Release From the DSMT

Table 4 lists the release rate constants (k_1) for the release of foscarnet from the DSMTs with polymer loadings of 50% to 70% wt/wt. Figure 4 displays the response surface plot of the estimated effects of the concentration (c) and type (t) of Resomer grade used in formulating DSMTs with a 50% to 70% wt/wt polymer loading on the release rate constant of foscarnet from the devices. Both variables (c and t) had a significant influence in the resultant release rate constant of the DSMT with a polymer loading range of 50% to 70% wt/wt (Table 3). The drift revealed by the surface plot (Figure 4) indicated that by increasing the concentration of polymer and employing a polymer of higher viscosity (surface plot converges to 1 for Resomer type = RG504), a significantly reduced release rate constant could be achieved.

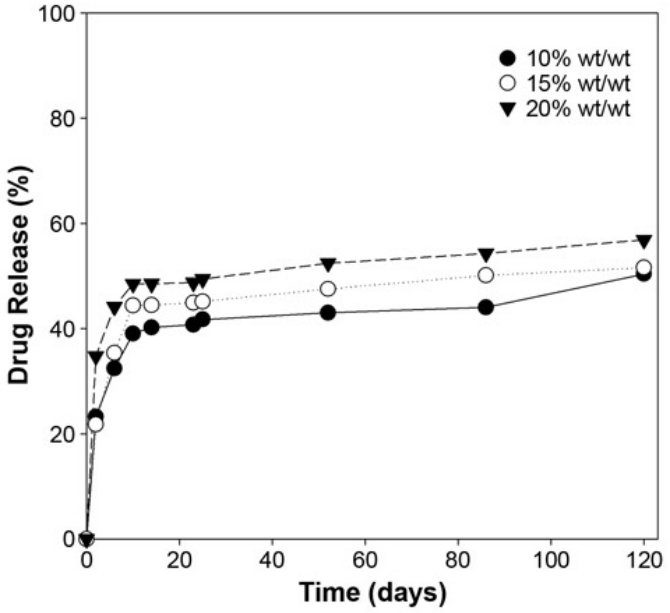

Figure 3. Effect of varying drug loads on the in vitro release from the DSMT device. DSMT indicates doughnut-shaped minitablet.

Table 4. Release Data and Statistical Descriptors Modeled on WinNonlin Version 4.2*

Formulation Codes	k_1	CN	AIC	SBC
Ganciclovir				
90RG502G	0.247	17.29	84.00	82.30
85RG502G	0.434	27.08	94.88	93.18
80RG502G	1.391	68.72	100.46	98.77
90RG503G	0.235	17.93	89.27	87.58
85RG503G	0.415	26.31	96.81	95.12
85RG503G	0.419	23.21	84.22	81.25
80RG503G	0.442	27.50	97.00	95.30
90RG504G	0.122	17.44	81.81	80.11
85RG504G	0.338	22.36	89.31	87.61
80RG504G	0.415	31.26	103.48	101.78
Foscarnet				
70RG502F	0.074	23.90	–5.59	–7.57
60RG502F	0.099	19.14	4.26	2.34
50RG502F	0.145	15.68	9.11	7.19
70RG503F	0.069	25.19	–4.10	–6.03
60RG503F	0.087	21.12	1.63	–0.29
60RG503F	0.076	23.24	1.21	0.32
50RG503F	0.119	17.26	4.32	2.40
70RG504F	0.045	22.64	–1.45	–3.37
60RG504F	0.077	23.10	0.07	–1.85
50RG504F	0.085	32.57	1.88	–0.04

*k_1 indicates the release rate constant; CN, condition number; AIC, Akaike information criterion; and SBC, Schwartz Bayesian criteria.

In order to produce a DSMT that is capable of releasing foscarnet for ~3 to 4 months, the concentration of Resomer (c) and the type of Resomer (t) could be adjusted to produce the required release rate constant. The best solution that could be achieved would be to employ 70% wt/wt of Resomer RG504 in formulating the DSMT, which would provide a release rate constant of 0.0431. Results obtained after optimizing for a release rate constant of 0.0431 are listed in Table 5.

Ganciclovir Release From the DSMT

Table 4 lists the release rate constants (k_1) for the release of ganciclovir from the DSMTs tested. Figure 5 displays the response surface plot of the estimated effects of the concentration (c) and type (t) of Resomer used in formulating the

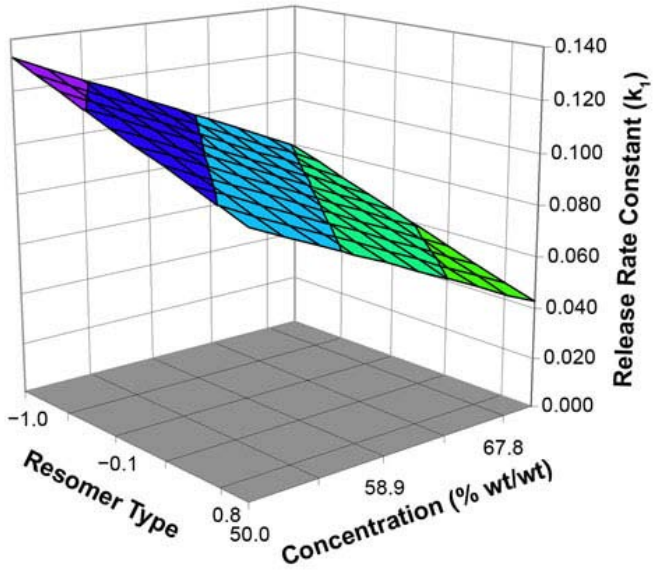

Figure 4. Response surface plot of the estimated effects of (*c*) and (*t*) on the release rate constant of foscarnet from the DSMT. DSMT indicates doughnut-shaped minitablet.

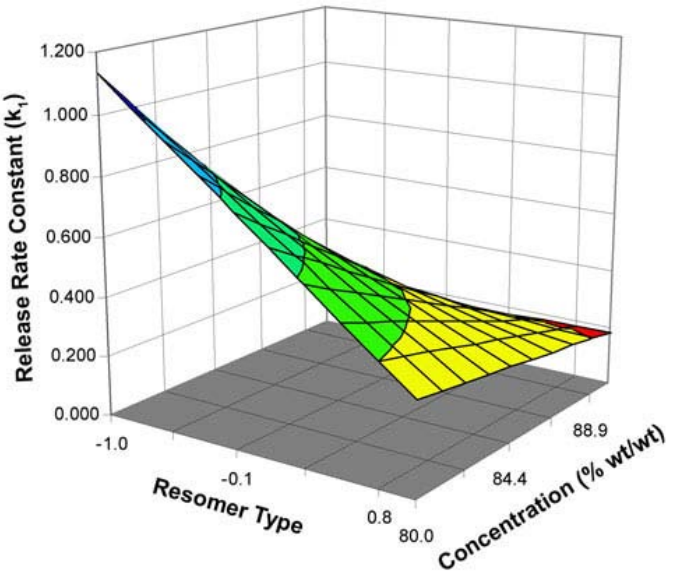

Figure 5. Response surface plot of the estimated effects of (c) and (t) on the release rate constant of ganciclovir from the DSMT. DSMT indicates doughnut-shaped minitablet.

DSMT on the release rate constant of ganciclovir from the matrix devices. Surface plot revealed a similar drift as with the foscarnet-loaded devices. Significant curvature was noted owing to possible interaction effects between the concentration and type of polymer employed (Figure 5). However, the profile retained convergence to a higher concentration of polymer and viscosity grade in order to achieve a reduced release rate constant. Using the Solver function available on the ERED software enabled the release rate constant to be optimized within constraints applied to the model.

The concentration of Resomer (*c*) had a statistically significant influence on the resultant release rate constant (Table 3). The higher molecular mass polymer, namely, Resomer RG504 resulted in a reduced release rate constant; however, the interaction effects between the concentration and polymer type were not statistically significant (Table 3). The superior aqueous solubility of the model drug ganciclovir was assumed as the rate-limiting step to drug diffusion rather than the polymeric erosion kinetics. The model with constraints of a minimum of 10% wt/wt polymer and a maximum of 100% wt/wt polymer found a suitable solution that provided an ideal release constant of 0.0431. The best solution to the release constant is by employing Resomer RG503 at a concentration of 92% wt/wt in the formulation, which provides the desired release rate constant of 0.0431.

Table 5. Optimized Independent Formulation Variables for Drug-Loaded DSMT Devices*

Variable	Optimized Result
Foscarnet Formulations	
Resomer type code (*t*)†	1
Concentration of polymer (*c*)	69.7% wt/wt
Release rate constant (k_1)	0.0431
Ganciclovir Formulations	
Resomer type code (*t*)†	0
Concentration of polymer (*c*)	92.4% wt/wt
Release rate constant (k_1)	0.0431

*DSMT indicates doughnut-shaped minitablet.

†Resomer type code: –1 = RG502; 0 = RG503; and 1 = RG504.

Constrained Optimization

A constrained optimization technique was employed to generate the optimum setting for the DSMT formulation using maximization of the type (< = 1; > = −1) and concentration (< = 100% wt/wt; > = 10% wt/wt) of polymer as the major optimization objective (for optimization computations, each polymer type was coded as follows: −1 = Resomer RG502; 0 = Resomer RG503; 1 = Resomer RG504). In this study, optimization was achieved by employing the Windows XP Microsoft Excel Macros (Add-Ins); namely, Essential Regression and Experimental Design Version 2.2 Solver function (Microsoft, Redmond, WA). Results obtained after optimizing for a release rate constant of 0.0431 are listed in Table 5.

CONCLUSION

The application of a 3^2 full-factorial experimental design with subsequent constraint optimization resulted in a useful tool for elucidating ideal antiviral-loaded PLGA intravitreal

implants prepared by direct compression tableting. According to the studied factors, the selected optimum formulation for implants formulated with foscarnet was 70% wt/wt of Resomer RG504, while 92% wt/wt of Resomer RG503 was optimum for implants formulated with ganciclovir. These formulations, therefore, may be suitable for intraocular drug delivery in order to treat posterior segment ocular pathologies such as cytomegalovirus retinitis (CMV-R) in human immunodeficiency virus (HIV)+ patients.

REFERENCES

1. Gotti R, Furlanetto S, Andrisano V, Cavirini V, Pinzauti S. Design of experiments for capillary electrophoretic enantioresolution of salbutamol using dermatan sulphate. *J Chromatog A.* 2000; 875:411–422.

2. McCarron PA, Woolfson AD, Keating SM. Response surface methodology as a predictive tool for determining the effects of preparation conditions on the physicochemical properties of poly (isobutylcyanoacrylate) nanoparticles. *Int J Pharm.* 1999;193:37–47.

3. Pillay V, Danckwerts MP. Textural profiling and statistical optimization of cross-linked calcium-alginate-pectinate-cellulose acetophthalate gelisphere matrices. *J Pharm Sci.* 2002;91:2559–2570.

4. Kimura H, Ogura Y, Hashizoe M, Nishiwaki H, Honda Y, Ikada Y. A new vitreal drug delivery system using an implantable biodegradable polymeric device. *Invest Ophthalmol Vis Sci.* 1994;35:2815–2819.

5. Martinez-Sancho C, Herrero-Vanrell R, Negro S. Optimization of acyclovir poly(d,l-lactide-co-glycolide) microspheres for intravitreal administration using a factorial design study. *Int J Pharm.* 2004;273: 45–56.

6. Vandervoort J, Ludwig A. Biocompatible stabilizers in the preparation of PLGA nanoparticles: a factorial design study. *Int J Pharm.* 2002;238:77–92.

7. Yasukawa T, Kimura H, Kunou N, et al. Biodegradable scleral implant for intravitreal controlled release of ganciclovir. *Graefes Arch Clin Exp Ophthalmol.* 2000;238:186–190.

8. Sanborn GE, Anand R, Torti RE, et al. Sustained-release ganciclovir therapy for treatment of cytomegalovirus retinitis. *Arch Ophthalmol.* 1992;110:188–195.

9. Martinez-Sancho C, Herrero-Vanrell R, Negro S. Poly (D,L-lactide-co-glycolide) microspheres for long-term intravitreal delivery of acyclovir: influence of fatty and non-fatty additives. *J Microencapsul.* 2003;20:799–810.

10. Martin DF, Parks DJ, Mellow SD, et al. Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol.* 1994;112: 1531–1539.

11. Fonner DE, Buck JR, Banker GS. Mathematical optimization techniques in drug product design and process analysis. *J Pharm Sci.* 1970;59:1587–1596.

12. Moritera T, Ogura Y, Honda Y, Wade R, Hyon SH, Ikada Y. Microspheres of biodegradable polymers as a drug delivery system in the vitreous. *Invest Ophthalmol Vis Sci.* 1991;32:1785–1790.

13. Smith TJ, Pearson PA, Blanford DL, Brown JD, Goins KA. Intravitreal sustained-release ganciclovir. *Arch Ophthalmol.* 1992;110: 255–258.