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Kinetic model of drug distribution in the urinary bladder wall following intravesical instillation

I. Grabnar [a], M. Bogataj [a], A. Belič [b], V. Logar [b], R. Karba [b], A. Mrhar [a,*]

[a] *Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, SI-1000 Ljubljana, Slovenia*
[b] *Faculty of Electrical Engineering, University of Ljubljana, Tržaška 25, SI-1000 Ljubljana, Slovenia*

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Abstract

Intravesical administration of cytotoxic agents is commonly used in urological practice for treatment of superficial bladder cancer. The leading motive is optimisation of drug delivery near the site of action and reduction of systemic toxicity. Bladder pharmacokinetics is complicated by several mechanisms. The objectives of this work were to develop a kinetic model of drug distribution in the bladder wall following intravesical instillation and to study the effect of various parameters on tissue and systemic drug exposure and explore the potential benefits of permeability enhancing effects of chitosan (CH) and polycarbophil (PC) through simulation. Key elements of the model are variable urinary drug concentration due to urine formation and voiding, biphasic diffusion in the bladder tissue and systemic absorption. Model parameters were estimated from bladder-tissue concentration profiles obtained in previous *in vitro* experiments with pipemidic acid (PPA) as a model drug. The results support further investigations on application of CH and PC in intravesical drug delivery. Both polymers increase permeability of the bladder wall by diffusion enhancement in the urothelium and presumably by improving the contact with the bladder surface. The developed mathematical model could serve for optimisation of intravesical drug delivery and future development of intravesical drug delivery systems.

Keywords: Urinary bladder; Chitosan; Polycarbophil; Permeability; Diffusion model

1. Introduction

Local administration of cytotoxic agents is commonly used in urological practice for treatment of superficial bladder cancer (Nseyo and Lamm, 1996; Witjes, 1997; Highley et al., 1999). The most frequently used drugs include mitomycin C, thiotepa, ethoglucid, doxorubicin, epirubicin, 5-fluorouracil, bacille Calmette-Guérin and more recently paclitaxel. They are applied intravesically in catheterised patients by instillation of 20–60 ml solution in one or more weekly treatments. Since most of these drugs have very narrow therapeutic indices and because of anatomical and physiological characteristics of the lower urinary tract there are several advantages of the local over systemic drug administration. Intravesical pharmacotherapy strives for optimal drug delivery near the site of action while minimising systemic exposure. Additionally, exposure time at the site of the tumour can be controlled (Highley et al., 1999).

Although empiricism-based dosage regimens are clinically effective, highly variable and incomplete response implies that further improvements are possible (Wientjes et al., 1993a; Montie, 2001; Au et al., 2001). Unsatisfactory intravesical therapy is in part due to the insensitivity of highly malignant tumours to the cytotoxic drugs and partially because of insufficient drug delivery to the tumour cells. Drug concentrations in the bladder tumour are frequently sub-therapeutic due to short retention times in the bladder lumen during the standard 2-h treatment, continuous dilution as a result of urine formation and limited penetration through tumour tissue because of low permeability of the bladder mucosa and loss by systemic absorption in the lamina propria and underlying muscular layers (Highley et al., 1999; Tannock et al., 2002).

There are several approaches to improve drug delivery to the bladder tumour. Prolongation of drug retention near the tumour site and maintenance of elevated drug concentration by controlled drug delivery are the main motives for development of intravesical drug delivery systems (Johnson et al., 1989; Frangos et al., 1990). Majority of the intravesical drug delivery systems under study are based on vesical mucoadhesion (Peppas et al.,

* Corresponding author. Tel.: +386 1 4769 541; fax: +386 1 4258 031.
E-mail address: ales.mrhar@ffa.uni-lj.si (A. Mrhar).

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1984; Ueda et al., 1992, 1994; Singh et al., 1996; Bogataj et al., 1999; Burjak et al., 2001; Kerec et al., 2002a). Among the mucoadhesive polymers the most prominent are chitosan (CH) and polycarbophil (PC). It is anticipated that improved drug delivery to the tumour would be achieved by a combination of their mucoadhesive and permeation enhancing effects (Kriwet and Kissel, 1996; Lueßen et al., 1996; Schipper et al., 1997). We recently demonstrated *in vitro* that CH and PC enhance penetration of hydrophylic drugs through the bladder tissue (Kerec et al., 2002b; Grabnar et al., 2003) by desquamation of urothelium cells (Kerec et al., 2005).

On the other hand considerable efforts were made to optimise intravesical pharmacotherapy by instillation of a drug solution. The group of Wientjes et al. (1993a) developed a mathematical model to predict drug exposure in bladder tumours after intravesical administration of mitomycin C. Their model (Eqs. (1)–(4)) is based on urine drug concentration data from patients treated with intravesical mitomycin C and drug penetration in the bladder wall data from patients undergoing cystectomy:

$$C_u = \frac{\text{dose}}{V_u} e^{-(k_a+k_d)t} \quad (1)$$

$$V_u = V_0 + k_0 t + V_{res} \quad (2)$$

$$C_x = C_u - \frac{C_u - C_{200}}{200} x, \quad 0\,\mu m < x < 200\,\mu m \quad (3)$$

$$C_x = (C_{200} - C_b)e^{-(0.693/w_{1/2})(x-200)} + C_b, \quad x > 200\,\mu m \quad (4)$$

Eqs. (1) and (2) describe urine pharmacokinetics. Urine drug concentration C_u is steadily decreasing due to drug degradation and systemic absorption (k_d and k_a are first order rate constants for these processes, respectively) and due to urine formation. Urine volume V_u at time t depends on volume of instilled drug solution V_0, residual urine volume V_{res}, which is present in the bladder at time of instillation and urine formation rate k_0. Bladder-tissue pharmacokinetics is described by Eq. (3), i.e. penetration across urothelium (0–200 μm), which is not blood perfused and Eq. (4), i.e. penetration across deeper capillary perfused tissues of lamina propria and muscular layers where systemic absorption occurs. Drug concentration C_x at depth x is dependent on drug concentration in urine C_u, in blood C_b and at the interface between urothelium and deep tissues C_{200}, and half-width $w_{1/2}$. The latter is the tissue thickness over which drug concentration declines by 50%.

Bladder-tissue exposure was related to the inhibition of tumour cell proliferation using patients' bladder tumour explants (Millenbaugh et al., 2000). Several approaches were suggested to improve intravesical therapy with mitomycin C (Wientjes et al., 1993a): increasing the dose to 40 mg from conventional 20 mg, reducing the volume of the instilled solution from 40 to 20 ml, minimising the residual urine volume and urine production and alkalinising urine by peroral sodium bicarbonate to minimise acidic degradation. It was hypothesised based on simulation results and later confirmed in a phase III trial (Au et al., 2001) that improved drug delivery would improve the recurrence free fraction of patients from 20 to 40%.

Although the usefulness of this model was undoubtedly demonstrated there are some limitations. First, although some animal studies (Wientjes et al., 1993b) suggest that steady state is achieved within a few minutes, the model of bladder drug distribution assumes unrealistic instantaneous equilibration between urine and tissue drug concentrations. Additionally, relationship between the parameters describing bladder permeability, namely half-width $w_{1/2}$, absorption rate constant k_a and C_u/C_{200} and C_u/C_b concentration ratios is not elaborated, although these parameters are related. Experimental estimation of all these parameters is problematic. Furthermore, it is anticipated that they are changed in the presence of CH or PC due to increased bladder permeability. Consequently, this model could not be applied to study the effects of mucoadhesive polymers on bladder drug exposure.

In this manuscript, we present a dynamic compartmental model of bladder drug distribution, which extends our previous work (Grabnar et al., 2003). The developed model was used to asses the effect of various parameters on drug distribution in the bladder wall and to explore the potential benefits of permeability enhancing effects of CH and PC in intravesical therapy.

2. Methods

2.1. Experimental

Development of kinetic model of drug distribution in the urinary bladder wall is based on our previously published experiments with pipemidic acid (PPA) as a model hydrophilic drug (Grabnar et al., 2003). Tissue diffusion of PPA was studied *in vitro* on isolated porcine bladders. Actual tissue drug concentration versus tissue depth profiles were determined following exposure of the luminal side of the bladder wall to the PPA solution (control) or polymer dispersion with the same PPA concentration in custom-designed diffusion cells for 25, 50 or 120 min. The polymers used were chitosan hydrochloride (CH) – Protasan CL213 (degree of deacetylation 86%) purchased from Pronova (Oslo, Norway) and polycarbophil (PC) – Noveon AA1 from BF Goodrich (Brecksville, USA). Two distinct PPA (80 or 160 mg/l) and polymer (0.5 or 1%, w/v) concentrations were applied.

Following exposure, segments of the bladder wall were rapidly frozen in liquid nitrogen, attached by the serosal sides to cryotome object holders and sectioned in 20 μm slices parallel to luminal surface. Following extraction of the tissue slices, PPA tissue concentrations were determined by HPLC with fluorescence detection.

2.2. Tissue diffusion model

Tissue PPA concentration versus tissue depth profiles were constructed, in which PPA concentrations at 20 tissue depths were expressed as an amount of PPA (μg) per gram of tissue. Careful observation of the profiles revealed two distinct diffusion media with a breakpoint at approximately 200 μm. Steeper

decrease of PPA concentration was observed in urothelium compared to tissue segments more than 200 μm below the luminal surface. Distribution of PPA in the bladder wall was therefore treated as diffusion in semi-infinite composite medium with the surface layer having different diffusion properties from the rest of the diffusion medium. The analytical solution of the diffusion problem for the given initial and boundary conditions (zero concentration throughout the diffusion medium at time 0 and surface maintained at constant concentration C_0) is given by Eqs. (5)–(8) (Crank, 1985):

$$C_{x,t} = C_0 \sum_{n=0}^{\infty} \alpha^n \left[\operatorname{erfc}\left(\frac{2nl + x}{2\sqrt{D_1 t}}\right) - \alpha \operatorname{erfc}\left(\frac{2(n+1)l - x}{2\sqrt{D_1 t}}\right)\right], \quad 0\,\mu\text{m} < x \leq 200\,\mu\text{m} \tag{5}$$

$$C_{x,t} = \frac{2kC_0}{k+1} \sum_{n=0}^{\infty} \alpha^n \operatorname{erfc}\left(\frac{(2n+1)l + k(x-l)}{2\sqrt{D_1 t}}\right), \quad x >= 200\,\mu\text{m} \tag{6}$$

where

$$k = \sqrt{\frac{D_1}{D_2}} \tag{7}$$

and

$$\alpha = \frac{1-k}{1+k} \tag{8}$$

Meaning of the symbols is as follows: $C_{x,t}$ is the tissue PPA concentration in depth x at time t, C_0 the PPA tissue concentration at the luminal surface, D_1 the PPA diffusion coefficient in the urothelium, D_2 the PPA diffusion coefficient in the rest of the bladder wall, l is the urothelium depth (200 μm). PPA tissue concentration at the luminal surface is related to the PPA concentration in the donor chamber of the diffusion cell C_L by Eq. (9), where K is PPA bladder tissue to luminal solution partition coefficient:

$$C_0 = KC_L \tag{9}$$

Since the estimated maximum amount of PPA in the bladder tissue did not exceed 8% of the initial amount in the donor chamber of the diffusion cell (Grabnar et al., 2003), constant drug concentration at the surface seems a reasonable approximation. Additionally, since both polymers are unabsorbed, it seems realistic to assume that they affect only diffusion in the urothelium (K and D_1), while diffusion in the underlying tissue remains unaffected. Diffusion problem was solved numerically. The model (Eqs. (5)–(9)) was simplified to the first six terms (N=0,. . .,5) of the series and simultaneously fit to all the tissue concentration-depth-time data. Model parameters, namely K_{PPA}, K_{PPA+CH}, K_{PPA+PC}, $D_{1,PPA}$, $D_{1,PPA+CH}$, $D_{1,PPA+PC}$ and D_2, where indexes PPA, PPA + CH and PPA + PC refer to the type of luminal solution applied, were identified in Microsoft Excel by applying its complementary error function (erfc) and Solver with Newton minimization algorithm. Objective function used for the parameter identification was weighted residual sum of squares, where weight assigned to individual tissue PPA concentration measurement was a reciprocal of the variance of measurements at the same location and under the same conditions. Fitting procedure was rerun several times with different initial estimates to minimise the problem of convergence to a local minimum.

2.3. Advanced compartmental tissue diffusion systemic absorption model

To examine the influence of mucoadhesive polymers on bladder permeability *in vivo*, diffusion model was extended by the process of systemic absorption in the lamina propria and muscular layers. For this purpose the diffusion problem was solved by a spatially discontinuous compartmental model and partial differential equations were replaced by a set of ordinary differential equations. An approach similar to the one used to predict the impact of physiological and biochemical processes on oral drug absorption was used (Agoram et al., 2001). Bladder wall was represented by 30 serially interconnected compartments representing tissue segments at various depths. Relationship between PPA concentrations, C in three adjoining compartments $N-1$, N and $N+1$ followed Fick's second law of diffusion (Eq. (10)):

$$\frac{dC_N}{dt} = D\frac{C_{N-1} - C_N}{(\Delta x)^2} - D\frac{C_N - C_{N+1}}{(\Delta x)^2} \tag{10}$$

It is assumed that rate of the drug capillary removal in the lamina propria and muscular bladder tissue is proportional to the tissue to blood concentration gradient. Net systemic absorption is therefore a sum of contributions of the individual tissue segments. Volume of each tissue segment, V_N can be estimated from the total bladder mass and thickness. Relationship between the diffusion model and blood plasma pharmacokinetics is given by Eqs. (11) and (12), where time course of drug concentration in blood is described by a simple one-compartment model (k_a: absorption rate constant; k_{el}: rate constant of systemic elimination, V_d: distribution volume):

$$\frac{dC_N}{dt} = -k_a (C_N - C_P) \tag{11}$$

$$\frac{dC_P}{dt} = -k_{el} C_P + \frac{k_a \sum_{N=5}^{30} V_N (C_N - C_P)}{V_d} \tag{12}$$

The compartmental diffusion absorption model is schematically presented in Fig. 1.

The approach presented allowed investigation of the time courses of tissue PPA concentration profiles under changing urine PPA concentration due to urine formation and urine voiding. Time course of urinary drug concentration C_u was modelled by Eqs. (13)–(16), where urine volume, V_u depends on urine formation rate, k_0, residual urine volume, V_{res}, volume of instilled solution, V_0, and maximum volume at voiding V_{max} while the amount of drug in urine, U_u is diminishing from the amount instilled, U_0 due to diffusion in the bladder wall and urine voiding described by hysteresis $G(t)$:

$$\frac{dV_u}{dt} = k_0 - G(t), \quad V_u(0) = V_{res} + V_0 \tag{13}$$

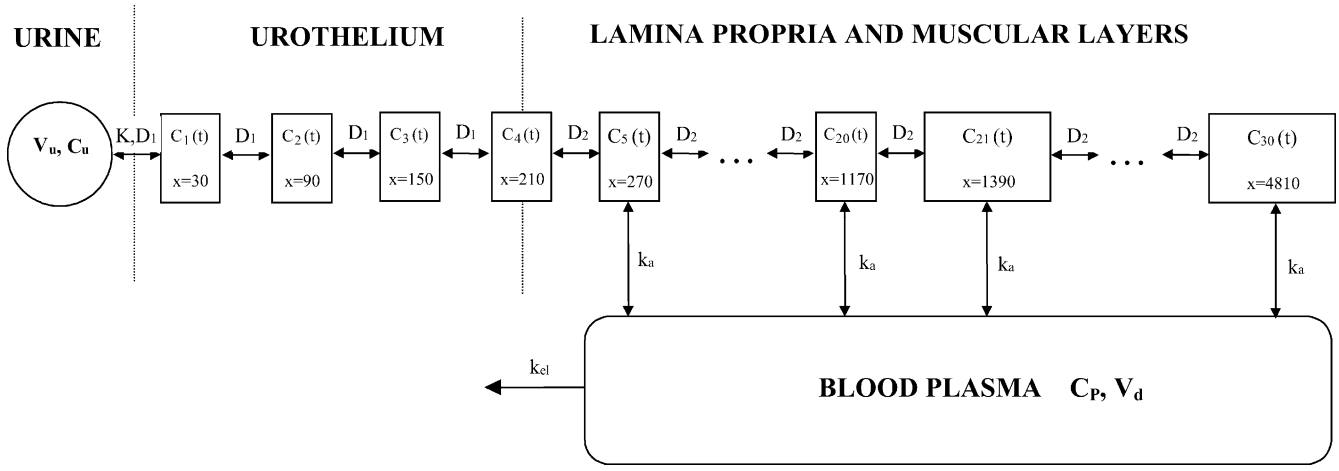

Fig. 1. Schematic presentation of the advanced compartmental diffusion absorption model (C_u: urine drug concentration; V_u: urine volume; C_1,. . .,C_{30}: 30 compartment diffusion model with tissue drug concentrations at depth x of the bladder wall; k_a: rate constant of systemic absorption, k_{el}: systemic elimination rate constant; V_d: volume of distribution).

$$\frac{dU_u}{dt} = -\frac{2D_1}{x_1^2}(KC_u - C_1)V_1 - G(t)C_u, \quad U_u(0) = U_0 \quad (14)$$

$$G(t) = \begin{cases} 0 & V_u < V_{res} \\ 30 & V_u > V_{max} \\ G(t-dt) & V_{res} \le V_u \le V_{max} \end{cases}, \quad G(0) = 0 \quad (15)$$

$$C_u = \frac{U_u}{V_u} \quad (16)$$

Compartmental tissue diffusion systemic absorption model comprised of urodynamic, diffusion and blood plasma part was built in Matlab 5.2.0 using Simulink 2.2 (MathWorks Inc., Natick, USA) and used for simulations of PPA distribution in the bladder tissue and its systemic absorption. Systemic absorption was evaluated by comparison of the area under plasma concentration time curves, while volume under tissue drug concentration-tissue depth-time profile was calculated to compare tissue drug exposure. The effects of mucoadhesive polymers and diverse residual urine volumes, instillation volumes, urine formation rates and systemic absorption rate constants on bladder tissue and blood plasma PPA concentration profiles were studied. For all simulations the set of ordinary differential equations was solved numerically using a variable-step Runge–Kutta method.

3. Results

Diffusion of PPA in bladder tissue was studied under various experimental conditions. To accurately estimate PPA diffusion properties in the bladder wall, two different PPA and polymer concentrations on the luminal side were applied, additionally exposure time was varied between 25, 50 and 120 min. All together 60 bladder-tissue concentration profiles were determined. Tissue drug concentrations were first analyzed by ANOVA. Dependent variable, bladder tissue PPA concentration was normalized to luminal PPA concentration before the analysis. The ANOVA model included five main effects: tissue depth, exposure time, type of luminal solution applied (PPA, PPA + CH and PPA + PC), luminal PPA and polymer concentration and their two-way interactions. As expected all main effects on the normalized PPA bladder-tissue concentration were significant ($p < 0.001$), except the luminal concentration of PPA ($p = 0.13$). It was therefore concluded that PPA diffusion parameters in the bladder wall are independent of its luminal concentration and all of the results were pulled for the estimation of diffusion parameters. Experimentally determined bladder tissue PPA concentration profiles following 50 min exposure and fit of the diffusion model are shown in Fig. 2.

As seen from standard diagnostic plots in Fig. 3 the model adequately describes the tissue concentration data. Although some trend in weighted residuals versus predicted concentration and weighted residuals versus tissue depth can be observed, it is clear that the choice of the weighting scheme improves the fitting procedure, as less weight is given on the highly variable concentrations in the shallow tissue. Compared to a previously published (Grabnar et al., 2003) single phase diffusion model, the current model is statistically superior as revealed by a highly significant drop in the objective function value from 2606.9 to 2118.5 per one additional parameter.

Model parameters are summarized in Table 1. These results demonstrate that urothelium looses its barrier function in the presence of both polymers, as both, bladder tissue to luminal solution partition coefficients K and diffusion coefficients in the shallow tissue D_1 are increased. This indicates that bladder-

Table 1
Influence of chitosan (CH) and polycarbophil (PC) on pipemidic acid (PPA) diffusion parameters in the bladder wall

		PPA (control)	CH	PC
PPA bladder tissue to luminal solution partition coefficient	K	0.380	0.734	0.636
PPA diffusion coefficient in urothelium	D_1 ($\times 10^{-7}$ cm^2/s)	2.94	5.49	5.66
PPA diffusion coefficient in underlying layers	D_2 ($\times 10^{-7}$ cm^2/s)	6.32	6.32	6.32

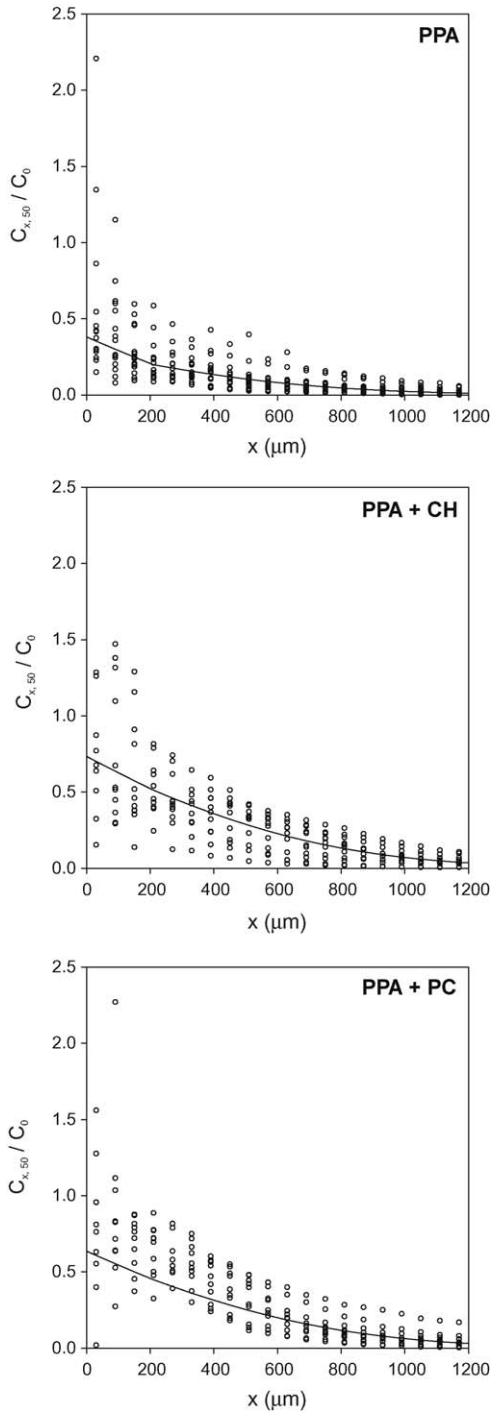

Fig. 2. Bladder tissue PPA concentration profiles following 50 min exposure to PPA solution or polymer dispersion with the same PPA concentration (PPA + CH and PPA + PC). Bladder tissue drug concentration is normalized to luminal drug concentration. Points: measured concentrations; curve: biphasic model fitted tissue concentration profile.

tissue drug exposure is substantially increased in the presence of CH and PC.

Compartmental diffusion absorption model was used to simulate PPA distribution in the bladder tissue and its systemic absorption *in vivo*. Studies on systemic absorption from the bladder are very scarce (Au et al., 1991; Dalton et al., 1992). Since there is currently no data on systemic absorption of PPA from the bladder we assumed that bioavailability of PPA following intravesical administration of solution is between 0.1 and 1%. Taking this into consideration absorption rate constant k_a was set in the range between 2.5×10^{-3} and 6.7×10^{-2} h^{-1} by simulation of the PPA plasma concentration time course, calculation of the area under the curve and its comparison with the clearance and intravesical dose administered.

4. Discussion

Although intravesical chemotherapy has been widely used in patients with superficial bladder cancer for more than 40 years, the importance of bladder pharmacokinetics is still often neglected. The main objective of the intravesical drug administration is optimisation of drug delivery in the tumour and its vicinity and reduction of systemic toxicity. Data on tissue drug exposure and its systemic absorption following administration in the bladder lumen are very sparse (Au et al., 1991; Dalton et al., 1992). Nonetheless, mathematical models of drug distribution in the bladder wall have been developed (Wientjes et al., 1993a) and successfully applied in practice to optimise intravesical treatment regimens with mitomycin C (Au et al., 2001). Urinary bladder wall is composed of unperfused transitional epithelium called urothelium, which is about 200 μm thick in human and due to its unique structures presents the basis of blood–urine barrier (Jost et al., 1989). There are two mechanisms involved. The first barrier to drug diffusion in the bladder tissue following drug administration in the lumen is the superficial highly negatively charged glycosaminoglycan layer (Hurst and Zebrowski, 1994) and membrane plaques, which prevent drug to reach the urothelium. Membrane plaques are a unique feature of apical membrane surface of superficial urothelium cells. They are much thicker than normal apical membrane regions and cover 70–90% of the apical membrane surface. The second barrier to paracellular drug penetration into the tissue are urothelial tight junctions. Underneath urothelium there is capillary perfused connective tissue-lamina propria and muscle layers, where systemic absorption occurs. Urinary bladder is a very accommodating organ and within the physiological volume range its barrier function is maintained irrespective of distension.

Bladder pharmacokinetics is complicated by several mechanisms and mathematical models are needed to study the influence of various parameters on tissue drug penetration and to subsequently optimise treatment (Wientjes et al., 1993a). However, currently available models cannot be applied to study the mechanisms of permeability enhancement effects by CH and PC, nor can be used to address the therapeutic benefit of the intravesical drug delivery systems when the contact between the drug and urothelium is altered. To address this problem we extended our previous work (Grabnar et al., 2003). Key kinetic elements of the presented model are variable urinary drug concentration due to urine formation and voiding, biphasic diffusion in the bladder tissue, and systemic absorption. Bladder wall was treated as a semi-infinite composite diffusion medium. A suitable choice of fitting procedure and weighting scheme allowed characterisation of diffusion process in urothelium and in deeper

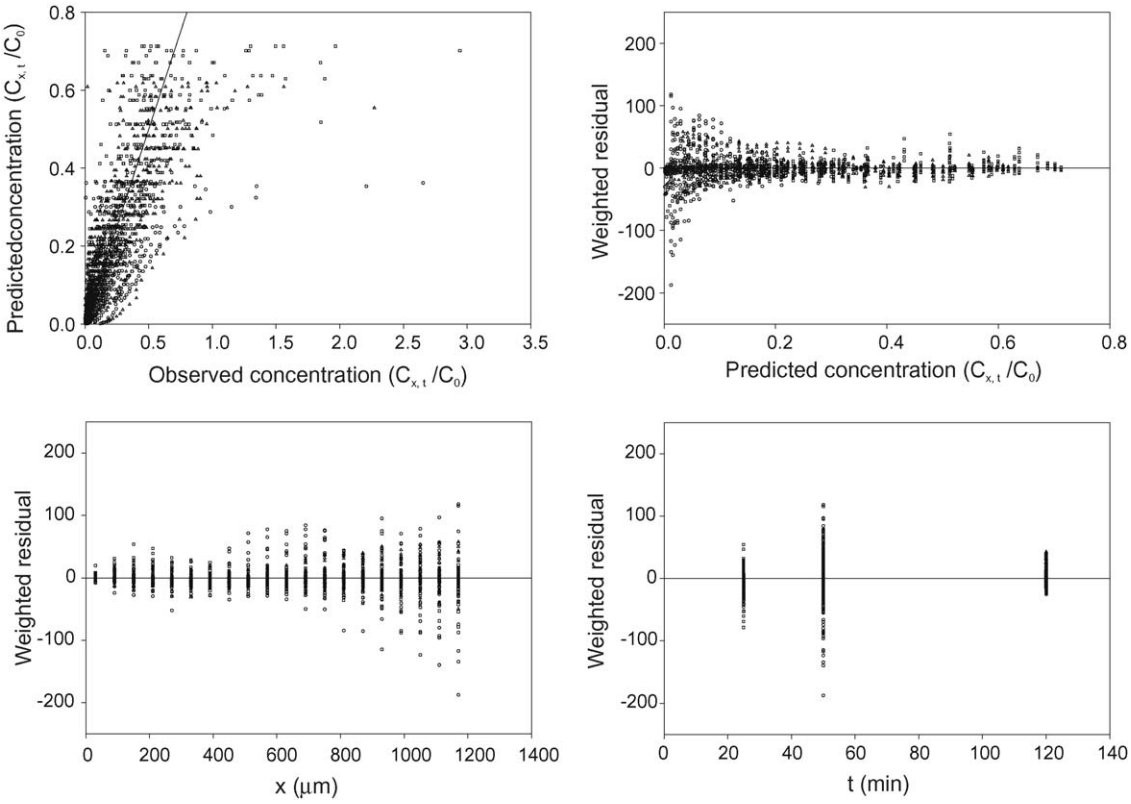

Fig. 3. Standard diagnostic plots of the biphasic diffusion model.

vascularised tissues, while bladder tissue to luminal solution partition coefficient K reflects the concentration drop in the thin layer of superficial glycosaminoglycans. Our model suggests that CH and PC increase the PPA permeability of the bladder wall by improvement of the contact with the exposed surface, which is observed as an increase in K, and by opening of the urothelial tight junctions, manifested as an increase in the diffusion coefficient D_1 (Table 1).

Simulation was used to study the effect of various parameters on tissue drug exposure *in vivo*. For this purpose constant urine formation rate of 1 ml/min was used, based on literature data (Davies and Morris, 1993). The maximum urine volume was set to 250 and 350 ml and due to incomplete bladder emptying a residual urine volume of 50 ml was selected. Blood plasma pharmacokinetic parameters of PPA ($V_d = 1.9$ l/kg, $t_{1/2} = 3.4$ h) were taken from the work of Klinge et al. (1984). Taking these data into consideration systemic absorption rate constant was fitted by monitoring the plasma concentration profile, so that the absolute bioavailability was in the range between 0.1 and 1%. Although the exact systemic bioavailability of PPA following intravesical administration is not known, this is a reasonable approximation. The effect of maximum urine volume on time course of urinary and tissue drug concentration is presented in Fig. 4 and Table 2. One can see that maximum urine volume at voiding has a pronounced effect on bladder-tissue drug exposure, as evidenced by 20% increase in cumulative tissue drug exposure by increasing the maximum urine volume from 250 to 350 ml.

CH and PC have marked effect on tissue drug exposure, irrespective of systemic absorption rate, as evidenced by approximately 100 and 75% increase, respectively (Fig. 5). As expected they have no effect on the time course of urinary drug concentration as the amount of drug entering the tissue is negligible compared to the dose administered. It can also be seen that after voiding (at 2.5 h after drug instillation) tissue drug concentrations are higher than urinary drug concentration. Due to the altered concentration gradient the flux direction reverses. This results in convex shape of the tissue concentration profile, a situation that was not predicted with a previously developed model (Wientjes et al., 1993a).

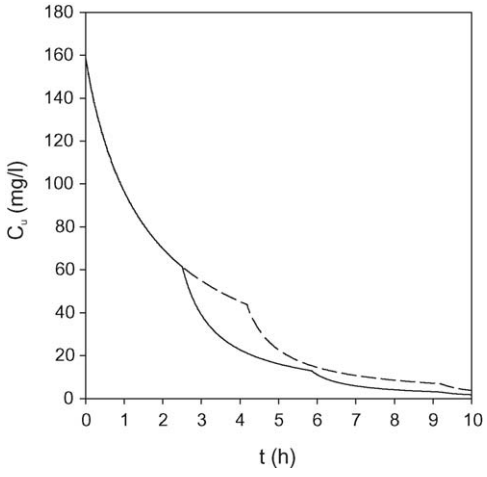

Fig. 4. Simulated time course of urinary PPA concentration following intravesical instillation of 16 mg PPA as solution (50 ml). Solid line: $V_{max} = 250$ ml; dashed line: $V_{max} = 350$ ml.

Table 2
Influence of chitosan (CH) and polycarbophil (PC), maximum urine volume at voiding and systemic absorption rate of pipemidic acid (PPA) on absolute bioavailability and tissue drug exposure

Instilled	V_{max} (l)	k_a (h^{-1})	Absolute bioavailability (%)	Tissue drug exposure[a]
PPA	0.25	2.5×10^{-3}	0.10	1.00
PPA + CH	0.25	2.5×10^{-3}	0.20	1.98
PPA + PC	0.25	2.5×10^{-3}	0.17	1.72
PPA	0.25	6.7×10^{-2}	1.01	0.40
PPA + CH	0.25	6.7×10^{-2}	2.11	0.84
PPA + PC	0.25	6.7×10^{-2}	1.84	0.73
PPA	0.35	2.5×10^{-3}	0.12	1.19
PPA + CH	0.35	2.5×10^{-3}	0.23	2.35
PPA + PC	0.35	2.5×10^{-3}	0.20	2.04
PPA	0.35	6.7×10^{-2}	1.20	0.48
PPA + CH	0.35	6.7×10^{-2}	2.51	1.00
PPA + PC	0.35	6.7×10^{-2}	2.19	0.87

Results of simulation.
[a] Relative tissue drug exposure is tabulated, evaluated by comparison of the volume under simulated tissue drug concentration–tissue distance-time profiles.

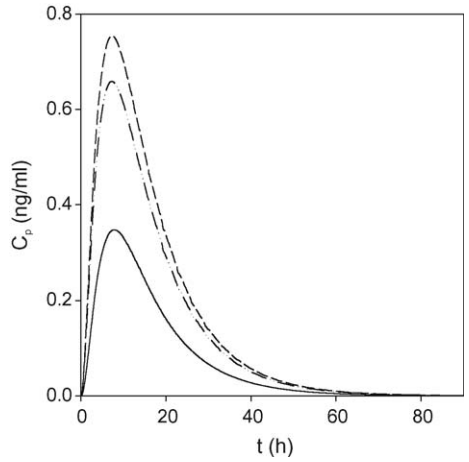

Fig. 6. The influence of CH (dashed line) and PC (dash-dotted) on systemic absorption of PPA following intravesical instillation (16 mg in 50 ml) of polymer dispersion or PPA solution (solid line). Results of the simulation: $k_a = 6.7 \times 10^{-2}\ h^{-1}$, $V_{max} = 250$ ml.

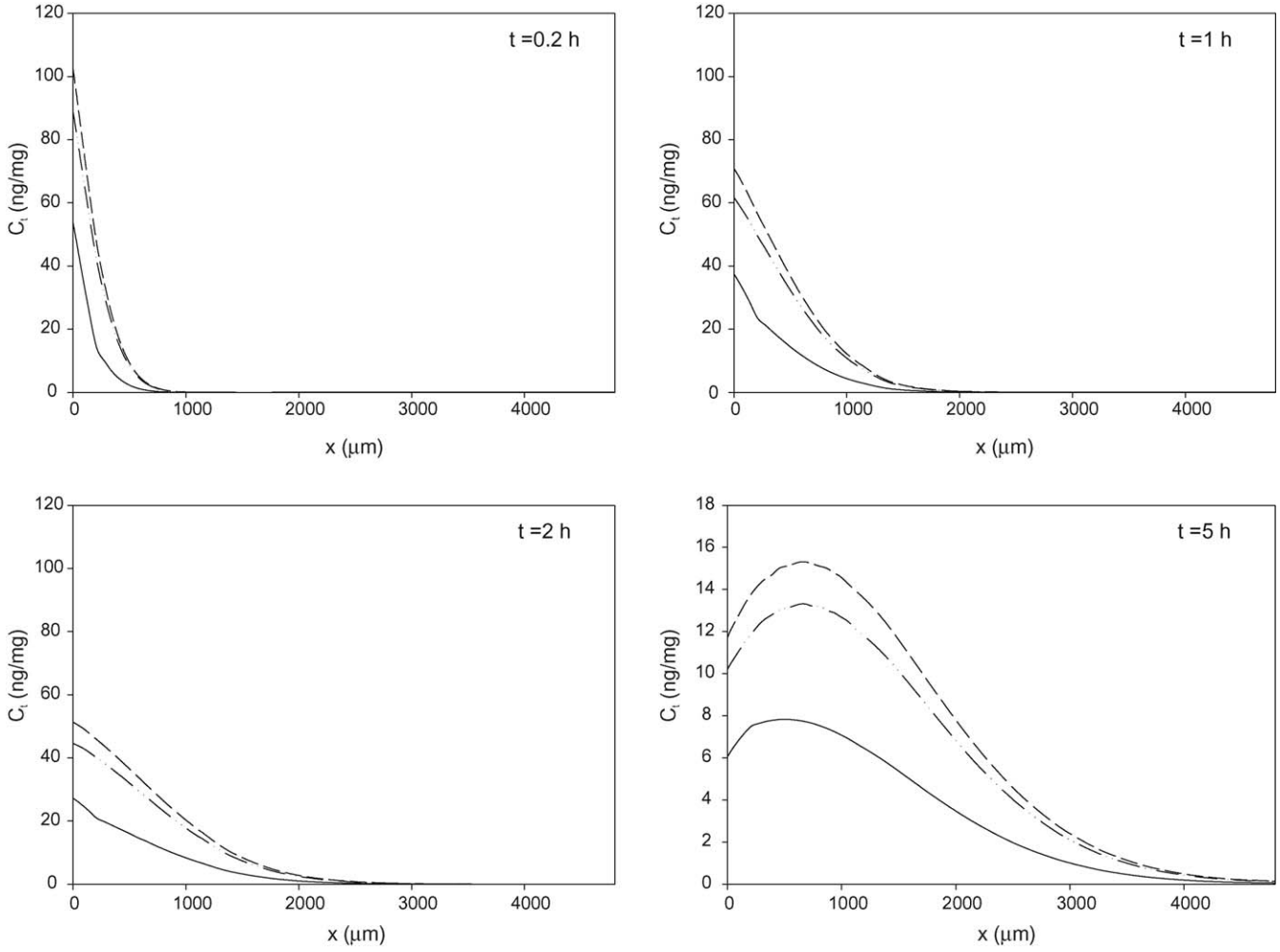

Fig. 5. Simulated PPA concentration profiles in the bladder tissue at 0.2, 1, 2 and 5 h following intravesical instillation of 50 ml solution with 16 mg of PPA (bottom line) or PC (middle line) and CH (upper line) dispersion. $k_a = 6.7 \times 10^{-2}\ h^{-1}$, $V_{max} = 250$ ml.

A maximum plasma concentration is observed approximately 8 h after dosing, irrespective of the type of solution administered and systemic absorption rate constant (Fig. 6). Nevertheless, the extent of systemic exposure is affected similarly as tissue drug exposure.

The developed mathematical model could serve for optimisation of intravesical drug delivery and future development of intravesical drug delivery systems. It can be used to study the effect of various parameters on bladder tissue and systemic drug exposure. However, further *in vivo* studies are necessary to validate the model.

5. Conclusion

Our results support further investigations on application of CH and PC in intravesical drug delivery. Both polymers increase permeability of the bladder wall by diffusion enhancement in the urothelium and presumably by improving the contact of drug with the bladder surface. The proposed mathematical model can be applied to evaluate the results of experiments with drugs employed in intravesical therapy.

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