Supporting Information

Diffusion and Uptake of Tobacco Mosaic Virus as Therapeutic Carrier in Tumor Tissue: Effect of Nanoparticle Aspect Ratio

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S1. Comparison of characteristic rates of diffusion and cellular uptake.

To determine the relationship between the cellular uptake rate (k) and the rate of TMV diffusion (D) in the spheroid, we expressed the dynamic mass concentration distribution of TMV within the spheroid in dimensionless form by defining the dimensionless variables:

$$\tau = kt; \quad \xi = \frac{r}{R}$$

where k is the constant rate of TMV cellular uptake, t is the time variable, r is the radial distance into the spheroid, and R is the radius of the spheroid. Subsequently, we obtained

$$\frac{\partial C_S}{\partial \tau} = \left(\frac{D}{kR^2}\right)\frac{1}{\xi^2}\frac{\partial}{\partial \xi}\left[\xi^2 \frac{\partial C_S}{\partial \xi}\right] - C_S \qquad \text{(S1)}$$

where C_S is the concentration of TMV in the interstitial space at any location in the spheroid and D is the constant TMV diffusion coefficient. The values of the dimensionless parameter group (in parentheses) for various aspect ratios of TMV can be found in Table T1. In this table, R was maintained to 200 μm and the cell density was kept to 0.5. In our simulations, the rate of endocytosis is a thousand to a hundred times greater than the rate of TMV diffusion through the spheroid (see Table T1).

Table T1. Computation of the order of magnitude difference between the rate of endocytosis and the rate of diffusion of TMV

TMV aspect ratio (L/d)	**Dimensionless parameter** $\left(\frac{D}{kR^2}\right)$
300/18	2.8×10^{-3}
135/18	6.4×10^{-3}
59/18	1.1×10^{-2}

In general, the rate of TMV mass loss from the surrounding medium equals the rate of diffusion into the spheroid:

$$V_M \frac{dC_M}{dt} = -4\pi R^2 D \frac{dC_S}{dr}\Big|_{r=R} \qquad \text{(S2)}$$

where V_M is the constant volume of the surrounding medium, C_M is the concentration of TMV in the surrounding medium and $N = -4\pi R^2 D$ is the diffusion rate of TMV into the spheroid from the surrounding medium.

To determine if the TMV concentration in the surrounding medium changes significantly over the expected course of an experiment, we also expressed this equation in dimensionless form:

$$\frac{dC_M}{d\tau} = -\left(\frac{4\pi RD}{kV_M}\right)\frac{dC_S}{d\xi}\Big|_{r=R} \qquad \text{(S3)}$$

In this case, the dimensionless parameter group (in parentheses) is approximately 10^{-6} (see Table T2). Therefore, over the time course of our experiment, we can assume that the changes in concentration of TMV in the surrounding medium are negligible.

Table T2. Computation of the order of magnitude difference between the rate of TMV diffusion in the surrounding medium and the spheroid interspace.

TMV aspect ratio (L/d)	**Dimensionless parameter** $\left(\frac{4\pi RD}{kV_M}\right)$
300/18	$6.98x10^{-7}$
135/18	$1.59x10^{-6}$
59/18	$2.76x10^{-6}$

S2. Model transformation.

We transformed the governing equation of the spheroid into rectangular coordinates with constant coefficients by defining $g(r,t) = rC_S(r,t)$

$$\frac{\partial C_S}{\partial r} = \frac{1}{r}\frac{\partial}{\partial r}\left(\frac{g}{r}\right) = \frac{1}{r}\frac{\partial g}{\partial r} - \frac{g}{r^2} \Rightarrow r^2\frac{\partial C_S}{\partial r} = r\frac{\partial g}{\partial r} - g \qquad \text{(S4)}$$

$$\frac{\partial}{\partial r}\left[r^2\frac{\partial C_S}{\partial r}\right] = r\frac{\partial^2 g}{\partial r^2} + \frac{\partial g}{\partial r} - \frac{\partial g}{\partial r} = r\frac{\partial^2 g}{\partial r^2} \Rightarrow \frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2\frac{\partial C_S}{\partial r}\right] = \frac{1}{r}\frac{\partial^2 g}{\partial r^2} \qquad \text{(S5)}$$

$$\frac{\partial C_S}{\partial t} = \frac{1}{r}\frac{\partial g}{\partial t} \qquad \text{(S6)}$$

$$\frac{\partial C_S}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2\frac{\partial C_S}{\partial r}\right] - kC_S \Rightarrow \frac{\partial g}{\partial t} = D\frac{\partial^2 g}{\partial r^2} - kg \qquad \text{(S7)}$$

S3. Method of lines.

We defined a discrete spatial domain i = 0,1,2,3,…,N corresponding to the continuous spatial domain $0 \le r \le R$, where N is the number of spatial intervals of size $\Delta = R/N$. The relationship between the continuous and discrete spatial variable is given as $r_i = i\Delta$ and $g_i(t) = g(r_i, t)$. Thus, the discretized equations become

$$\frac{dg_i}{dt} = D\left[\frac{g_{i+1} - 2g_i + g_{i-1}}{\Delta^2}\right] - kg_i \quad (i = 1,2,3,...,N-1) \qquad \text{(S8)}$$

The boundary condition at the center of the spheroid becomes

$$i = 0: \quad g_0 = 0 \qquad \text{(S9)}$$

which can be incorporated into the governing equation for i=1:

$$\frac{dg_1}{dt} = D\left[\frac{g_2 - 2g_1}{\Delta^2}\right] - kg_1 \qquad \text{(S10)}$$

The boundary conditions at the interface become

$$i = N: \quad g_N = RC_M \qquad \text{(S11)}$$

which can be incorporated into the governing equation for i=N-1:

$$\frac{dg_{N-1}}{dt} = D\left[\frac{RC_M - 2g_{N-1} + g_{N-2}}{\Delta^2}\right] - kg_{N-1} \quad (i = N - 1) \qquad (S12)$$

The initial conditions become

$$t = 0: \quad g_i = 0 \quad (i = 1, 2, 3, ..., N) \qquad (S13)$$

Conversion to original variables

$$C_S\left(r_i, t\right) = \frac{g_i(t)}{r_i} = \frac{g_i(t)}{i\Delta} \quad (i = 1, 2, 3, ..., N); \quad C_M = \frac{g_N}{R} \qquad (S14)$$

From the boundary condition, we see that

$$r = 0: \quad \frac{\partial C_S}{\partial r} = 0 \Rightarrow C_S\left(r_0, t\right) = C_S\left(r_1, t\right) = \frac{g_1(t)}{r_1} = \frac{g_1(t)}{\Delta} \qquad (S15)$$

S4. Estimation of the characteristic axial and transverse velocity of TMV.

The equations of the axial (ν_t) and transverse (ν_r) velocity of TMV, which were obtained from a study by Broersma[1], are displayed below. We computed the value of the axial and transverse velocity for specific TMV aspect ratios (L/d) (see Table T3).

$$\nu_t = -.114 - \frac{.15}{\ln\left(2\frac{L}{d}\right)} - \frac{13.5}{\ln^2\left(2\frac{L}{d}\right)} + \frac{37}{\ln^3\left(2\frac{L}{d}\right)} - \frac{22}{\ln^4\left(2\frac{L}{d}\right)} \qquad \text{(S16)}$$

$$\nu_r = -.886 - \frac{.15}{\ln\left(2\frac{L}{d}\right)} - \frac{8.1}{\ln^2\left(2\frac{L}{d}\right)} + \frac{18}{\ln^3\left(2\frac{L}{d}\right)} - \frac{9}{\ln^4\left(2\frac{L}{d}\right)} \qquad \text{(S17)}$$

Table T3. Computation of the axial and transverse velocity of specified TMV dimensions.

	(300/18)	**(135/18)**	**(59/18)**
Axial velocity of TMV (ν_t)	0.5421	0.5562	0.2065
Transverse velocity of TMV (ν_r)	0.5224	0.4451	0.4828

S5. Estimation of diffusion coefficients in the surrounding medium and in the spheroid.

The values of the diffusion coefficient of TMV in the surrounding medium (D_{rt}) were computed from equation (12) for specific aspect ratios of TMV. The corresponding values of the diffusion coefficient of TMV in the spheroid (D_{int}), which takes into account the presence of ECM proteins, are also calculated from equation (13) (see Table T4).

Table T4. Computation of the diffusion coefficient of TMV in the surrounding medium (D_{rt}), and the corresponding diffusion coefficient of TMV in the presence of ECM proteins (D_{int}) as a function of TMV aspect ratio.

TMV aspect ratio (L/d)	Diffusion coefficient of TMV in the surrounding medium (D_{rt}) [mm^2/sec]	Diffusion coefficient of TMV in the spheroid (D_{int}) [mm^2/sec]
300/18	$5.07x10^{-6}$	$2.15x10^{-6}$
135/18	$8.47x10^{-6}$	$3.59x10^{-6}$
59/18	$1.18x10^{-5}$	$5.01x10^{-6}$

The final diffusion coefficients of TMV (D) were obtained from equation (14) and take into account the shape and the dimensions of the nanoparticle, the presence of ECM proteins, and the presence of cells in the spheroid (see Table T5).

Table T5. Computation of the diffusion coefficient of TMV in the porous spheroid containing cells.

Cell density	D [mm^2/sec] (300/18)	D [mm^2/sec] (125/18)	D [mm^2/sec] (59/18)
0.4	$7.74x10^{-7}$	$1.29x10^{-6}$	$1.80x10^{-6}$
0.5	$5.38x10^{-7}$	$8.98x10^{-7}$	$1.25x10^{-6}$
0.6	$3.44x10^{-7}$	$5.75x10^{-7}$	$8.01x10^{-7}$
0.7	$1.94x10^{-7}$	$3.23x10^{-7}$	$4.51x10^{-7}$
0.8	$8.60x10^{-8}$	$1.44x10^{-7}$	$2.00x10^{-7}$
0.9	$2.15x10^{-8}$	$3.59x10^{-8}$	$5.00x10^{-8}$

References

1. Broersma, S., Viscous Force and Torque Constants for a Cylinder. *J. Chem. Phys.* **1981,** *74*, 6969–6970.