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Accelerated release of a sparingly soluble drug from an injectable hyaluronan–methylcellulose hydrogel

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ABSTRACT

An injectable hydrogel, comprised of hyaluronan and methylcellulose (HAMC), shows promise for localized, sustained delivery of growth factors for treatment of spinal cord injury (SCI). To better understand its potential for the delivery of small molecules, the release of sparingly soluble neuroprotectant, nimodipine, was investigated experimentally and *via* continuum modeling. This revealed that the MC in HAMC increased the solubility of sparingly soluble drug by over an order of magnitude, and enabled highly tunable release rates to be achieved by varying the method by which the drug was introduced into the scaffold. When nimodipine was introduced into HAMC in solubilized form, it was rapidly released from the scaffold within 8 h. Conversely, when nimodipine was blended into HAMC in particulate form, the release rates were greatly reduced, giving rise to complete release over 2–3 days for small, sub-micron particles, and longer times for large, 100 μm particles. The nimodipine particle-loaded gels yielded particle size-dependent, biphasic release profiles, which reflected rapid release of the solubilized drug followed by the slow, dissolution-limited release of solid nimodipine. This suggests that injectable hydrogel matrices can act as polymeric excipients that accelerate the delivery of poorly soluble drugs and yield highly tunable release rates.

1. Introduction

Traumatic spinal cord injury (SCI) is a devastating condition for which there is no cure. The initial mechanical trauma, termed the primary injury, causes damage to blood vessels and localized cell death [1]. These in turn lead to excitotoxicity, inflammation, hemorrhage, vasospasm, and edema, which result in functional deficits in the patient [2,3]. These pathological events can occur from days to months after injury and are known as the secondary injury [4,5]. Both neuroregenerative and neuroprotective therapeutics are being pursued to limit the devastation that occurs after injury, yet their delivery remains challenging.

There are three common delivery strategies – systemic, pump/catheter, and bolus – yet each has its drawbacks. Systemic delivery is limited because most molecules cannot cross the blood–spinal cord barrier and those that do may have profound systemic side effects [1]. The external pump/catheter system pumps drugs from a reservoir into the intrathecal space through a catheter. While a constant dose can be administered, this method is open to infection and has not been approved for long-term delivery in SCI patients in the USA. Bolus injection into the intrathecal space is compromised by cerebral spinal fluid (CSF) flow, which disperses the drug, thereby requiring repeated administration.

Given the limitations associated with current delivery strategies, a minimally-invasive injectable, thermally-responsive hydrogel was designed for sustained and localized release. Comprised of hyaluronan (HA) and methylcellulose (MC) [6], this physical blend has been shown to be safe and provide greater neuroprotection when used to deliver erythropoietin than traditional delivery strategies [7].

To extend the use of HAMC to the delivery of low molecular weight drugs, we investigated its use in the sustained release of nimodipine, a hydrophobic, sparingly soluble vasodilator and calcium channel blocker used for treating central nervous system (CNS) disorders [3,8]. Much research effort is devoted to improve the therapeutic efficacy and delivery of hydrophobic drugs which is often limited by low solubility [9–11]. In solid pharmaceutical formulations, polymeric excipients similar to MC, such as hydroxypropyl methylcellulose or poly(vinylpyrrolidone), are incorporated into the drug particles to increase the solubility of sparingly soluble drugs [10,12–15]. This is typically achieved by disrupting the crystalline drug particle structure [16], thereby producing a less-stable amorphous drug particle that can

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be up to orders of magnitude more soluble than the crystalline drug [17]. These polymeric excipients are also used as stabilizing additives in supersaturated solutions [14,15,18–21] and gels [15,18] for oral and transdermal drug delivery, where a layer of adsorbed, "antinucleating" polymer on the surface of the nascent crystal is believed to inhibit further crystallization of the drug [22,23].

Here, we show that the incorporation of polymeric excipients into an injectable hydrogel (e.g., MC in the case of HAMC) can increase the solubility of sparingly soluble drugs such as nimodipine and tune their rate of release. The rate of nimodipine dissolution in MC solution is slow, and depends on the initial drug particle size. Experimental and model analyses indicate that these differences in particle dissolution kinetics are reflected in the nimodipine release profiles from HAMC, and can be exploited in tailoring drug release rates. This suggests that injectable hydrogel matrices can accelerate the delivery of hydrophobic, poorly soluble drugs, and can yield highly tunable release profiles that are dependent on how the drug is introduced into the *in situ* gelling scaffold.

2. Materials and methods

2.1. Nimodipine preparation

To prepare nimodipine (Sigma Aldrich, Oakville, ON, Canada) for the release study, two types of nimodipine formulations were prepared at room temperature: (1) 0.5 mg/ml of nimodipine particles dissolved in 20 v/v % ethanol in water; and (2) 0.5 mg/ml of nimodipine particles dispersed in a 0.1 wt.% methylcellulose (MC, Sigma Aldrich) solution in artificial CSF (aCSF). To vary the drug particle size, the particulate dispersions were either used as received (non-sonicated particles); or sonicated to reduce particle size for 1 or 5 min at 20 kHz, 40% amplitude, using a Sonics Vibra Cell CV18 tip sonicator (Sonics & Materials Inc., Newtown, CT, USA). The nimodipine particles dispersed in MC were sized *via* dynamic light scattering (DLS, Malvern Zetasizer Nano ZS, Worcestershire, UK) for the sonicated sub-micron particles, and laser diffraction (Malvern Mastersizer 2000, Worcestershire, UK) for the non-sonicated particles. The particle dispersions were left for 3 days at room temperature to ensure that particles were stable in dispersion before incorporation into HAMC.

2.2. Incorporation of nimodipine in HAMC

Thermogelling, sterile-filtered HAMC blends were prepared as previously described [6] by dissolving hyaluronan (HA, Novamatrix, Sandvika, Norway) at 2 wt.% into MC at 7 wt.%. For nimodipine release studies, 100 µl of nimodipine formulation (Section 2.1) was added to 900 µl of MC dissolved in aCSF, yielding a 7 wt.% MC/nimodipine dispersion, with a nimodipine concentration of 50 µg/ml. HA was then dissolved into the MC/nimodipine dispersion at 2 wt.%. The HAMC solution was then vortexed (Vortex-Genie 2, 120 V, 60 Hz 0.65 A, Scientific Industries Inc., New York, NY, USA) until a clear, homogeneous, highly-viscous solution was obtained [6].

2.3. Nimodipine dissolution kinetics

To determine the effect of MC and HA on nimodipine dissolution in HAMC, 0.5 mg/ml nimodipine dispersions (composed of either non-sonicated larger particles or 1 or 5 minute sonicated sub-micron particles) was dispersed in 10 ml of either 7 wt.% MC or 0.25 wt.% HA in aCSF. Here, the HA solution composition was adjusted to match the viscosity of the 7 wt.% MC (*ca.* 0.5 Pa· s,), to maintain similar hydrodynamic conditions and mass transfer coefficients between the two receiving mediums. The dispersions were allowed to dissolve at 25 °C under constant stirring. The concentration of solubilized nimodipine was tracked over a 9 day period using the NanoDrop Spectrophotometer ND-100 (Wilmington, DE, USA, $\lambda = 275$ nm, extinction coefficient = 4.217 ml mg^{-1} cm^{-1}).

2.4. Drug release studies

One hundred microliters of HAMC containing nimodipine was injected onto the bottom of a 2 ml eppendorf tube containing 900 µl of aCSF at 37 °C [6], thereby mimicking the 10% volume dilution expected in the intrathecal space of a rat animal model. At various time points, the supernatant was removed and replaced with the same volume of fresh aCSF. To determine the amount of drug released between each time point, the absorbance of supernatant containing released nimodipine was measured using the NanoDrop Spectrophotometer.

3. Results and discussion

3.1. Nimodipine dissolution kinetics

The particle size and the properties of the dissolution medium are expected to influence the dissolution kinetics and release profiles of nimodipine. To investigate the effects of particle size and the presence of MC and HA on the solubilization of nimodipine, we quantified the dissolution of three polydisperse populations of nimodipine particles with average diameters of 100 ± 30 µm, 900 ± 60 nm (second order polydispersity factor, PI = 0.48), and 380 ± 20 nm (PI = 0.64), as sized by laser diffraction and DLS, over time in well-stirred MC and HA solutions. To ensure that the liquid phase mass transfer coefficients would be similar for the two polymer solutions, the viscosity of the HA solution was matched to that of 7 wt.% MC, resulting in an HA concentration of 0.25 wt.%. Fig. 1 shows that the concentration of nimodipine ultimately solubilized in 7 wt.% reached a plateau at approximately 30–40 µg/ml, which may be interpreted as its solubility limit. This solubility is an order of magnitude higher than nimodipine's literature aqueous solubility of 2–4 µg/ml [24], which we also observed in 0.25 wt.% HA. In contrast to previous work where polymeric excipients prevented crystallization of supersaturated drug solutions over time [8,20], here the addition of MC leads to amplified drug solubilization. Conversely, the presence of HA had no measurable impact on nimodipine solubility.

The dissolution of each particle type in 7 wt.% MC appeared to occur in two stages. The first stage corresponded to the solubility

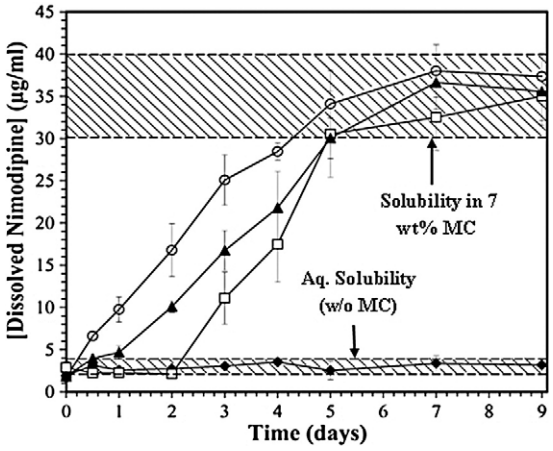

Fig. 1. Comparison of nimodipine solubility in MC and HA, with different nimodipine particle sizes: (◆) 100-µm nimodipine particles in 0.25 wt.% HA; and (□) 100-µm, (▲) 900-nm, and (○) 380-nm nimodipine particles in 7 wt.% MC. The upper shaded concentration range indicates nimodipine solubility values achieved in 7 wt.% MC, while the lower shaded range indicates aqueous nimodipine solubility reported in the literature [24].

of nimodipine in water (2–4 μg/ml) and occurred within minutes, whereas the second stage corresponded to its solubility in MC (30–40 μg/ml) and occurred within several days. Interestingly, the larger 100-μm (and to a lesser extent the 900-nm) nimodipine particles showed an induction period in their dissolution profiles in MC, where the enhanced solubilization mediated by MC was not observed until 1–3 days into the dissolution process. The induction time increased with particle size. For all nimodipine particles studied, the plateau of solubilized drug was attained after approximately 1 week in MC solution.

Visual observation of the nimodipine particles revealed that MC also affects their dispersion properties. All three particles formed large ~O(1000 μm) aggregates in HA, and smaller ~O(10 μm) aggregates in MC (data not shown). This indicates that when dispersed in MC solution the large, 100-μm particles fragment and disperse, while the small, sub-micron particles undergo some aggregation. The improved colloidal stability that is mediated by MC suggests that MC adsorbs to the surface of the nimodipine particles and prevents flocculation of nimodipine into larger particles through steric stabilization. This improved colloidal stability is consistent with the polymer-mediated stabilization reported for colloidal drug dispersions in aqueous hydroxypropyl methylcellulose solutions [20].

To further probe the mechanism of nimodipine dissolution in the presence of MC, the mass transfer coefficient, k_m, for the slower second stage of particle dissolution in MC was estimated *via* [25]:

$$\frac{dC_A}{dt} \sim \frac{k_m a}{V} C_A^{Sat} \quad (1)$$

where a is the total surface area of the 10-μm nimodipine particle flocs, V is the volume of the receiving MC solution, C_A^{Sat} is the saturation concentration of nimodipine in 7 wt.% MC, and dC_A/dt is the approximate slope of the dissolution curves estimated to be ~O(10 μg/ml day) from Fig. 1. This analysis yields a mass transfer coefficient of $k_m \sim O(10^{-6}$ cm/s), which is more than three orders of magnitude lower than the minimum mass transfer coefficient predicted for solution mass transfer-controlled dissolution. The k_m for solution mass transfer-controlled dissolution is $\sim 2\times10^{-3}$ cm/s, estimated for the 10-μm nimodipine aggregates in the absence of convection, where the Sherwood number (Sh) is equal to two [26]: $Sh = k_m d_p/D_A$, where d_p is the drug particle diameter, and D_A is the molecular diffusivity of the drug. This suggests that the solubilization of nimodipine is not limited by the solution mass transfer of nimodipine, but is rather governed by another slower process. A layer of adsorbed polymer may be slowing down the dissolution of nimodipine particles. The hypothesis that adsorption of MC improves drug solubility is supported by the following: (1) the steric stabilization of the nimodipine particles observed in the presence of MC; and (2) the high diffusivity of nimodipine observed in HAMC ($D_A \sim O(10^{-5}$ cm^2/s), see Section 3.2.1). This high D_A value is characteristic of small molecule diffusion, suggesting that once the nimodipine is solubilized in HAMC, it remains in a molecular state. Importantly, while the presence of MC retards the rate of drug particle dissolution, the solubility is enhanced. Thus, the increased amount of solubilized drug at the beginning of the release process (e.g., from ≤4 to ≤40 μg/ml nimodipine) should accelerate the rate of drug release when MC is present. From these results, we expected that the slow, particle size-dependent process of MC-mediated drug dissolution would enable tunable acceleration of hydrophobic drug release from HAMC (and other similar injectable gels) by modulating the drug fraction that is solubilized at the beginning of the release profile. This can likely be achieved by either varying the size of the drug particles that are used in the hydrogel preparation or the time period between the preparation and application of the HAMC blend.

3.2. Nimodipine release from HAMC

3.2.1. Release of solubilized nimodipine

HAMC may be classified as a matrix drug delivery system where nimodipine is distributed throughout the gel network [27,28]. Solubilized nimodipine, which was predissolved in ethanol to produce a 50 μg/ml nimodipine and 2% v/v ethanol solution in HAMC, was fully released within 8 h (Fig. 2). The square root scaling of the release profile (see Fig. 2 inset) suggests that it is diffusion-controlled. For a planar geometry, such as the release of nimodipine from the top of a cylindrical HAMC gel, drug release can be estimated by the analytical approximation [29]:

$$\frac{M_t}{M_\infty} = \frac{2}{L}\sqrt{\frac{D_A}{\pi}} \cdot t^{0.5} \quad (2)$$

where M_t/M_∞ is the fraction of drug molecules released from the hydrogel at time t, D_A is the diffusivity of the drug in the matrix, and L is the scaffold thickness [29]. For an estimated gel thickness of 0.37 cm, the fitted diffusivity value of 1.0×10^{-5} cm^2/s is characteristic of the diffusion of small molecules and suggests that the drug remains dissolved during the release process. The proportionality to the square root of time is maintained for the first 70–80% of release [28,30], after which drug depletion affects the concentration gradient, thus reducing the driving force for drug release. This also supports our previous findings that diffusion is the dominant mechanism of drug release from HAMC [8].

3.2.2. Release of particulate nimodipine

When nimodipine was introduced in particulate form, its release from HAMC was significantly slower than the soluble form. The complete release of 380 nm and 900 nm nimodipine particle formulations from HAMC was achieved at 48 h and 72 h, respectively (Fig. 3). For 100 μm nimodipine particles, only ~40% of the drug was released from HAMC after 3 days, likely because only a fraction of the total nimodipine is soluble and able to diffuse from the gel at a given time.

The release profiles obtained using gels loaded with nimodipine particles were biphasic. Submicron particles yielded a high initial burst release (*ca.* 80% for the 380 nm particles, and *ca.* 60% for the 900 nm particles), occurring within the first few hours, similar to that of the release of solubilized nimodipine. This initial burst release

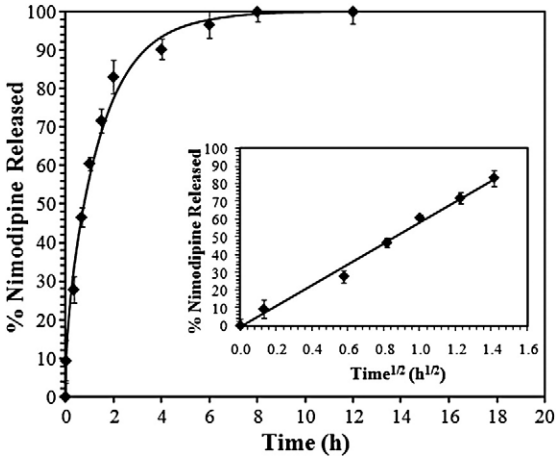

Fig. 2. Release of solubilized nimodipine plotted against time (mean ± standard deviation, $n = 3$). The curve represents the model fit (Eq. (3b)) for the release data. The inset shows that the drug release scales linearly with the square root of time, according to Eq. (2), for first 70–80% of released nimodipine.

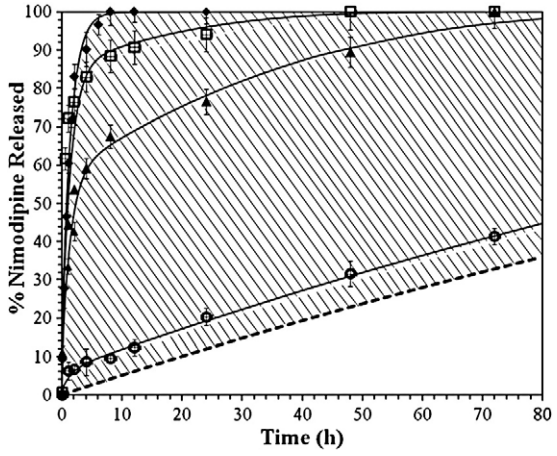

Fig. 3. Comparison of model predictions to experimental data for: (◆) solubilized nimodipine, (□) 380 nm particulate nimodipine, (▲) 900 nm particulate nimodipine, (○) 100 μm particulate nimodipine (mean ± standard deviation, $n=3$). The solid lines (—) depict the model predictions, the dashed line (---) represents the slowest release predicted by Eq. (6), and the shaded region indicates the range of release profiles obtained by varying the formulation of nimodipine. This range is bounded by the Fickian model (upper limit) and that described by Eq. (6) (lower limit).

phase was followed by a second slower release phase, which takes place over 2–3 days. These two phases likely correspond to the rapid release of the drug that is solubilized at the beginning of the release process followed by slower dissolution-limited release of the drug that remains in particulate form. Likewise, the 100-μm particles yielded a 5–10% burst release followed by the slow dissolution-controlled release. This burst release is consistent with the slower solubilization rates of larger nimodipine particles in MC solution, and indicates that the release profiles can be tuned over a wide range of release rates by varying the method by which sparingly soluble drug is introduced into the gel.

3.3. Model analysis of the release profiles

To analyze the release of nimodipine from HAMC, we developed a generalized model based on diffusion- and particle dissolution-controlled mass transport. We assumed that the nimodipine particles were uniformly distributed within HAMC, and that the solubilized drug concentration and the radii of the dissolving drug particles varied with respect to both time and spatial position within the gel. Using these assumptions, the temporal variation in drug particle size and solubilized drug concentrations can be estimated using two coupled differential equations:

$$\frac{dR_1}{dt} = -k_m \frac{MW_A}{\rho_A}\left(C_A^{Sat} - C_A\right) \tag{3a}$$

$$\frac{\partial C_A}{\partial t} = D_A \frac{\partial^2 C_A}{\partial z^2} + 4\pi k_m R_1^2 n_p \left(C_A^{Sat} - C_A\right) \tag{3b}$$

Here, C_A is the drug concentration at specific spatial (z) and temporal (t) points within the matrix, C_A^{Sat} is the saturation concentration of the drug in the gel, and n_p is the number of particles per unit volume within the matrix, MW_A is the molecular weight of the drug (418 g/mol for nimodipine), and ρ_A is the density of the drug particle (estimated at ~1 g/cm^3). D_A is the diffusivity of drug molecules in the hydrogel matrix, and k_m is the mass transfer coefficient for drug particle dissolution. R_1 is the drug particle radius, which varies with respect to time, t, and position, z. R_1 is a function of drug particle position within the gel because dissolution is driven by the concentration gradient of dissolved molecules around the particle. For regions closer to the surface of the gel, the drug diffuses out more quickly compared to the interior regions of the gel, leading to faster particle dissolution. Eq. (3a) describes the dissolution of the drug particles over time [31,32]. Likewise, Eq. (3b) provides a microscopic materials balance on the solubilized drug in the gel matrix, where the change in the local solubilized drug concentration reflects the balance between the dissolution of the drug particles and the diffusion of the drug out of the gel. Using the appropriate boundary conditions, where flux at the inner boundary and the drug concentration at the outer boundary are both equal to zero, this system of equations was solved numerically with MATLAB *via* finite difference approximation. Using the D_A value fitted to Eq. (2) in Section 3.2.1 (1.0×10^{-5} cm^2/s) and an approximate C_A^{Sat}-value of 40 μg/ml and initial particle diameter of 10 μm (from Section 3.1), the numerical solutions given in terms of $C_A(z,t)$ and $R_1(t,z)$ (not shown) were obtained. These profiles were then integrated over the volume of the scaffold to generate the release curves showing the amount of drug released over time. The model release curves were fitted to the experimental release profiles by varying the fraction of the drug that was dissolved at the beginning of the release experiment ($f_{dissolved}$, which affects the initial solubilized drug concentration and the drug particle radius at the start of the release process) and k_m (see Table 1).

The model fits were in excellent agreement (see Fig. 3) with all four experimental release profiles. Although there was some uncertainty in the initial particle size and, to a lesser extent, C_A^{Sat}, the models support our interpretation of the biphasic release mechanism. They revealed consistent k_m-values on the order of 10^{-5} cm/s and $f_{dissolved}$ values that varied from 6% for the 100 μm particles, to 62% for the 380 nm and 85% for the 900 nm particles, to 100% for the solubilized nimodipine. This suggests that a full range of $f_{dissolved}$ values can be achieved by varying the way in which the drug is introduced into HAMC. Interestingly, the fitted k_m-values reported in Table 1 decrease with increasing drug particle size. This suggests that, although each HAMC formulation contains *ca.* 10 μm particle aggregates, aggregates formed from smaller primary particles may have higher surface to volume ratios, which would lead to faster drug dissolution.

Given the broad range of release profiles that can be achieved using HAMC, it is useful to define "limiting" analytical expressions for the fastest and slowest possible release profiles. The fastest possible release occurs when the entire amount of drug is dissolved, as in the case of the solubilized nimodipine, where the release profile can be estimated using Eq. (2). Conversely, the release profile is slowest when all loaded drug starts out in the particulate state (i.e., $f_{dissolved}=0.00$). A simple analytical expression for the release profile in this situation can be obtained under two sets of circumstances: (1) the release rate is controlled only by diffusion through the gel matrix, where drug particle dissolution is faster than the diffusion of the drug out of the gel, or (2) the release rate is controlled only by the dissolution of the drug particle, where the diffusion of the drug out of the gel is faster than the drug particle dissolution. The time scales of these two processes can be compared by defining a dimensionless number (ξ) that represents the ratio

Table 1
Model parameters fitted to experimental data using Eqs. (3a) and (3b).

Formulation	$f_{dissolved}$	k_m (cm/s)
Solubilized nimodipine	1.00	N/A
380 nm nimodipine particles	0.85	2.5×10^{-5}
900 nm nimodipine particles	0.62	2.3×10^{-5}
100 μm nimodipine particles	0.06	7.5×10^{-6}

between the characteristic times of drug diffusion out of the gel and drug particle dissolution:

$$\xi = \frac{k_m n_p R_1^2 L^2}{D_A}. \quad (4)$$

When $\xi \gg 1$, the release profile is governed exclusively by the diffusion of the drug through the aqueous gel matrix, and the release profile can be described by the Higuchi shrinking core model [33]:

$$\frac{M_t}{M_\infty} = \sqrt{\frac{D_A}{L^2}\left[\frac{3C_A^{Sat}MW_A}{2\pi R_{1,0}^3 \rho_A n_p} - \left(\frac{3C_A^{Sat}MW_A}{4\pi R_{1,0}^3 \rho_A n_p}\right)^2\right]} \cdot t^{0.5} \quad (5)$$

Conversely, when $\xi \ll 1$, release is governed exclusively by slow dissolution of the drug particles. The release of the particulate nimodipine from HAMC ($\xi \sim O(10^{-2} - 10^{-3})$) exemplifies this situation, and enables the determination of a limiting release profile equation through the solution of Eq. (3a). In this case, since the diffusion of the drug out of the gel is rapid relative to the particle dissolution rate, it is reasonable to assume that C_A is negligible relative to C_A^{Sat}. This decouples Eq. (3a) from Eq. (3b), and enables the analytical solution for $R_1(t)$, yielding:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_m MW_A C_A^{Sat}}{\rho_A R_{1,0}} t\right)^3 \quad (6)$$

which is the scaling predicted by the Hixson–Crowell model [34]. Assuming the k_m-value that was fitted in the case of the 100 μm particles, which is the closest condition to this limit that was tested, Eq. (6) predicts a limiting release profile (dashed lines in Fig. 3) that is similar to the experimental profile obtained for the large nimodipine particles, but has a starting point at the origin.

As can be seen from the shaded region of Fig. 3, by varying the method by which the nimodipine is introduced into HAMC a broad range of release profiles can be achieved. These are bounded by the Fickian release obtained in the case of the fully-solubilized nimodipine and the nearly linear release that is predicted by Eq. (6). Significantly, under each condition described above, the drug release rate increases with increasing C_A^{Sat}, as indicated by Eqs. (3a), (3b), (5) and (6).

3.4. HAMC as a delivery platform for hydrophobic drugs

We have shown that the incorporation of polymeric excipients as structural elements of an injectable hydrogel, such as MC in the case of HAMC, can increase the aqueous solubility of hydrophobic drugs. Unlike previous work where polymer additives reduced the rate of drug crystallization [8,9,18–23], we reveal that the presence of 7 wt.% MC in aqueous solution gives rise to a tenfold amplification in nimodipine solubility. This increase in drug solubility significantly accelerates drug release from the hydrogel, and suggests that injectable hydrogel matrices can act as polymeric excipients that accelerate the delivery of hydrophobic, poorly soluble drugs.

The differences in the size-dependent particle dissolution kinetics are reflected in the nimodipine release profiles from HAMC, and can be exploited in tailoring drug release rates. In the case where the drug is completely solubilized at the beginning of the release process, its release is rapid and governed by Fickian diffusion [26]. In the case of particulate nimodipine, however, release occurs over longer time scales due to the slow dissolution of the drug particles. The release profiles obtained from these particulate formulations are biphasic and dependent on the size of the drug particles introduced into HAMC. Experimental and model analysis of the drug dissolution and release reveals that the biphasic release profiles reflect a rapid release of solubilized drug, followed by a slow dissolution-controlled release of the solid nimodipine. Because the amount of nimodipine that is solubilized at the beginning of the release process varies with the initial drug particle size, the release profiles depend strongly on the size of the drug particles that were used in the preparation. This suggests that HAMC and its homologues can yield highly tunable release profiles that are dependent on how the drug is introduced into the *in situ* gelling scaffold. Similarly, because the dissolution of the drug particles in MC occurs over the course of several days, these variations suggest that these release profiles can also likely be adjusted by modulating the time between the preparation and application of the gel.

Additionally, the general model we developed for the release of nimodipine from HAMC is transferrable to other similar systems where sparingly soluble drugs are released from hydrogel scaffolds. The model allows us to both better understand the mechanism that controls the release of drugs from these systems, as well as predict drug release behaviour in future studies. Likewise, the use of MC and its homologues in other products, such as foods and personal care formulations, suggests that hydrogels such as HAMC can be used to achieve highly tunable, accelerated delivery of other types of active ingredients, such as hydrophobic neutraceuticals [35], the use of which are limited by their low solubilities.

4. Conclusions

We have demonstrated that the incorporation of polymeric excipients in an injectable hydrogel can accelerate the release of hydrophobic drugs, and that the addition of MC to water increases the aqueous solubility of sparingly soluble nimodipine. We have exploited the effect of varying initial particle sizes on the particle dissolution rates to obtain a broad range of release profiles. These release profiles depend on the method by which the nimodipine is introduced into HAMC, namely the fraction of pre-dissolved drug. Model analysis of these release profiles supports the release mechanism described above, and suggests that an injectable hydrogel bearing MC and its homologues can provide a versatile platform for rapid and controlled release of hydrophobic drugs and other sparingly soluble compounds.

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