Low Energy Nanoemulsions as Templates for the Formulation of Hydrophobic Drugs

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Most small molecule active pharmaceutical ingredients (APIs) are hydrophobic which poses formulation challenges due to their poor water solubility. Current approaches are energy intensive and involve presenting the API in a nanoparticle form that is then combined with other additives into a stable formulation. Here, a bottom-up and scalable method that formulates nanoparticles (crystalline or amorphous) of poorly water-soluble APIs directly embedded in composite hydrogel beads is presented. Using nanoemulsions prepared from a low energy method as templates, the flexible approach allows to vary the embedded API nanoparticle size from 100 to 500 nm and the hydrogel bead size from 100 to 1200 µm, and subsequently achieve control over the dissolution kinetics. To better understand the dissolution process, a physical model is build that allows to collapse the kinetic data onto a master curve and predict the dependence of release rates on size of both API nanoparticles and hydrogel beads. Lastly, it is demonstrated that the dissolution kinetics of multiple drugs embedded in the same hydrogel matrix can be tuned simultaneously, an attractive property for commercial multi-drug dosage applications. The new approach not only leads to process intensification, but also improved performance.

1. Introduction

Estimates suggest that approximately 70% of newly discovered drug candidates and 40% of the marketed immediate release oral drugs have poor aqueous solubility, many of which are categorized as practically insoluble (<100 µg mL⁻¹). Limited aqueous solubility of these drugs poses a challenge to develop formulations. Further, their delivery through an oral route is difficult due to poor and variable bioavailability. Over the past decade or so, several strategies have been proposed to tackle these challenges, such as particle size diminution, emulsion (micro/nano) based formulations, self-emulsifying systems, salt formation, micronization, liposomes, micelle formation, cyclodextrin inclusion complexation, and solid dispersions. Nanoemulsion synthesis can be divided into two categories: high energy and low energy methods. High energy methods such as high-pressure homogenization and ultrasonication are brute-force techniques that use excess shear to breakup droplets into sub-micron sizes. These methods require energy on the order of \(10^7 - 10^9 \text{ W kg}^{-1}\) that limits their utility at an industrial scale. In contrast, low energy methods exploit favorable interfacial properties and require significantly less energy input of about \(10^3 - 10^5 \text{ W kg}^{-1}\), providing an easy and scalable route.

Recently, we developed a general route to prepare nanoemulsions using low energy methods where we showed that to make nanoemulsions, depending on the interaction of surfactant(s) with liquid phases, a specific mixing order is required. Due to stability issues, it is preferred to convert the nanoemulsion into a nanoparticle.

Several prior works encapsulate oil nanodroplets containing hydrophobic API inside a hydrogel, and some of them also solidify API to make nanocrystals by evaporating the oil phase. These studies report enhanced dissolution rate, improved bioavailability of lipophilic compounds, and controlled release of water-insoluble molecules within the human gastrointestinal tract. Engineered hydrogels containing solid API particles and excipient(s) are of industrial interest since they can provide tailored dosage and release profiles, and also enable intensification (and simplification) of the traditional pharmaceutical manufacturing processes. In particular, the latter is possible since solidified API-laden composite hydrogels can be directly integrated into customized solid dosage forms, that is, tablets and capsules. However, the aforementioned studies used high energy methods to generate nanoemulsions and are not
favorable for industrial scale up. Moreover, they currently lack a quantitative understanding of parameters that control release patterns and rely on phenomenological, power-law, and semi-quantitative transport models. Lastly, prior studies do not provide a route to include multiple drugs in a single gel matrix, an important feature for solid dosage forms.

In this article, we develop a novel formulation strategy for poorly water-soluble drugs by incorporating low energy nanoemulsions into a biocompatible alginate hydrogel matrix. This strategy is controlled and predictable, adhering to the concept of design of experiments (DOE). Figure 1 summarizes our overall experimental strategy. We use nanoemulsions prepared using our general low energy method as templates to create nanoparticles of two poorly water-soluble model APIs: fenofibrate and ibuprofen. Fenofibrate (FEN) and ibuprofen (IBU) are chosen as model compounds in this study because of their poor aqueous solubility. Both APIs are relatively lipophilic (Class II in Biopharmaceutics Classification System) with log P values of 4.0 (IBU) and 5.3 (FEN). The alginate nanoemulsion solution is prepared by mixing nanoemulsion solutions containing different API prior to the bead generation step.

The nanoemulsion mixture is dripped into a bath of CaCl₂ solution that crosslinks alginate due to the presence of Ca²⁺ ions and traps nanoemulsion droplets containing APIs. Subsequent evaporation of the both water and oil phases generates hydrogel beads with API nanoparticles either in crystalline or amorphous form embedded within the polymer matrix. We characterize the physicochemical properties of nanoemulsions and embedded API nanoparticles by dynamic light scattering (DLS), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). We further demonstrate a multi-length scale control over the dissolution kinetics since we independently control the size of both API nanoparticles and hydrogel beads. We also build a physical model and perform an order of magnitude analysis to identify the mechanism of API release from hydrogel beads. This model helps us understand the effect of nanoparticle size and hydrogel bead size on the in vitro dissolution profiles. To our knowledge, this is the first demonstration of a low energy method that uses nanoemulsions as templates to reliably control dissolution profiles of hydrophobic APIs. Moreover, our model is useful to understand the dissolution process and set design parameters.

2. Results and Discussion

2.1. Characterization of API Nanoparticles

We first discuss and characterize the results of optimal nanoemulsion formulations with ibuprofen and fenofibrate individually. Controlling the emulsion droplet size is crucial in emulsion based formulation since the confined environment of droplet dictates the drug particle attributes (size, shape). We showed in our previous work that fenofibrate crystal size is dictated by the nanoemulsion droplet size, which subsequently influences the dissolution kinetics. Figure 2 shows the variation of nanoemulsion droplet size with formulation parameters such as the order of mixing of different phases (method A or method B), hydrophilic–lipophilic balance (HLB) of surfactants, and surfactant-to-oil ratio (SOR). The composition of the nanoemulsion solution is: 30 wt% oil phase (anisole containing saturated amount of API) : SOR wt% surfactant – 70 wt% alginate aqueous phase. We examine the variation of droplet size with HLB (HLB of a surfactant estimates the relative interaction of the surfactant with the liquid phases). We also vary SOR to see the range of accessible compositions since that ultimately dictates the scalability of the process. It is seen from Figure 2a that the average droplet size decreases with increase in HLB for both methods A and B, and for both hydrophobic APIs. We also observe that method A yields lower droplet sizes when compared with method B, consistent with results from previous work. HLB is thus a useful parameter and can be used to control the droplet size. We note that HLB range can be extended further by using different surfactant(s). We refer the readers to our recent work for more strategies to tune the droplet size through choice of surfactant, mixing order, and composition. Increase in SOR also decreases droplet size for both methods A and B, and for both APIs (Figure 2b). This is also consistent with expectation since increasing the relative amount of surfactant improves the surfactant migration to nanoemulsion interface, leading to...
Figure 2. Summary of average nanoemulsion droplet size with a mixture of anisole containing soluble hydrophobic API as dispersed phase and aqueous alginate solution as continuous phase. a) Variation of average droplet size $d$ with HLB of surfactants for methods A/B using either fenofibrate (FEN) or ibuprofen (IBU) as a model API. $d$ decreases with increase in HLB for both methods and for both APIs. Moreover, method A is superior to method B for all HLB values. SOR = 1 is kept constant and HLB value is varied by using a mixture of Span 80 (HLB = 4.3) and Tween 80 (HLB = 15). b) Variation of average droplet size $d$ with surfactant-to-oil ratio SOR. $d$ decreases with increase in SOR for both methods and for both APIs. Here also, method A is superior to method B for all SOR values. HLB = 14.3 is kept constant. The composition of nanoemulsion used is $\frac{30}{\text{SOR}}$ wt% oil phase (anisole containing saturated amount of API) - $\frac{1}{\text{SOR}+1}$ wt% surfactant – 70 wt% alginate aqueous phase. Error bars represent variation in polydispersity.

Figure 3. Characterization of fenofibrate and ibuprofen nanoparticles embedded inside hydrogel beads. a) Powder X-ray diffraction (PXRD) data suggests that fenofibrate is present in crystalline form since the pattern from standard fenofibrate crystal is consistent with the pattern from nanoparticle embedded inside hydrogel beads. b) Differential scanning calorimetry (DSC) data shows the effects of SOR (used in the formulation step) on the melting point of fenofibrate particles. The nanoemulsion droplet size changes from 650 (SOR = 0.25) to 220 nm (SOR = 2) and their corresponding melting points change from 79 to 67 °C. c) PXRD data suggests that ibuprofen particles are present in amorphous form since patterns from ibuprofen nanoparticles are not consistent with data from a standard crystal. d) DSC data corroborates finding in c) since no melting point is observed for ibuprofen nanoparticles.

a more effective droplet breakup. Since even low SORs (such as SOR = 0.25) enable efficient nanoemulsion formation, we can achieve high drug loading capacities (see Supporting Information for more details). Thus, our methodology has a high potential for scale up.

We investigate the crystallinity of encapsulated API nanoparticles inside the hydrogel matrix by PXRD and DSC. We summarize the characterization results of embedded nanoparticles in Figure 3. Fenofibrate nanoparticles in the beads are present in crystalline form since the PXRD pattern is consistent with the standard pattern of fenofibrate crystals (Figure 3a). Naturally, it is also important to understand and control the crystal size of the API as it greatly influences the dissolution kinetics. We showed in our previous work that fenofibrate crystal size is dictated by
the nanoemulsion droplet size and and is approximately equal to the initial drop letsise.\textsuperscript{[22,23]} This is corroborated by DSC results where we observe a decrease in melting point from 79 to 67 °C with changes in nanoemulsion droplet size from 650 to 220 nm (Figure 3b). This is consistent with the prior reports in literature where DSC measurements show that the melting point of fenofibrate decreases with the decrease in API nanocrystal size.\textsuperscript{[33]} In addition, the amount of embedded fenofibrate nanocrystals (% drug loading on dry basis) can also be tuned by varying the SOL. The drug loading capacity increases from 32 to 50% when the SOL decrease from 2.0 to 0.25 (see the Supporting Information).

In contrast to fenofibrate, we find that ibuprofen nanoparticles do not show an XRD pattern consistent with standard ibuprofen crystals (Figure 3c). This implies that ibuprofen particles are present in an amorphous state. DSC results further confirm the amorphous form of embedded nanoparticles (Figure 3d), as we do not see any endothermic peak at 78 °C—a characteristic of the melting of the bulk phase of ibuprofen.\textsuperscript{[34]} The loss of crystalline nature of ibuprofen may be explained by the molecular interaction between ionized ibuprofen and the alginate, which may induce the formation of nanoconjugates by disrupting the crystal lattice of ibuprofen.\textsuperscript{[34]} Previous studies show that the API–polymer interactions due to ionic or intermolecular H-bonding interactions stabilize solid dispersions and prevent re-cristallization during dissolution.\textsuperscript{[35]} It should be noted that amorphous form of a poorly soluble API has higher apparent solubility and improved dissolution rate as compared to its crystalline form since no crystal lattice has to be broken down for dissolution to take place.\textsuperscript{[16,37]} Though the amorphous form of APIs represents another promising technique to improve the bioavailability of poorly water-soluble drugs, their stabilization is a major concern.\textsuperscript{[35,36]} However, in this study, the ibuprofen amorphous particles encapsulated inside the ionic polymer (alginate) hydrogel matrix remain stable for at least 4 months at 25 °C and 60% relative humidity (see the DSC/XRD results in the Supporting Information). We also observe that with the change of SOL (from 0.25 to 2.0) the formulated products do not show any crystallinity or any transformation from amorphous state to crystalline state. The porous nano-confinement environment within the alginate hydrogel matrix is believed to prevent re-crystallization of the homogeneously dispersed ibuprofen drug molecules. Recently, micro- or mesoporous materials such as SBA-15, MCM-41, controlled porous glass (CPG), that exploit their nano-space confinement and surface chemistry, have been used for amorphization of poorly water-soluble drugs with long-term storage stability.\textsuperscript{[39–41]} Moreover, we can increase the drug loading capacity up to 30% with a decrease of SOL to 0.25 (Supporting Information). Unlike the fenofibrate nanoparticles, the ibuprofen particle size is not the same as that of the nanoemulsion droplet size, probably because of being in the amorphous state, and the saturation solubility difference between fenofibrate and ibuprofen in the dispersed phase (anisole). It is also observed that the loading capacity of ibuprofen (21%) is lower than that of fenofibrate (39%) at a fixed oil weight fraction (15%) due to their solubility difference in anisole. Typically, the embedded ibuprofen amorphous nanoparticles are found to be 40–60% of the original nanoemulsion droplet size (see Supporting Information Figure 3).

### 2.2. Dissolution Results

Figure 4 provides a summary of dissolution profiles profiles of fenofibrate and ibuprofen from different formulations. We independently vary the hydrogel bead size (radius: $R_b$) as well as the API nanoparticle size (radius: $R_p$), and measure relative concentration of drug(s) in bulk ($\theta_b$) with time. Increasing $R_p$ and/or $R_b$ slows down the dissolution rate for fenofibrate nanocrystals (Figure 4a,b). Increasing $R_b$ from 50 to 500 µm changes $t_{50}$ from 12.5 to 100 min and increasing $R_b$ from 165 to 650 nm changes $t_{50}$ from 12.5 to 45 min ($t_{50}$ is the time to reach $\theta_{50} = 0.7$). Similar to fenofibrate, for ibuprofen, increasing the value of $R_b$ from 50 to 550 µm, changes $t_{50}$ from 3.7 to 33.3 min. These dissolution rates are comparable and in some cases even faster than those reported in the literature.\textsuperscript{[22,11,40,42,43]} For example, Dwyer et al. showed that fenofibrate nanocrystals prepared from the 70 nm CPG matrix achieve $t_{50} = 42$ min.\textsuperscript{[13]} In addition, the dissolution kinetics of our fenofibrate nanocrystal formulations is also comparable to that of the state-of-the-art fenofibrate formulation commercialized as TriCor tablets which are prepared by a nano-milling technique.\textsuperscript{[32]} Shen et al. reported that amorphous ibuprofen prepared from co-sprayed solid dispersion with SBA-15 have $t_{50} = 15$ min whereas commercial ibuprofen only shows $\theta_{50} = 0.16$ in the same time frame.\textsuperscript{[39]} Zhang et al. found $t_{50} = 60$ min for amorphous ibuprofen dissolution from mesoporous Mg-carbonate.\textsuperscript{[42]} Though the above-mentioned studies show similar dissolution rates to the ones we report, our ability to access a wide range of $R_b$ and $R_p$, and vary both parameters independently, provides us with flexibility to control the dissolution profile. We now use an order of magnitude analysis to develop a physical picture of the complete dissolution process and to estimate the importance of different physical parameters.

Results from our theoretical analysis are summarized in Figure 5. We assume that both drug nanoparticles and beads are spherical with radius $R_p$ (initial radius) and $R_b$, respectively (Figure 5a). Since the nanoparticles dissolve, their size varies with time, denoted here by $R_p(t)$. We also assume that drug nanoparticles are distributed uniformly throughout the bead. We can expect the concentration of dissolved drug in the bead to evolve over time, as shown in Figure 5b. Initially, the concentration of drug is uniform inside the bead but as the time goes on, concentration decays radially outward. This happens because the drug will first dissolve at the radially outermost layer of nanoparticles and then move inward. Therefore, at any given time, the concentration only decays between $R_p(t) < r < R_b$, where $R_b$ is the radial distance below which the drug concentration is uniform. Naturally, at $t = 0$, $R_p(0) = R_b$, or the concentration is uniform throughout the entire bead. For the sake of simplicity, we only perform an order of magnitude analysis. We note that at any given time $t$, the drug dissolves from the nanoparticles between $R_p(t) < r < R_b$, diffuses radially outward in the bead, and then dissolves in the bulk. The drug dissolution and diffusion step can be described as:

\[
N_{NP} = k(C_{sat} - C)4\pi R_p(t)^2,
\]

where $N_{NP}$ is the amount of drug diffusing out per unit time from a single nanoparticle, $k$ is the mass transfer coefficient,
Figure 4. Dissolution profiles for different $R_b$ and $R_c$. a) Evolution of $\theta_\infty$ for fenofibrate crystals in alginate beads for different values of $R_b$ keeping $R_c$ constant. We observe that increasing $R_b$ slows down the dissolution rate. b) Evolution of $\theta_\infty$ for fenofibrate crystals in alginate beads for different values of $R_c$ keeping $R_b$ constant. Similar to $R_b$, increase in $R_c$ slows down the dissolution rate. c) Evolution of $\theta_\infty$ for ibuprofen particles were similar to fenofibrate, increase in $R_b$ slows down the dissolution rate.

Figure 5. Physical model and collapse of dissolution data. a) Schematic of our physical model that assumes spherical nanoparticles with radius $R_c$ are uniformly distributed in the bead with radius $R_b$. The concentration decays between $R'_b(t) < r < R_b$. Initially, $R'_b(0) = R_b$. Upon re-scaling the variation of $\theta_\infty$ with $\tilde{t}$, we are able to collapse entire dissolution data for b) fenofibrate and c) ibuprofen. $\tilde{t} = \beta t R_b / R_c$ where we fit the value of $\beta$. The values of $\beta$ used for fenofibrate and ibuprofen are $4.25 \times 10^{-15}$ m$^2$ s$^{-1}$ and $7.5 \times 10^{-15}$ m$^2$ s$^{-1}$, respectively.

$C_{sat}$ is the saturated concentration of the drug in the bead, and $C$ is the concentration of the drug just outside the nanoparticle. Since there is no flow within the bead, mass transfer coefficient is given by $k \sim \frac{D}{\delta}$, where $\delta$ is the boundary layer thickness, or the thickness when concentration changes. Based on our physical picture in Figure 5, $\delta \sim R_b - R'_b(t)$, and $\delta$ varies with time. However, for an order of magnitude estimate, we can assume $\delta \sim R_b$ and $k \sim D / R_b$. Similarly, $C_{sat} - C$ is a function of position as well as time. However, as a first approximation, we can
assume \( C_{\text{sat}} - C \sim C_{\text{sat}} \). We also note that the nanoparticle radius \( R(t) \) is not a constant and ultimately vanishes. However, the relevant scale of \( R(t) \) is the initial radius \( R_c \). We can estimate the order of magnitude value of \( N_{\text{NP}} \) from Eq. (1) as (neglecting numerical prefactors):

\[
N_{\text{NP}} \sim \frac{D}{R_c} C_{\text{sat}} R_c^2.
\]  

(2)

Now, we estimate the amount of drug dissolving into the bulk solution from all beads. The number of nanoparticles dissolving per bead in a given time \( t \) is:

\[
n_{\text{NP,B}} \sim \frac{\phi \rho_b (R_c^3 - R_b^3(t)^3)}{\rho_c R_c^3} = \frac{\phi \rho_b R_c^3}{\rho_c R_c^3}.
\]  

(3)

where \( \phi \) is the fraction of drug inside the bead (either by weight or mole), \( \rho_b \) is the density of the alginate bead, and \( \rho_c \) is the density of the nanoparticle. We note that for a given time \( t \), the nanoparticles would only be dissolving between \( R_b(t) < r < R_c \). As before, we approximate \( R_c^3 - R_b^3(t)^3 \sim R_b^3 \). Now, the total number of beads in bulk for a fixed amount of alginate \( m_b \) is:

\[
n_0 \sim \frac{m_b}{4\pi \rho_b R_b^3}.
\]  

(4)

Therefore, the amount of drug dissolving from all beads is (neglecting numerical prefactors):

\[
N_{\text{total}} \sim n_0 n_{\text{NP,B}} N_{\text{NP}} \sim \frac{m_b \phi DC_{\text{sat}}}{\rho_c R_b R_c}.
\]  

(5)

Since \( N_{\text{total}} \) is the amount of drug uptake in the bulk, it can also be estimated as:

\[
N_{\text{total}} \sim V \frac{dC}{dt} \sim V C_{\infty} \frac{t}{1},
\]  

(6)

where \( V \) is the volume of bulk solution, \( C_{\infty} \) is the concentration of drug in bulk, and \( t \) is time. Comparing the two estimates:

\[
\frac{VC_{\infty}}{t} \sim \frac{m_b \phi DC_{\text{sat}}}{\rho_c R_b R_c}.
\]  

(7)

or

\[
\frac{C_{\infty}}{t} \sim \frac{DC_{\text{sat}}}{\rho_c R_b R_c}.
\]  

(8)

or

\[
\theta_{\infty} \sim \frac{t}{\beta}.
\]  

(9)

where \( \theta_{\infty} \) is the relative amount of drug dissolved in the bulk and \( \beta = \frac{D}{\rho_c R_b R_c} \) is a dimensionless time scale. According to our calculations, all of our data for various concentrations (\( \theta_{\infty} \)) should collapse when plotting against \( \beta \). We re-plot the data presented in Figure 4 by scaling the time \( t \) as \( \beta = \frac{t}{m_b \phi R_b R_c} \), where we fit the value of \( \beta \) for fenofibrate as well as ibuprofen such that the scale of \( \beta \) is of the order of unity. The values of \( \beta \) used for fenofibrate and ibuprofen are \( 4.25 \times 10^{-15} \text{ m}^2 \text{ s}^{-1} \) and \( 7.5 \times 10^{-15} \text{ m}^2 \text{ s}^{-1} \), respectively (a discussion on the fitted values of \( \beta \) and their significance is provided in the Supporting Information). \( R_c, R_b \) are taken from experiments. The results are provided in Figure 5b,c. The results clearly show that we are able to collapse the data on a master curve. This is especially promising since we collapse the entire dissolution profile, unlike recent reports.\(^{[22,23]}\) We also note that the collapse of experimental data onto a single curve is independent of the fitting parameter \( \beta \) since the value of \( \beta \) is kept constant across different data sets. Overall, our model provides useful information about the dissolution kinetics. For instance, since the system is governed by \( \beta \), we know that increasing \( R_b \) by a factor of 10 will increase dissolution time by tenfold. Similarly, if we increase \( R_c \) by ten times, dissolution time will increase by tenfold. Since we only perform an order of magnitude analysis and neglect effects such as re-hydration of the alginate bead, our current analysis is only a first-order approximation. However, the analysis still provides critical information about parameters governing the physical process.

### 2.3. Co-Formulation of Drugs

As discussed in Figure 1, using a mixture of two or more nanoeulsion provides a route to embed multiple drugs inside a single polymer matrix (i.e., co-formulation). We note that it is also possible to separately mix the beads containing different APIs. However, it is preferred to have them inside a single matrix since that opens up the possibility to exploit synergistic effects.\(^{[44–46]}\) Moreover, it is easier to mix nanoemulsions prior to bead generation as compared to generating different sized beads, thus adding the dosing compliance. Figure 6 shows the in vitro dissolution properties of co-formulation of fenofibrate nanocrystals (≈500 nm in diameter) and ibuprofen amorphous nanoparticles (≈80 nm in diameter) contained in a hydrogel bead of 100 \( \mu \text{m} \) in diameter. The dissolution kinetics results are consistent with the trends obtained for APIs reported in Figure 4, suggesting that...
there is no detrimental effect on dissolution due to the presence of multiple drugs. To vary the release profiles of both ibuprofen and fenofibrate, we can vary the bead size. However, to vary the dissolution profile of an individual drug, we can tune the nanoparticle size by varying any formulation parameter. Thus the flexibility of our approach offers the possibility to design dosages of multiple hydrophobic drugs with future tailor-made controlled release formulations. In addition, hydrogels loaded with multiple drugs could reduce the frequency of drug administration, potentially facilitating patient compliance.

3. Conclusion and Outlook

We present here a low energy method to make composite hydrogel beads encapsulated with single and multiple hydrophobic drugs. Characterization of the API particles embedded inside the hydrogels by SEM, DSC, and PXRD proved that both embedded fenofibrate and ibuprofen particles are in nanometer size range, and crystalline and amorphous in nature, respectively. Since our bottom-up formulation approach only requires simple unit operations such as mixing and dripping, there is significant potential to adapt this technique at an industrial scale. Further, due to our ability to control the size of both API particles and hydrogel beads, we can adjust the time of drug release profile anywhere from 10 to 200 min. This is particularly useful since it might be desirable to have a faster dissolution of a particular drug and a slower release of another, or to have faster release of both drugs to optimize the therapeutic efficacy. In fact reports indicate an increasing demand in dosage forms that carry multiple drugs to optimize the therapeutic efficacy. In fact reports indicate an increasing demand in dosage forms that carry multiple drugs to optimize the therapeutic efficacy. In fact reports indicate an increasing demand in dosage forms that carry multiple drugs to optimize the therapeutic efficacy.

4. Experimental Section

Materials: Non-ionic surfactants (Span 80 and Tween 80), fenofibrate (> 99% pure), anisole (methoxybenzene, > 99% pure), calcium chloride (≥ 93% pure), ibuprofen (> 99%), and sodium dodecyl sulfate (≥ 99% pure) are products from Sigma-Aldrich. Sodium alginate (CAS no. 9005383), a polysaccharide that consists of approximately 61% mannuronic (M) and 39% guluronic (G) acid is also purchased from Sigma-Aldrich. 30 gauge and 15 gauge stainless steel blunt-tip needles are used using gravity dripping to prepare around 650 and 1200 µm sized dried hydrogel beads, respectively. However, to produce ~450 µm sized beads, centrifugal synthesis is used (the preparation method is described in the Supporting Information).

To prepare the co-formulated APIs inside a hydrogel bead, two separate nanoemulsion solutions are mixed in 1:1 ratio by weight. The first nanoemulsion solution is 20 wt% anisole containing saturated amount of ibuprofen –10 wt% surfactant (HLB 14.3) –70 wt% alginate solution (SOR = 0.5, nanoeulsion size ≈ 140 nm) and the second solution is 20 wt% anisole containing a saturated amount of fenofibrate –10 wt% surfactant (HLB 15) –70 wt% alginate solution (SOR = 0.5, nanoeulsion size ≈ 520 nm).

Analysis of Hydrogel Beads Containing Drug Nanoparticles: The dried composite hydrogel beads with fenofibrate or ibuprofen nanoparticles embedded inside the polymer core matrix are analyzed by PXRD in reflectance mode (Panalytical X’pert MPD Pro). The samples are ground and then placed on a zero background disk. The PXRD is operated at 40 kV, 30 mA, and at a scanning rate of 2° min^{-1} over the range of 2θ = 10°–40°, using Cu-Kα radiation wavelength of 1.54 Å. The samples are also analyzed by DSC using TA Instruments (Q2000 DSC). 10–15 mg of sample is crimped in a sealed T-zero aluminum pan and heated at 10°C min^{-1} in the range of −20°C to 150°C using an empty sealed pan as a reference. Dry N2 is used as purge gas and the flow rate is 50 mL min^{-1}. The embedded API nanoparticles are also characterized with high-resolution scanning electron microscopy (Zeiss HRSEM) at 5 kV accelerating voltage and at various magnifications. Prior to imaging, all samples are prepared on conventional SEM stubs with carbon tape and are coated with about 10–15 nm of Au by sputter coating.
(equivalent to about 20 mg of API) are added to the dissolution media manually. For maintaining sink conditions during dissolution experiments, the mass of drugs added for a dissolution experiment is at least three times less than the amount required to saturate the media. The UV measurements are obtained using an automatic Varian UV-vis Cary 50 apparatus and an in situ probe set. All reported measurements are repeated at least three times under identical conditions to obtain an average value.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgments

A.Z.M.B. and A.G. contributed equally to this work. The authors acknowledge the Novartis-MIT Center for Continuous Manufacturing for financial support from the Hugh Hampton Young Fellowship.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

controlled release, dissolution, fenofibrate, formulation, ibuprofen, nanocrystals, nanoemulsions

Received: November 6, 2017
Revised: December 1, 2017
Published online: February 6, 2018

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