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Responsive Foams for Nanoparticle Delivery

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Abstract

We have developed responsive foam systems for nanoparticle delivery. The foams are easy to make, stable at room temperature, and can be engineered to break in response to temperature or moisture. Temperature-responsive foams are based on the phase transition of long chain alcohols and could be produced using medical grade nitrous oxide as a propellant. These temperature-sensitive foams could be used for polyacrylic acid (PAA)-based nanoparticle delivery. We also discuss moisture-responsive foams made with soap pump dispensers. Polyethylene glycol (PEG)-based nanoparticles or PMMA latex nanoparticles were loaded into Tween 20 foams and the particle size was not affected by the foam formulation or foam break. Using biocompatible detergents, we anticipate this will be a versatile and simple approach to producing foams for nanoparticle delivery with many potential pharmaceutical and personal care applications.

Graphical Abstract

Keywords

foams; nanoparticle; surfactant; quick-break

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found in the online version.

1. Introduction

Foams are promising drug delivery vehicles when compared to conventional ointments and creams, lotions or gels [1, 2]. In topical applications, foams products can be applied and spread easily over large areas without leaving greasy residue [3, 4]. Ideally, the foams are sufficiently stable at room temperature to facilitate application, but would break to a liquid state upon application to a desired state thus delivering the active ingredient. Foams are attractive vehicles to replace gels for vaginal and rectal delivery since foams offer convenient, single-step application while avoiding leakage of fluids that occurs with current formulations [2, 5]. Since foams provide coverage of large surface areas and access to difficult to reach areas, they have been used for nasal and auditory canal delivery [6, 7]. In these applications, the foam is made in the desired body cavity. Use of a foam can increase the surface area of application. Foams that would break into a small amount of liquid immediately (within seconds to minutes) upon application may serve to minimize any potential discomfort.

Our goal is to develop responsive foams for the delivery of nanoparticle therapeutics. Foams provide uniform application of actives over large surface areas with minimal liquid volume. The responsive aspect of the delivery comes from designing a “triggered” response to a physiologically relevant state that occurs during administration. Upon triggering, the foam should break to deliver the therapeutic nanoparticles to the tissue surface with minimal free aqueous phase. [1, 2, 8-10]. We focused on using methods that are easy to use to allow for self-administration [5], which involve only biocompatible components, and for which there are current foam delivery devices. The selection of biocompatible components in generating foams with high foam to liquid volume fractions is a significant challenge. Many existing foam systems with such as shaving cream utilize hydrocarbon or hydrofluoralkane based propellants which are inappropriate for drug delivery applications. Nanoparticles are of interest because they enable sustained release of therapeutics. Our specific interest is in nanoparticle formulations of HIV drugs that can be delivered by foams to rectal or vaginal sites, which will quickly break, and which do not involve large liquid boluses. Such formulations would enhance patient compliance and, therefore increase the effectiveness of treatment and prevention.

We have developed two platforms for foam delivery of nanoparticles; one uses thermal triggered breakage at 37°C, and another uses wet surfaces as the trigger mechanism. The first is a propellant-based foam using medical grade nitrous oxide as a propellant. The temperature responsiveness comes from long chain alcohol crystals that stabilize the foams, but the crystals melt and are solubilized near physiological temperature. The second is a mechanically generated foam for which the responsiveness comes from local dilution of the surfactant stabilizer upon contact with a wet surface. Nanoparticle loading in both foam systems was explored.

2. Materials and Methods

Stearyl alcohol, potassium hydroxide, poly(ethylene glycol) with an average M_n of 4,600 (PEG5K) and Tween 20 were obtained from Sigma Aldrich (St. Louis, MO.).

Tetrahydrofuran (HPLC grade), propylene glycol and absolute ethanol were purchased from Fisher Scientific (Waltham, MA). Cetyl alcohol and 3, 3'-dioctadecyloxacarbocyanine perchlorate (DiO) was obtained from MP Biomedicals (Santa Ana, CA) and Invitrogen (Carlsbad, CA), respectively. Polystyrene (PS) and block copolymers, polystyrene (1.6 kDa)-b-polyethylene glycol (5 kDa) (PS-b-PEG) and polystyrene (2.2 kDa)-b-polyacrylic acid (11.5 kDa) (PS-b-PAA) were bought from Polymer Source, Inc. (Montreal, Canada) and branched, 50-100 kDa polyethylenimine (PEI) was obtained from Polysciences, Inc. Hostasol Yellow 3G and phosphate buffered saline were obtained from Clariant Pigments (Tianjin) and Lonza (Basel, Switzerland), respectively. Red food coloring from McCormick & Company, Inc. (Sparks, MD) and 8 g cartridges of medical grade nitrous oxide N₂O from whip-it!TM brand (Vancouver, Canada) were used. Acrylic-latex particles (300 nm) were obtained from Arekma. Dialysis tubing with a 6-8 kDa MWCO was obtained from Spectrum Labs. All materials were used as received.

Nanoparticles were prepared using Flash NanoPrecipitation in a confined impinging jet mixer as previously described [11-13]. For PEG based nanoparticles, PS-b-PEG (10 mg/mL) and Hostasol Yellow 3G (10 mg/mL) were dissolved in THF. Equal volumes (0.5 mL) of the THF stream and ultrapure water (Milli-Q) were rapidly mixed and immediately dispersed into ultrapure water (4 mL, final THF:water 1:9 by volume). Similarly, PAA based nanoparticles were formulated by dissolving PS-b-PAA (5 mg/mL), PS (5 mg/mL) and DiO (0.1 mg/mL) in 1:1 volume mixture of THF and DMSO. The organic stream was rapidly mixed and immediately dispersed into PBS (1:9 organic:PBS by volume). Nanoparticle samples were dialyzed (6000-8000 MWCO Spectra/Por®, Spectrum Labs) against ultrapure water (1:100 volume of nanoparticle sample to volume of water) for 24 hours with four changes of water. Nanoparticle size (hydrodynamic diameters (peak size from intensity distribution) and polydispersity indices (PDI)) before dialysis, after dialysis and after foam break was measured by dynamic light scattering (DLS) using a Malvern-Zetasizer Nano Series DLS.

2.1 Temperature-Responsive Foam Formulations

Temperature-responsive foam formulations were prepared by combining ethanol, cetyl alcohol, stearyl alcohol, Polysorbate 60 and propylene glycol in various proportions (sample formulation is provided in Table 1) based on previous reports [14] and stirring briefly at room temperature until homogenous. Water and aqueous solutions potassium hydroxide (10 wt.%) were combined with red food coloring, PEG5K, PEG-based or PAA-based nanoparticles and stirred briefly at room temperature. Immediately prior to foam production, the ethanol and water solutions were combined and stirred briefly. A small amount of the foam formulation with and without Polysorbate 60 was placed between crossed polarized and imaged with an optical microscope (Nikon Eclipse E200) at room temperature and with heating. Approximately 50 mL of the mixture was loaded in a reusable stainless steel foam dispenser (Whip-It Brand Specialist Plus 1/2-liter, North Vancouver, BC, Canada), charged with nitrous oxide and prepared according to the manufacturer's specifications. Foams (approximated 3 g) were dispensed onto glass petri dishes which were at either room temperature or heated to 37°C and the time for foam breaking was measured based on visual inspection. Foam-to-liquid volume ratios were also measured and ratios of at least 5 were

considered “acceptable”; however, higher ratios are desirable to maximize surface coverage and minimize leakage of the vehicle [2, 5].

2.1 Moisture-Responsive Foams

Moisture-responsive foams were produced by dissolving a small amount (0.5 –5 wt. %) of Tween 20 in DI water. In some samples, PEG5K, PEG-based nanoparticles, or Acrylic-latex particles were also included. Foams (~2 g) were dispensed from 10 mL Tween 20 solution using pumps manufactured by Paragon Marketing Global, Inc. (BF50, New Hill, NC). Foam-to-liquid volume ratios were measured. Stability when the foam was applied to a dry surface (polystyrene Petri dishes) or moist surface (a section of dialysis tubing presoaked in water) was monitored for up to 1 hour.

3. Results and Discussion

3.1 Temperature responsive foam for nanoparticle delivery

Using red coloring for visualization, we examined the stability of the temperature-responsive foams at room temperature and at 37°C. The composition of the foam is given in Table 1. At room temperature, the foam is relatively stable, as shown in the Appendix (Figure A.1), with only a minimal amount of drainage after 10 minutes. Some foam remains after 30 minutes and no further breakage is observed. In contrast, when applied to a plate initially heated to 37°C the foam has broken completely in less than 3.5 minutes.

The mechanism of foaming and temperature responsiveness arises from the state of the long chain alcohols in the formulation. As shown in Figure 1, the foam formulations without Polysorbate 60 (Figure 1a) are opaque at room temperature due the cetyl and steryl alcohol crystals in suspension. When placed between two crossed polarizers, birefringence from the long-chain (fatty) alcohols particulates can be observed at ambient temperature. Upon dispensing with the nitrous oxide, the formulation solidifies due to freezing of the long-chain alcohols. Optical microscopy of the bulk formulation at room temperature (Figure 1a) demonstrates the particulate nature of the long-chain alcohol crystals which provide foam structure. The foam lamellae are stabilized by solid particles of long-chain alcohols and the amphiphilic surfactant Polysorbate 60 (Figure A.1) [15, 16], as is seen in other foam systems and Pickering emulsions [17]. Colloidal stabilization of foams has been used to create magnetically responsive [18] and Fameau et al. created temperature responsive foams; however, the temperature of foam rupture was limited to 60°C [19]. The long-chain alcohols are solid at room-temperature, thus, the foams at room temperature are relatively stable.

The foam break is triggered by melting of the long-chain alcohol crystals that stabilize the foam. The components of the formulation, specifically the concentration of the long-chain alcohols, has been chosen to tune the melting temperature to 37°C. Upon heating, the long-chain alcohols melt, the samples become transparent and birefringence from the particulates that stabilize the foam disappear (Figure 1b). As the long-chain alcohols melt, they are soluble in the alcohol-water mixture containing the Polysorbate 60 surfactant. In the absence of the Pickering particles, the foam rapidly ruptures. A representative video (at 2× speed) of the change in birefringence upon heating is included in the Supporting Materials.

With Polysorbate 60, the crystal size created during formulation with the aqueous phase (aqueous quench) was smaller than crystals created without the surfactant (Figure A.2). This is consistent with what is known about Polysorbate 60 as a crystal modifier, affecting the size and melting temperature of the fatty acids [20]. The modified crystal structure resulted in a slightly lower melting temperature as indicated by the transition to a transparent solution. The formulation of Polysorbate 60 transitioned from opalescent to transparent at ~32°C whereas the melting transition for the formulation without Polysorbate 60 occurred at ~34°C. Thus, the amount of Polysorbate 60 in the formulation can be used to adjust the size of the long-chain alcohol particulates that constitute the foam structure to tune the melting temperature and time to break.

The ethanol concentration in the formulation is important in creating foams with the desired foam volume to liquid volume ratio as it greatly affects the solubility of the propellant nitrous oxide (N₂O). For uniform foaming, the blowing agent must be uniformly dissolved in the fluid phase so that upon depressurization homogeneous nucleation occurs. For example, whipped cream foams (with large foam volumes) can be produced only with milk containing 30% butterfat because the fat globules become the reservoirs to solubilize N₂O. In these formulations, the foaming propellant nitrous oxide (N₂O) is miscible with organic media i.e. ethanol, but not water. Figure 2 shows that there is a small window of ethanol concentration between 52 and 58wt.% ethanol that yield acceptable foams (foam volume to liquid volume ratios of at least 5). Below 52 wt.% ethanol N₂O is not solubilized sufficiently to produce homogeneous foams. Above 60 wt.% ethanol, Polysorbate 60 is soluble and does act as an amphiphilic stabilizer. Therefore, stable foams are not produced. This result suggests that the surfactant is required for the foaming and indicates that the foam lamellae are stabilized by solid particles of long-chain alcohols and the amphiphilic surfactant Polysorbate 60. Thus, formulations containing 58 wt.% ethanol were used for all further formulations.

The therapeutic nanoparticles we intend deliver via these foams have a dense PEG steric coating to allow them to penetrate mucous layers in vaginal and rectal applications [21-25]. The preparation of the particles involves lyophilization using PEG as a lyoprotectant to produce dry powders that redisperse to nanoparticle form without aggregation. Therefore, we examined the effect of adding PEG5K on foaming, foam stability and foam degradation kinetics by including 1 to 10 wt.% PEG5K homopolymer to the aqueous phase. The PEG-loaded foams were stable at room temperature. Further, the addition of the PEG5K (up to 10 wt.% of the foam formulation) did not significantly affect the foam-volume to liquid-volume ratio (Supporting Information Figure A.3) nor the time to break when applied to a plate at 37°C. The addition of the PEG and PEG-coated nanoparticles are not expected to affect the long-chain alcohol crystals, thus the foam stability and responsiveness at 37°C should not be affected which agrees with our experimental observations.

Next, nanoparticles containing Hostasol Yellow dye for visualization encapsulated with PS-b-PEG (1.6K-b-5K) were added to the liquid phase at 0.02 wt.%. The foams were thermally responsive and broke within 2 minutes of dispensing onto the 37°C surface (Figure 3). However, dye-containing nanoparticle aggregation was observed.

PEG-coated nanoparticles were not stable in 60 wt.% ethanol as the 68 nm nanoparticles grew or aggregated to over 1 micron. In 60 wt.% ethanol, the PEG-coating does not provide sufficient steric stabilization to the particles and the particles aggregate due to van der Waals interactions as previously reported [26]. Since the nanoparticles have a negative surface charge of ~ -10 mV [27, 28], we attempted to stabilize the nanoparticles by encapsulation within a coacervate based on electrostatic interactions with a cationic polymer. The addition of the positively charged polymer polyethylene imine (PEI) forms a coacervate layer with the negatively charged PEG-coated nanoparticles. The electrostatic polymer complex adds steric stabilization and limits aggregation of the nanoparticles. In the absence of PEI nanoparticles grew from 67 ± 2 nm to over 1 micron, whereas with a 20 fold weight ratio of PEI:NP the size increased only to 104 ± 4 nm, as shown in Figure 4. Due to the large excess of PEI used, electrostatic repulsion may also provide stabilization [26].

An alternative approach to stabilizing the NPs in 60 wt.% ethanol is to replace the PEG-block of the amphiphilic block copolymer with a polymer that is less soluble in the mixed ethanol and water solvent system so that the block copolymer is not solubilized in the alcoholic solution. For proof of concept, we demonstrate this approach using PAA instead of PEG by replacing the PS-b-PEG with PS-b-PAA. The less soluble PS-b-PAA polymer conferred sufficient stability in 60% ethanol that the size and size distribution of the PAA-based nanoparticles in water and in 60% ethanol were comparable (Figure A.4.). Further, the foaming process i.e. the imbibition of N_2O and subsequent gas nucleation, did not affect the particle size or size distribution (Figure A.4.). The nanoparticle-loaded foams broke quickly (less than 1 minute) when applied to a plate initially heated to 37°C (Figure A.4.). Based on these results, the PAA-based particles are promising for delivery from ethanol-based temperature-responsive foams.

3.2 Moisture Responsive Foam for Nanoparticle Delivery

As a second, complementary, foam platform for nanoparticle delivery, we explored the use of surfactant based foams dispensed by pumps for propellant-free formulations. The pump mechanisms produce foams by forcing a surfactant liquid formulation and air through a porous mesh. Surfactants with high hydrophilic-lipophilic balance (HLB) were considered. HLB for non-ionic surfactants is a measure of the molecular weight of the hydrophilic portion of a surfactant compared to the molecular weight of the entire molecule. Surfactants with HLBs ~ 15 are considered detergents and are expected to foam using pumps designed for dispensing soap foams. Using the pumps, we made foams from a range of sorbate-based surfactants (Tweens from Croda Ltd.) at 2 wt.%, concentrations, well above the critical micelle concentration [29] for any of the surfactants (Appendix, Table A1). Tween 20 with an HLB of 16.7 yielded the highest foam volume ratios with above 10.

In the case of the mechanically-made surfactant foams, the foam forms due to the assembly of the surfactant. Air bubbles are stabilized by a surfactant-water-surfactant film which provide the foam structure. Since the small sorbitan head group of the Tween 20 and its relatively small tail make it an ineffective molecular stabilizer, high concentrations are required to produce foams. The best foams were achieved for surfactant concentrations 270 times higher than the CMC. For formulations at concentrations substantially above the

CMC, two mechanism of stabilization have been observed. One involves lamellar structures that are template parallel to the liquid interface [30, 31]. In these cases, the interfacial regions are birefringent; this was not observed in our systems. The second mechanism is the steric repulsion of spherical micelles in the surfactant-water-surfactant thin films [32-34]. This has been observed in several experiments involving direct observation of the thinning of liquid films. Therefore, the moisture-responsive foams are stabilized by steric repulsion of the Tween 20 micelles in the surfactant-water-surfactant film (Figure A.5).

The moisture responsiveness of these foams are a result of the solubility of the surfactant. The high HLB surfactants which result in foams with high foam volume to liquid volume ratio are also soluble in water. Upon contact with a wet surface local dilution of the foam liquid phase decreases the volume of micelle phase and destabilizes the film.

Since PEG-based nanoparticles are of considerable therapeutic interest [35, 36], and since PEG is expected to be an excipient that will be part of the nanoparticle formulation, we examined how the addition of PEG5K affected the foam properties, namely the foam-to-liquid volume ratio. PEG5K without surfactant did not produce foams with appreciable volume ratios (Appendix, Table A.1). However, formulations of Tween 20 with and without PEG5K had foam volume of liquid volume ratios over 10 (Table A.2). Tween concentration from 0.5 to 5 wt.% (CMC 0.0074 wt.%) and PEG loading up to 50% (based on mass of Tween) had only a small effect on the foam volume ratio.

The effect of nanoparticle additives on foaming were studied Tween foams with PEG-based nanoparticle loaded with Hostasol Yellow dye for visualization. The foams are stable when applied to a dry surface at room temperature over with no drainage observed over 10 minutes (Figure 5). When applied to a moist surface, the surfactant in contact with the moisture solubilizes, the foam breaks, and the nanoparticles are delivered. For example, when nanoparticle loaded foams were applied to a moist surface, drainage began immediately upon application to a moist surface and completed within 10 minutes as shown in the Figure 5. The addition of the nanoparticles did not affect the foam structure or stability, which suggests the nanoparticles are likely in the aqueous phase stabilized by surfactant micelles. Since we did not observe a significant change in foam properties (bubble size based on the digital images, stability and time to break on a wet surface) upon addition of the nanoparticles to the formulation, further characterization of bubble size using optical microscopy were not pursued. In contrast to the ethanol-based foams considered above, the Tween had no effect on nanoparticle size or aggregation (Figure A.5). The hydrophobic anchoring block does not partition into the aqueous phase and particle stability is not compromised.

The foams are to perform as carriers for therapeutic nanoparticles and delivery of high concentrations of nanoparticles may be allow for local delivery of high drug concentrations. We tested the effect of particle loading on foaming, foam stability, and foam breakage using both PEG-based nanoparticles and anionic PMMA latex (300 nm), serving as a model nanoparticle. Foams with high nanoparticle loading could be achieved (Appendix, Figure A. 6) which still demonstrated triggered breakage. Formulations with 2 wt.% Tween 20 and 34 wt.% PMMA-latex nanoparticle also produced foams with foam volume to liquid volume

ratios of at least 10 that also began to drain immediately when applied to a moist surface at room temperature. The mechanism for breaking on a wet surface is thought to be related to the mechanism of interfacial stabilization by micellar structures. Certainly, a more quantitative understanding of the dependence of foam stability and the volume of the micelle phase in the presence of high concentrations of nanoparticles would be of interest.

Non-ionic surfactants with an HLB ~15 and a cloud point near physiological temperature may yield a temperature responsive foam similar to the system achieved with the long-chain alcohol, propellant based foam we described earlier. However, since surfactants with high HLB are preferred for foaming using the existing soap pump dispensers are soluble in water, they are responsive to moisture. When applied to a moist surface such as an internal body cavity, the foam will break due to local dilution as desired. For the intended application, foams that break upon application to physiological temperature or a moist surface is sufficient. Thus, non-ionic surfactants with high HLB (~15) required for foaming and a cloud point near physiological temperature for potential temperature responsiveness were not considered.

4. Conclusions

We have developed and evaluated two foam systems for nanoparticle delivery and triggered release. The common requirement is that the foam has a high volume fraction of gas so that upon breakage the nanoparticles can be delivered with minimal deposition of free liquid. The foams are stable at room temperature but can be designed to break in response to temperature or moisture. Temperature-responsive foams were formulated with long chain alcohols using medical grade nitrous oxide as a propellant and biocompatible Polysorbate 60 surfactants. The long chain alcohols are insoluble at room temperature producing a particulate-stabilized foam. The melting temperature of the long chain alcohol is tuned so that at physiological conditions of 37°C the melted alcohol is solubilized into the aqueous micellar solution, which triggers foam collapse. Fine tuning of the alcohol concentration to between 50-60 wt.% was required to balance the solubility of the N₂O foaming agent and the interfacial activity of the surfactants. In this narrow range of alcohol content foams with volume ratios greater than 6 were produced. The alcohol had an adverse effect on PEG-b-PS (5 kDa-b-1.6 kDa) nanoparticles but particles made with a less soluble PAA-b-PS (11.5-b-2.2K) were stable.

Moisture-responsive foams were made with commercially available foam pump dispensers and biocompatible Tween 20 surfactants. With these mechanically generated foams, high foam-volume to liquid-volume ratios (> 10) were produced. They could be loaded with PEG-stabilized therapeutic nanoparticles or with up to 30 wt.% model latex colloids. We anticipate that both approaches will be applicable vaginal and rectal therapeutic administration where temperature and moisture are potential triggering mechanisms. *In vivo* studies, which we are pursuing, will be required to determine which foam formulation route is best. The decreased liquid volume fractions required for the mechanically generated foams, and the stability of nanoparticles in the simpler surfactant mixtures, are advantages of the mechanically generated foams. The *in vivo* results on foam breakage and nanoparticle deposition will ultimately determine which foam administration route to apply.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Highlights

- Temperature-responsive foams based on phase change of fatty alcohols
- Moisture-responsive foams based on biocompatible detergents
- Both foam systems are easy to use and can be loaded with polymer nanoparticles
- Nanoparticle size not affected by incorporation into foam or foam break

Figure 1. Foam formulations visualized between crossed polarizers (a) at room temperature heated without polysorbate 60, (b) heated without polysorbate 60. The corresponding bulk samples are included as insets.

Figure 2. Foam to liquid volume ratios as a function of ethanol concentration for nitrous oxide based foams.

Figure 3. PEG-based nanoparticle loaded nitrous oxide foam breakage at room temperature and applied to a surface initially at 37°C. Nanoparticles contain Hostasol yellow dye for visualization and green tape was used to adhere the thermocouple to the plate during the heated plate experiment. Nanoparticle aggregation is evident upon foam break.

Figure 4.

PEG-based nanoparticle size distributions in water (solid circles) in 60% ethanol (solid squares) with 5:1 wt. PEI:wt. NP (empty triangles), 10:1 wt. PEI:wt. NP (empty circles), 20:1 wt PEI: wt. NP (empty squares) measured by DLS.

Figure 5.

Particle size distributions of the nanoparticles in water (dialyzed), in a 2 wt.% Tween 20 solution (foam formulation), and after foam break. Nanoparticles contain hostasol yellow dye for visualization.

Table 1

Sample temperature-responsive foam formulation

Component	Amount (wt.%)
Ethanol	58.21
Cetyl alcohol	1.16
Stearyl alcohol	0.53
Polysorbate 60	0.42
Propylene Glycol	2.11
Ultrapure water	36.21
Potassium hydroxide (10 wt.% aq.)	0.11
Food coloring	1.25