AAPS PharmSciTech 2007; 8 (3) Article 57 (http://www.aapspharmscitech.org).

Themed Issue: Process Analytical Technology
Guest Editor - Ajaz Hussain

Solventless Photocurable Film Coating: Evaluation of Drug Release, Mechanical Strength, and Photostability

Received: May 14, 2006; Final Revision Received: January 26, 2007; Accepted: January 31, 2007; Published: July 13, 2007

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ABSTRACT

A new solventless photocurable film-coating system was investigated in which nonpareil beads were coated in a mini-coating pan with liquid prepolymer (L) and powdered solid pore-forming agents (S) and cured by UV light. Release from the coating could by altered by changing the material, the number of layers, and the coating thickness. Immediate release of a blue dye contained in the nonpareils was obtained with sodium starch glycolate as a pore former that swelled the coating and yielded large pores; through these pores the dye quickly released while leaving behind the scaffold provided by the photocured prepolymer. Simple pore formers (lactose and sodium chloride) dissolved away without swelling and provided a more sustained release. The nature of the scaffold and pore structure of the coating were determined by simultaneously monitoring the release of sodium chloride from the coating and blue dye from the beads. At least 50% of the sodium chloride that was incorporated into the coating released before the dye released through the coating, except at an S/L ratio (ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer) of 2.4, where 40% of the sodium chloride was released before the release of dye. The coupling between dye release and pore formation was found to be dependent on the S/L ratio of the coating. Simulation based on percolation theory showed that the coupling of pore formation and dye release was higher when the variance in tortuosity was lower. The coating was photostable and could withstand normal handling stress.

KEYWORDS: Coating, photocurable, solventless, photoinitiator, process and formulation parameters, functional release, photostability.

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INTRODUCTION

Film coating is widely employed to improve aesthetic quality (eg, color, texture, mouth feel, taste masking), protect drugs from chemical or physical degradation, and modify drug release. With the general move toward "green" processing in all industries, solventless coating techniques are actively being explored in the pharmaceutical industry.[1] Unlike other solventless coating techniques that rely on changes in the physical state of the coating material to obtain a coating, photocuring is a chemical approach proposed to rapidly coat tablets at or below room temperature.[2,3] Photocuring systems generally consist of 3 major components: a UV/visible light source, specially functionalized liquid prepolymers or monomers, and an initiator.[4] Light generates a polymerization reaction that involves free radical, cationic, or anionic mechanisms, depending on the functional groups of the prepolymers or monomers and the initiators or catalyst used.[5] Chemical reaction of the functionalized liquid prepolymers or monomers results in transition from liquid to solid film. Oxygen can slow down and/or reduce the extent of curing in some acrylate-functionalized silicone systems by quenching excited states and scavenging free radicals from the initiator and the growing polymer network.[6] Thus, photocurable systems are usually purged with nitrogen to reduce this complication.

Photocuring has wide commercial application in dental and medical fields. Composite dental fillings,[7,8] preventive treatment for caries,[9-11] assembly of medical devices,[12] and wound dressing[13-17] are a few examples of its use. Photocuring for film coating of pharmaceuticals is still in the investigational stage. In an early report, norbornenyl polydimethylsiloxane prepolymers along with a photoinitiator, benzoin methyl ether (BME), were used with UV light to cure the derivatized silicone polymer films on nonpareil beads in small-scale coating equipment.[18] After curing, coatings of sufficient integrity were obtained in which chemical reaction of the functionalized liquid prepolymers resulted in a transition from liquid prepolymer to solid coating film. However, these silicone polymers were inherently useful only for preparing a complete and almost perfect barrier to drug release.[18]

A previous report described functional pharmaceutical coatings (eg, immediate, sustained, or enteric coatings) composed

of powdered pore-forming agents (superdisintegrants or simple pore formers) added to an acrylate silicone matrix.[19] That study evaluated different formulation and processing factors to delineate the design space for manufacturability of this solventless coating system. The formulation and processing parameters that were investigated along with their optimum operating ranges are listed in Table 1. Using a variety of pore-forming materials, we found that the ratio of the amount of solid pore-forming agent (S) to the volume of liquid prepolymer (L), or the S/L ratio; the particle size of the pore-forming agent; the concentration of the initiator; the light intensity; and the exposure time of light were critical to the coating efficiency (ie, the percent of coating material incorporated into the coated beads) and the uniformity of the coating as measured by image analysis of the color and shape of the coated beads.[19] A robust operating range was identified wherein the coating process could be operated with minimum variability in coating uniformity and maximum coating efficiency. Once the variability in the processing was reduced such that reliable batches could be produced, the pharmaceutical performance of the photocurable coatings could be assessed. This article reports on the pharmaceutical performance of the coating—drug release, mechanical strength, and photostability.

Materials and Methods

Materials

Two prepolymers, acryloxypropyl methylsiloxane homopolymer (HP) and acryloxypropyl methylsiloxane-dimethylsiloxane (15%-20% [acryloxypropyl] methylsiloxane–80%-85% dimethylsiloxane) copolymer (CP), were purchased from Gelest Inc (Morrisville, PA). The photoinitiator, BME, was purchased from Aldrich (St Louis, MO). Nonpareil beads (14-18 mesh) containing FD&C #1 as a marker dye were obtained from Ozone Confectioners (Elmwood Park, NJ). Explotab (sodium starch glycolate) was purchased from Penwest Pharmaceutical Co (Patterson, NY); the 45-63μ particle size fraction was used. Lactose (spray-dried, grade #315) was obtained from Foremost (Baraboo, WI); the 75-106μ particle size fraction was used. Polyethylene glycol 8000 (PEG) was obtained from Dow Chemical Co (Midland, MI); the 75-106μ particle size fraction was used. Sodium chloride was purchased from Fisher Scientific (Fairlawn, NJ); the 75-106μ particle size fraction was used. Ac-Di-Sol (croscarmellose sodium) was obtained from FMC Biopolymer (Newark, DE); the 45-63μ particle size fraction was used. All materials were stored as advised by the providers with no further processing.

Methods

Coating Process

Five grams of FD&C #1 containing nonpareil beads was placed in a mini-coating pan consisting of the bottom portion of a 500-mL Erlenmeyer flask in a rotating drum driven by an all-purpose motor (Erweka, Milford, CT). A chamber was fitted over the coating pan and continually purged with nitrogen at a rate of 0.5 L/min to reduce the presence of oxygen. The coating pan was rotated at 18 to 19 rpm. Through a small port in the chamber, the prepolymer liquid (HP:CP 95:5 and 1% wt/vol BME) was pipetted onto the bed of beads and allowed to distribute for 1 minute. Next, a powdered

Table 1. Summary of Formulation and Processing Parameters and Their Ranges/Values*

Factor	Range Investigated	Optimum Operational Range[19]	What the Factor Affects
Homopolymer-to-copolymer ratio	100:0 to 0:100	95:5	Film strength
Type of photoinitiator	Darocur, benzoin methyl ether	Benzoin methyl ether	Prepolymer-to-polymer conversion
Distribution times of polymer and pore-forming agents on beads to be coated	1-5 minutes	1 minute	Process efficiency and coating uniformity
S/L ratio	1.2-5.0	Material-specific	Process efficiency and coating uniformity
Particle size of pore former	45-325 μ	Material-specific	Process efficiency and coating uniformity
Concentration of photoinitiator (benzoin methyl ether)	0.1%-10% wt/vol	1% wt/vol	Prepolymer-to-polymer conversion
Exposure time	10 seconds to 5 minutes	2 minutes	Prepolymer-to-polymer conversion
UV light intensity	0.2-2 mW/cm^2	2 mW/cm^2	Prepolymer-to-polymer conversion
Nitrogen turnover time	1-10 minutes	3 minutes	Prepolymer-to-polymer conversion
Nitrogen flushing rate	0.1-2 L/min	0.5 L/min	Prepolymer-to-polymer conversion
Speed of coating pan	2-40 rpm	18-19 rpm	Process efficiency and coating quality

*The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

Table 2. Pore-Forming Agents and Their Optimum S/L Ratios for Optimum Process Efficiency and Coating Uniformity*

Pore-Forming Agent (particle size range)	Optimum S/L Ratio (ranges studied)	Amount of Pore Former (mg)	Volume of Liquid (μL)†
Lactose (75-106μ)	2.4 (1.8-3.0)	1200	500
Sodium chloride (75-106μ)	3.6 (3.0-4.2)	1800	500
Polyethylene glycol 8000 (75-106μ)	2.4 (2.1-2.7)	1200	500
Explotab (45-63μ)	3.0 (2.7-3.3)	1500	500
Ac-Di-Sol (45-63μ)	2.1 (1.8-2.4)	1050	500

*The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer. The S/L ratios used were found to be optimal in terms of coating efficiency and uniformity.[19] The operational range (in parenthesis) is the range where coating efficiency and uniformity are independent of S/L ratio.

†Homopolymer:copolymer 95:5 with 10% wt/vol benzoin methyl ether.

pore-forming agent (lactose, sodium chloride, PEG, Explotab, or Ac-Di-Sol) was dusted onto the bed of coated beads for 10 to 15 seconds and allowed to distribute for 1 minute. Table 2 lists the volume of L and S used to prepare batches with various S/L ratios found to produce optimal coating uniformity.[19] The chamber was purged with nitrogen for an additional 3 minutes. Finally, the beads were exposed to 2 mW/cm^2 of light (Spectroline, Model SB-100PC, Westbury, NY) through the front quartz panel of the nitrogen-filled chamber for 2 minutes. The coating procedure was repeated to produce 4 to 6 layers. All batches were prepared in triplicate.

Release Performance

From each of the 3 batches prepared for each set of conditions, coated beads (weight equivalent of 3 g of uncoated beads) were placed separately in a US Pharmacopeia (USP) type II apparatus (Vanderkamp 600, Vankel Industries, Inc, Chatham, NJ) with 250 mL of double-distilled water at 37°C stirred at 50 rpm. The release of FD&C blue #1 from the coated nonpareils was determined over a 1-hour period for immediate-release coatings and over 12 or 24 hours for sustained-release coatings. Absorbance of the released FD&C #1 was measured at λ_{max} = 628 nm in a UV spectrophotometer (Model 8450A, Hewlett-Packard, Palo Alto, CA). The release profiles were compared by similarity factor analysis.[20] Values of f_2 in the range of 50 to 100 ensure the equivalence of the 2 dissolution profiles.[20]

The pore structure of the coating was assessed by monitoring the release of sodium chloride (1 of the pore formers) by conductance (Model 34, YSI, Yellow Springs, OH) at the same time points that were used to monitor dye release.

Simulation of Percolation Through the Porous Coating

Each cell in a matrix of 110 × 110 × 6 was randomly set to either 1 (containing pore former) or 100 (containing undissolvable scaffold polymer matrix) in a proportion that reflected the volume ratio of pore former to polymer matrix. This simulation assumed Cartesian coordinates as a first approximation. An algorithm was written to search for the shortest possible path (ie, minimum number of connected [value = 1] cells) to connect pore-forming particles between the 6 layers in the inner 100 × 100 × 6 matrix to avoid end effects. In 1 simulation, the algorithm searched 21 possible connections, whereas in an enhanced algorithm, the search was increased to 30 possible ways to connect to the next layer. The cells that contained pore-forming particles in the first of 6 layers and that were also connected to a particle-containing cell or cells in the sixth layer were considered available surface pores. For the purposes of evaluating apparent diffusion through the film, the porosity was calculated as the fraction of available pores over total cells in the first layer. For each of those available pores, the minimum path through the 6 layers (generally, 6-12 cells) was calculated. The average path length divided by 6 (ie, the true film thickness) was reported as the tortuosity of the coating. The variance of the tortuosity was also calculated. It was noted that the enhanced algorithm resulted in higher porosities and lower tortuosities; the differences were more prominent at lower volume fractions of pore former, but the results were qualitatively similar in the curve shapes and inflection points.

Thickness of the Coating

The diameters of ~200 beads from each batch were determined using a 5.1-pixel charge-coupled device (CCD) camera and software (Image-pro, Media Cybernetics, Silver Spring, MD). The average thickness of the coating from each batch was measured by subtracting the average diameter of an uncoated batch from that of a coated batch of beads and dividing by 2. The means and SDs of these pairwise calculations were reported as average coating thicknesses and their SDs.

Mechanical Strength of the Coating

Six batches of nonpareil beads were coated with 4 layers of acrylate-terminated siloxane prepolymers (HP:CP 95:5 with

1% wt/vol BME) and lactose in an S/L ratio of 2.4. Samples from 3 batches of coated beads, equivalent to 3 g of uncoated beads, were stressed in a friabilator (TA, Erweka GmbH, Heusenstamm, Germany) at 25 rpm for 16 minutes for a total of 400 revolutions. The same amounts of coated beads from the remaining batches were used as controls. Beads were removed from the friabilator and placed in a USP type II dissolution apparatus with 250 mL of water at 37°C stirred at 50 rpm, and their profiles were compared. Samples were withdrawn at intervals and monitored for dye release at λ_{max} = 628 nm. The release of dye from the 3 control batches (ie, the batches not subjected to stress) was similarly monitored.

Photostability of the Coating

The photostability of the coating was evaluated using a light cabinet (CPS+ Suntest, Atlas Materials Testing Technology, Chicago, IL). Twenty-one batches of nonpareil beads were coated with 4 layers of acrylate-terminated siloxane prepolymers (HP:CP 95:5 with 1% wt/vol BME) with lactose as a pore-forming agent using an S/L ratio of 2.4. A portion of the coated beads (equivalent to 3 g of uncoated beads) from each batch was exposed to light according to International Conference on Harmonization (ICH) guidelines, with 1 dose of light equivalent to 1.2 million lux hours (ie, 21.8 hours with the irradiance of 250 W/m^2).[21,22] Three sets of samples of coated beads were exposed to 1, 2, or 3 doses of light in closed glass bottles placed on their sides for maximum light exposure (Qorpak clear glass bottles, 0.5 oz, AP #2101, Fisher Scientific, Springfield, NJ). As controls, 3 sets of samples were exposed to 1, 2, or 3 doses of light in closed glass bottles covered with aluminum foil. One set of samples of coated beads were directly exposed to 1 dose of light in an open glass petri dish. The temperature in the light cabinet was maintained at 30°C with a cooler attached to the instrument. All studies were done in triplicate. Each exposed coated batch and each control batch were separately placed in a USP type II dissolution apparatus with 250 mL of water at 37°C and a paddle speed of 50 rpm. Samples were withdrawn periodically and monitored for dye release at λ_{max} = 628 nm.

Results and Discussion

A previous study showed that the most significant parameter to the coating efficiency and coating uniformity of this solventless coating process was the S/L ratio of the solid pore-forming particles in the liquid photocurable polymer matrix.[19] The range of S/L ratios within which coating efficiency and uniformity remained high was determined for several pore-forming agents. For example, when Explotab was used as the pore-forming agent, the product quality in terms of coating efficiency and coating uniformity was greatest at an SL ratio between 2.4 and 3.6 (with 500 μL of prepolymer and 1200 to 1800 mg of Explotab per layer) when particle sizes of Explotab between 45 and 63μ were used. Thus, an S/L ratio of 3.0 (ie, the midpoint of 2.4 and 3.6) was selected for evaluation of the release when Explotab was used in the film in order to ensure the lowest inter-bead variability. The optimum S/L ratio for each pore former (Table 2) was used for the present study unless otherwise specified. In each case, we used the particle size range that allowed the widest range of S/L ratios to be used without reducing the coating efficiency or uniformity. Here, the release of a marker dye (contained in the beads) through pores formed by dissolution or swelling of pore-forming agents in the coating was investigated.

Release Studies Using Simple Pore Formers

Lactose was evaluated as a pore former at 3 S/L ratios and 4, 5, or 6 layers of coating using HP:CP 95:5 with 1% wt/vol BME. The optimum operational range in terms of S/L ratio for lactose was 1.8 to 3.0 where the coating uniformity was superior.[19] Therefore, 3 S/L ratios, 1.8, 2.4, and 3.0, were investigated to determine the effect of different S/L ratios as well as different coating layers on release.

At each S/L ratio, the release of dye from coated beads was significantly lower with each additional layer of coating over the 3-hour evaluation period (Figure 1). For the release from beads coated with 4, 5, or 6 layers, there was no significant effect on release profiles as a function of S/L ratio, except for 1 instance with 5 layers where the release was significantly greater from the coating with an S/L ratio of 1.8 than 3.0. While S/L has little or no effect on release, the number of layers has a more direct effect on release of dye through the coating. However, it was noted that both the number of layers and the S/L ratio affected the coating thickness (Figure 2A). The complex effect of S/L ratio and number of layers on the release of dye can be directly attributed to the thickness of the coating. The percent dye release was negatively correlated with coating thickness independent of S/L ratio or number of layers (Figure 2A). Thus, the S/L ratio, which was found to be a key factor in coating efficiency and coating uniformity, is not a significant factor in determining release in the range studied, except in its effect on thickness.

Sodium chloride was also evaluated as a pore-forming agent for this siloxane-based coating. The range of S/L ratios in which sodium chloride provided superior uniformity of coating was 3.0 to 4.2.[19] Dye release was measured with S/L ratios of 2.4, 2.7, 3.0, 3.6, and 4.2 with 4 layers of coating and with an S/L ratio of 3.6 with 6 layers of coating. Here, it should be noted that the 2 lowest S/L ratios (2.4 and 2.7) were outside of the optimal range in terms of coating efficiency. The rate of dye release increased with increasing

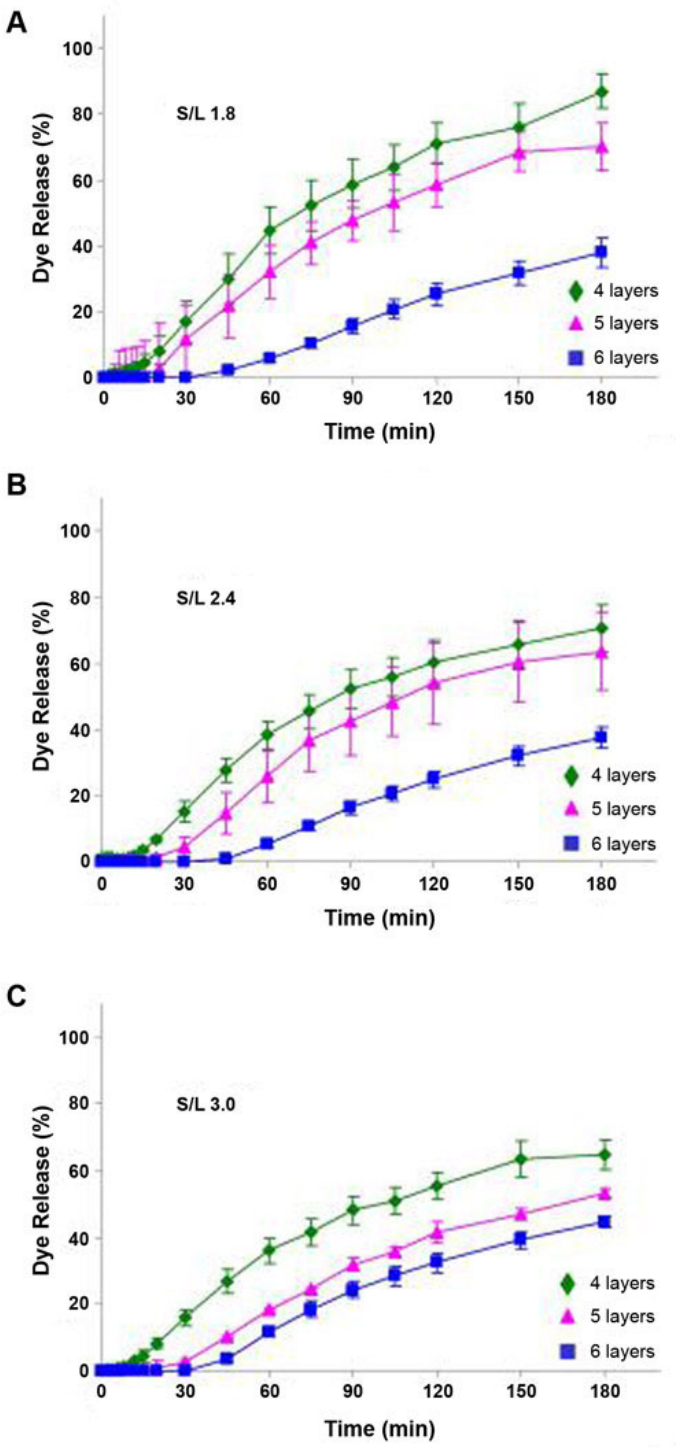

Figure 1. Dye release from nonpareil beads coated with 4, 5, or 6 layers of coating with liquid prepolymer and powdered lactose: (A) S/L ratio = 1.8, (B) S/L ratio = 2.4, and (C) S/L ratio = 3.0. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

S/L ratio (Figure 3A). When the number of layers of coating (S/L ratio 3.6) was increased to 6, there was a significant lag time (1 hour) for dye release (Figure 3A). Thus, as seen with lactose-filled coatings, the number of layers of coating and the S/L ratio affected release of the marker dye from the nonpareil beads. Again, the number of layers of coating was a more significant factor than the S/L ratio was. However, unlike with the lactose-filled coatings, the release of dye from the sodium chloride–filled coatings could not be explained simply by coating thickness (Figure 2B). A direct comparison of lactose- and sodium chloride–filled coatings showed that the release profiles of dye from 4 layers of coating incorporating either sodium chloride or lactose were remarkably similar at the 2 common S/L ratios (2.4 and 3.0) (Figure 4).

The release profiles of sodium chloride incorporated into the coatings made with S/L ratios of 2.4, 2.7, 3.0, 3.6, and 4.2 were measured. The release of sodium chloride from

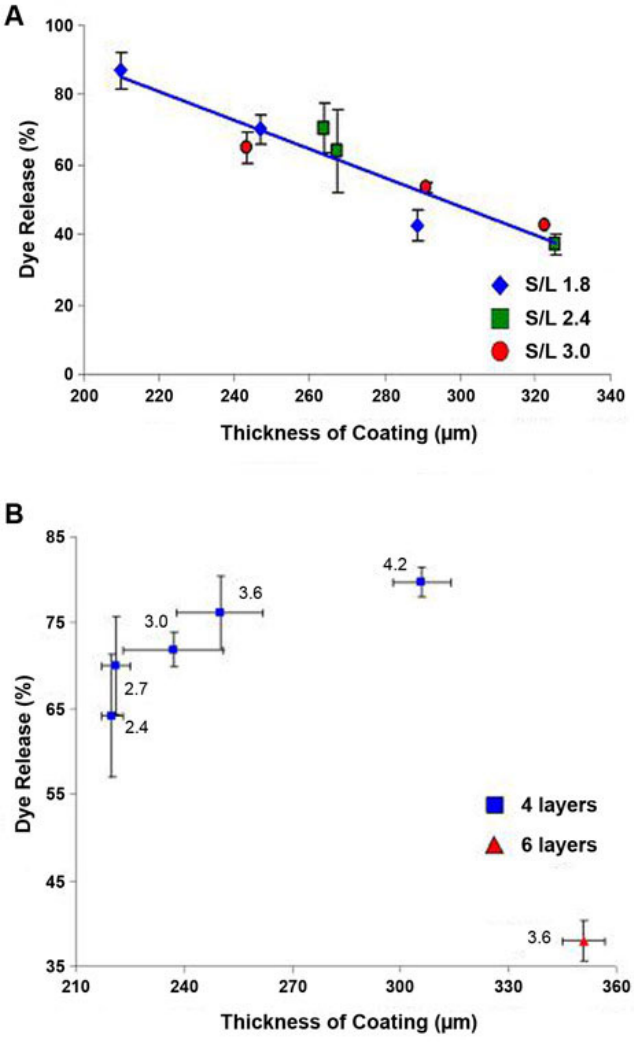

Figure 2. Dye release (at 180 minutes) from nonpareil beads coated with 4, 5, or 6 layers of coating as a function of measured coating thickness: (A) lactose with S/L ratios 1.8 to 3.0, and (B) sodium chloride with S/L ratios 2.4 to 4.2. In Figure 2B, the numbers next to each data point indicate the S/L ratio at that point. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

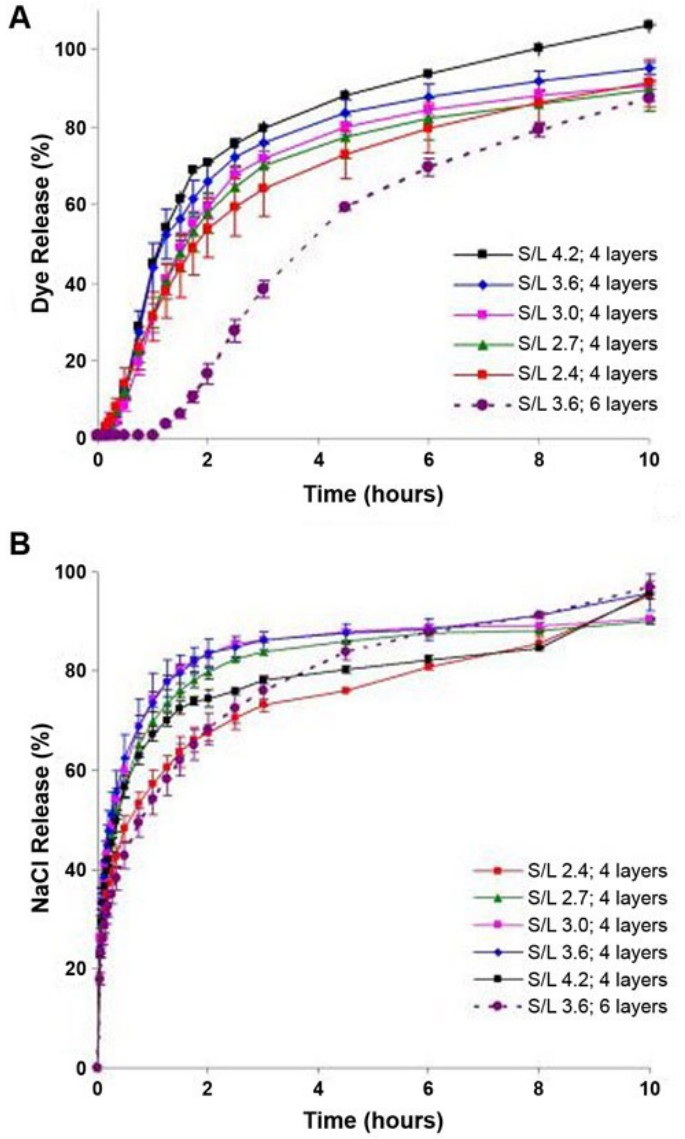

Figure 3. Release of (A) marker dye and (B) sodium chloride from the coated nonpareil beads, with 4 layers (or 6 layers) of coating using powdered sodium chloride in different S/L ratios. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

4-layer coatings with an S/L ratio of 2.4 was slower than the release from the 4-layer coatings with higher S/L ratios (Figure 3B). The 6-layer coatings with an S/L ratio of 3.6 initially released more slowly, but at 3 to 10 hours, the release was faster than it was for the corresponding 4-layer coating. A comparison between the release of sodium chloride from the coating and the release of dye from the bead is shown in Figure 5A in terms of the fraction of dye and sodium chloride released at corresponding time points. On average, 40% to 50% of the sodium chloride that was incorporated into the coating released before the dye released through the coating. This is not surprising, as pore formation is necessary prior to the release of the marker dye. There was a remarkably linear portion of each curve in Figure 5A, and this portion could be interpreted as a coupling between dye release and pore formation through sodium chloride release. The slope of that linear portion, which indicates the degree of coupling between the 2 release profiles, is called the release coupling coefficient. Figure 5B shows that the coupling between dye release and pore formation is dependent on the S/L ratio of the coating. The coupling value in Figure 5B indicates the rate of dye release relative to the rate of sodium chloride release (ie, pore formation) in the linear portion of the figure. A coupling value of 1 would indicate that the rates of dye release and sodium chloride release are equal. Higher values indicate that the release of dye is faster than the release of sodium chloride. At S/L ratios above 3.0, the release coupling is independent of the S/L ratio. However, below S/L ratios of 3.0, the release coupling coefficient increases with increasing S/L ratio. One explanation for this finding is that the 2 lower S/L ratios were outside the range of optimum coating efficiency.

An alternate explanation can be found in the variance in the tortuosity of coating determined by simulation. The coupling of pore formation and dye release would be expected to be higher when the variance in tortuosity is lower. A lower variance in tortuosity suggests that all the paths through the pores are similar, such that the difference between the time to form the first path and the time to form the last path upon dissolution of sodium chloride is small. The degree of coupling between release of sodium chloride from the coating and release of dye from the core would be expected to be high.

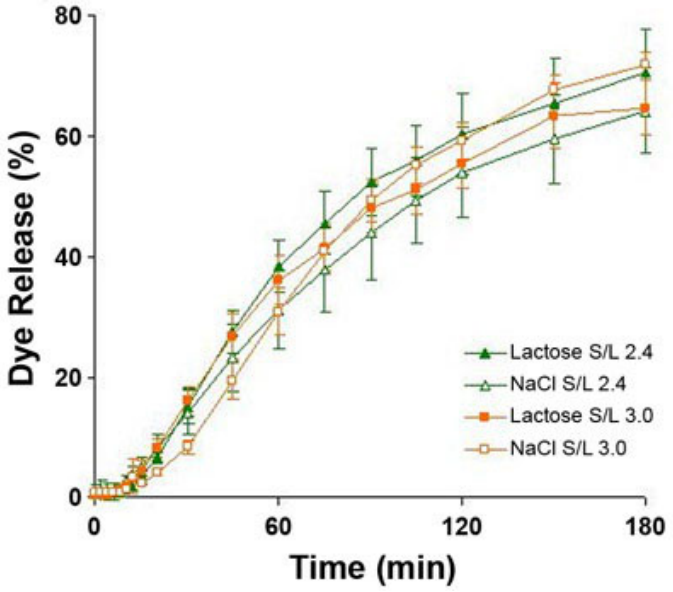

Figure 4. Dye release from nonpareil beads coated with liquid prepolymer and powdered lactose and sodium chloride (both with particle size 75-106μ) as pore-forming agents at S/L ratios of 2.4 and 3.0 with 4 layers of coating. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

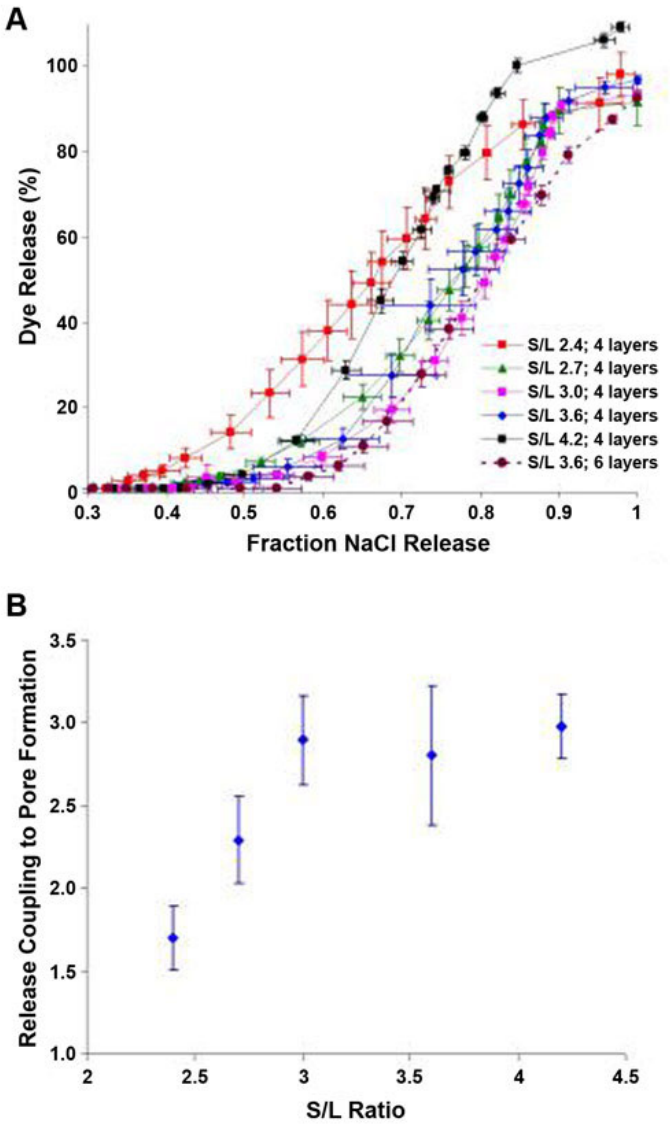

Figure 5. Nonpareil beads coated with 4 layers (or 6 layers) with liquid prepolymer and powdered sodium chloride with different S/L ratios: (A) dye released through the coating as a function of sodium chloride released from the coating at the same time point; (B) release coupling coefficient (slope of plot A) vs S/L ratio. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

On the other hand, a larger variance in tortuosity would mean that the first path is formed well in advance of the last, much more tortuous path, leading to a lower slope in Figure 5A. A simulation of the connectedness of pores remaining after the dissolution of the pore formers included in the coating at various volume fractions was done using percolation theory. Table 3 shows the tortuosity, porosity, and variance in porosity for 2 coatings as a function of their S/L ratio. The porosity increases and the tortuosity decreases as the S/L ratio increases. The apparent diffusion coefficient, which is a function of both porosity and tortuosity (ie, porosity/tortuosity), increases with S/L ratio, because the increase in porosity is greater than the decrease in tortuosity. It should be noted that not all of the sodium chloride in the coating was released, particularly at the lower S/L ratios, where some of the salt particles may be isolated and not available for release. Such a phenomenon was previously described experimentally by simulation in matrix systems.[23] Still, the increase in S/L ratio is accompanied by a dramatic decrease in the variance of tortuosity, indicating that there is a greater homogeneity of the paths through the coating at a high S/L ratio. With greater homogeneity of the paths, a higher coupling of release rates is expected and seen experimentally.

The use of PEG as a pore-forming agent was also explored. With an optimum range of S/L ratios between 1.8 to 3.0,[19] dye release was evaluated for beads coated with an S/L ratio of 2.4. The diameter and roundness uniformity were comparable to those of other pore formers, but the color uniformity of the coating was found to be significantly lower than that associated with other pore-forming agents.[19] The release of dye was faster than it was for sodium chloride and lactose (data not shown), probably because of the variation in coating uniformity (ie, comparatively higher interbatch diameter variation as well as roughness of the coated beads measured by roundness value). Thus, PEG was not considered a useful pore-forming agent for the coating system.

In summary, lactose and sodium chloride were found to be useful simple pore formers. In dissolution media, the powdered pore-forming agents slowly dissolved away and produced pores without swelling. When these pores connected with each other, they produced channels in the coating through which the dye was released. Simple pore formers provided a sustained profile of release of dye from the core.

Release Studies Using Superdisintegrants to Form Swollen Pores

The dissolution profiles of coatings containing Explotab or Ac-Di-Sol as pore formers were evaluated over 1 hour. It was observed that when coatings containing Explotab came into contact with the dissolution media, Explotab swelled the coatings without breakage to form larger pores than those formed by lactose or sodium chloride. The time for 80% release of the dye from the nonpareil was 7 minutes, and 100% of the dye was released within 15 minutes (Figure 6). The immediate release from the superdisintegrant-filled coatings is in sharp contrast to the slower release from the lactose- and sodium chloride–filled coatings. For beads coated with Ac-Di-Sol as the pore-forming agent, the total release of dye plateaued at 70%. It was observed that coatings filled with Ac-Di-Sol agglomerated to form a thick gel at the bottom of the dissolution vessel. Thus, Ac-Di-Sol was not investigated further.

Table 3. Data on Tortuosity, Porosity, and Tortuosity Variance for Various Coatings as a Function of S/L Ratio of Lactose and Sodium Chloride Simulated Using Percolation Theory*

Solid Fraction	Corresponding Lactose S/L Ratio	Corresponding Sodium Chloride S/L Ratio	Porosity	Tortuosity	Tortuosity Variance
0.30	0.7	0.9	0.07	1.56	2.85
0.35	0.8	1.2	0.17	1.52	2.71
0.40	1.0	1.4	0.27	1.48	2.44
0.45	1.3	1.8	0.38	1.43	2.07
0.50	1.5	2.2	0.46	1.36	1.63
0.55	1.9	2.6	0.53	1.31	1.25
0.60	2.3	3.2	0.59	1.25	0.95
0.65	2.9	4.0	0.65	1.21	0.72
0.70	3.6	5.1	0.69	1.17	0.58
0.75	4.6	6.5	0.75	1.14	0.46
0.80	6.2	8.7	0.80	1.11	0.37

*The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

In general, the data show that release can be modified by changing the material, the number of layers, and the thickness of the coating. Release can be further modified as required by mixing fast-releasing and slow-releasing beads. For example, a mixture of 10% beads coated with Explotab as the pore former and 90% beads coated with lactose as the pore former provided a more sustained release with no time lag (Figure 7).

Mechanical Strength and Photostability

Friability testing is often used to evaluate the mechanical strength of dosage forms. This handling stress test may cause some defects in the coating that are not visually identifiable but may affect the functioning of the coating. Therefore, release profiles were evaluated before and after the friability test. The pore former lactose produced a sustained-release profile with a lag time (Figure 1B). If there were defects (ie, microcracks) in the coating due to the stress, the time lag would be shortened or eliminated from the release profile. The release profiles from the stressed and the unstressed sets of coated beads were not significantly different, based on similarity factor analysis and t test ($\alpha = 0.05$) for all time points (Figure 8). This result suggests that the coating is strong and can withstand the usual handling stress during manufacturing and shipping.

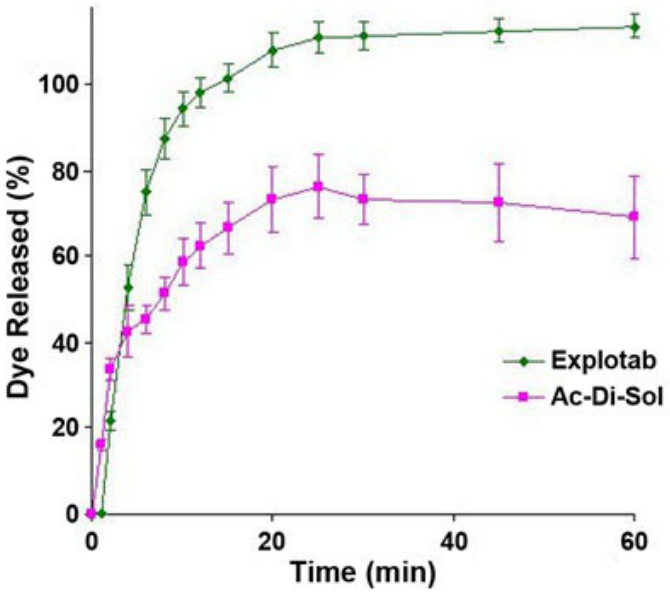

Figure 6. Dye release from nonpareil beads coated with 4 layers of liquid prepolymer and powdered Explotab or Ac-Di-Sol.

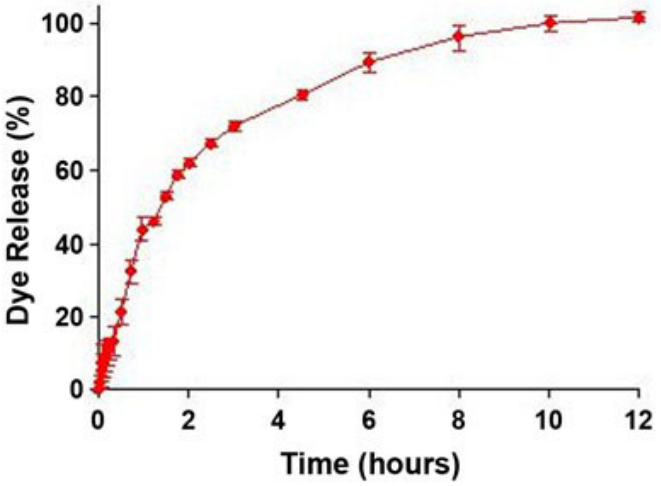

Figure 7. Dye release from nonpareil beads coated with liquid prepolymer and powdered lactose (5 layers of coating, S/L ratio 2.4) or Explotab (4 layers of coating, S/L ratio 3.0) where 10% of the beads contained Explotab as the pore former and 90% of the beads contained lactose as the pore former. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

As noted above, in photostability studies, 1 dose of light is defined as 1.2 million lux hours (ie, 21.8 hours with the irradiance of 250 W/m^2).[21,22] This is equivalent to 1 year of exposure to sunlight in Arizona. Coated beads were treated to 3 light conditions: (1) exposed to light in closed glass bottles, (2) directly exposed to 1 dose of light in an open glass petri dish, and (3) placed in the light cabinet in closed glass bottles covered with aluminum foil as a control. When the dye release profiles of the exposed and control batches were compared and analyzed by similarity factor (f_2) analysis,[20] it was found (Figure 9) that the release profiles were not significantly different (f_2 >50 in all cases). This result demonstrates that the function of the coating is photostable according to ICH guidelines.

Conclusion

It is possible to obtain functional (ie, sustained or immediate) release from solventless photocurable coatings. Lactose and sodium chloride were found to provide a more sustained release, whereas Explotab was found to be useful as an immediate-release pore former. This coating technique provides the flexibility to modify the release by changing the pore-forming material or the number of layers of coating as well as by mixing different coatings made by different pore-forming agents. Finally, studies demonstrated that the coating is photostable (according to ICH guidelines) and can withstand handling stress.

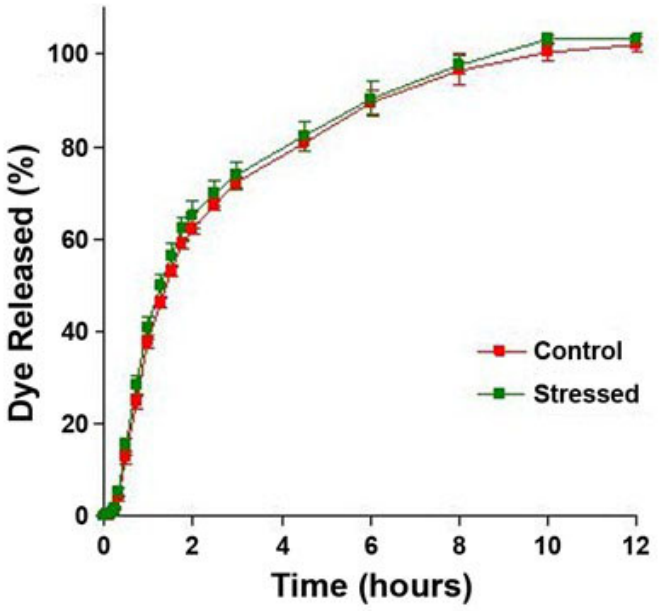

Figure 8. Dye release from nonpareil beads coated (with 4 layers) with liquid prepolymer and powdered lactose in an S/L ratio of 2.4. A portion of each batch of the coated beads was stressed in a friabilator. The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

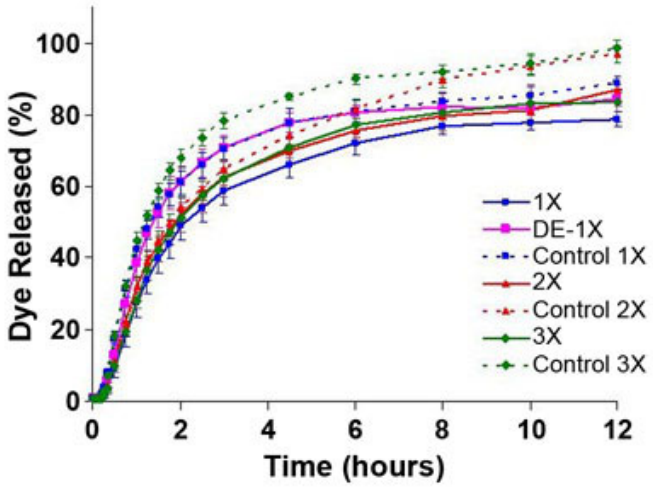

Figure 9. Dye release from nonpareil beads coated (with 4 layers) with liquid prepolymer and lactose (S/L ratio 2.4). Coated beads were either directly exposed to 1 dose of light or exposed to 1, 2, or 3 doses of light in closed glass bottles or closed glass bottles wrapped in aluminum foil (as controls). The S/L ratio is the ratio of the amount of solid pore-forming agent to the volume of liquid prepolymer.

Acknowledgment

The authors acknowledge the assistance of summer interns Brendan Kelly, Rosemary Ndolo, and Rose Tran. The authors also acknowledge the help of Dr Sheri Shamblin in performing the photostability studies. Financial support for this project was provided by the National Science Foundation Center for Pharmaceutical Processing Research (CPPR), now the Dane O. Kildsig CPPR.

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