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# Solventless visible light-curable coating: I. Critical formulation and processing parameters

Sagarika Bose[a,1], Robin H. Bogner[a,b,*]

[a] Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, 69 North Eagleville Road, Storrs, Connecticut 06269, United States
[b] Institute of Material Science, University of Connecticut, 97 North Eagleville Road, Storrs, Connecticut 06269, United States

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ABSTRACT

Film coating is generally accomplished by spraying polymers dissolved in solvents onto a cascading bed of tablets. The limitations associated with the use of solvents (both aqueous and organic) can be overcome by the use of solventless coating technologies. In this proposed solventless photocurable film coating system, each layer of coating onto the pellets (non-pareil beads) was formed using liquid photocurable monomer, powdered pore-forming agents, photosensitizers and photoinitiators in a mini-coating pan and later cured by visible light. Yield, coating efficiency, variation in color, diameter and roundness were determined for each batch to evaluate process efficiency and coating quality. It was found that the ratio (S/L ratio) of the amount of solid (S) pore-forming agent to volume of liquid (L) monomer, particle size and type of the pore-forming agent, concentration of initiator, and total exposure (light intensity × exposure time) of light were critical formulation and processing parameters for the process. Using lactose as a pore-forming agent, an optimum ratio of pore-forming agent to photocurable polymer was 1.8–3.0 to achieve good process efficiency and uniformity. The ratio was sensitive to particle size and type of pore-forming agent.

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## 1. Introduction

Film coatings are often applied to drug particles, drug loaded pellets, tablets and capsules to provide modified or delayed release characteristics (Porter, 1982). However, there are several disadvantages associated with organic (toxicity, flammability, higher cost) and aqueous (use of heat and water) based coatings. In response to the issues associated with the use of solvents including water, several solventless coating techniques are being investigated. Compression coating (or dry coating or press-coating) (Ozeki et al., 2004), hot-melt coating (Achanta et al., 1997; Kennedy, 1995), super-critical fluid coating (Thies et al., 2003; Tom and Debenedetti, 1991), dry powder coating electrostatic coating (Grosvenor, 1991) and photocuring are the primary methods being investigated for solventless pharmaceutical coating (Bose and Bogner, 2007).

Photocuring is an alternative solventless coating method that often involves a free-radical polymerization reaction. Functional moieties on the liquid photocurable materials react to form a solid crosslinked network. The photocuring system has three major components: a light source, specially functionalized liquid prepolymer or monomers, photoinitiator and/or photosensitizer (Pappas, 1985). Photocurable systems are usually purged with nitrogen to reduce the presence of oxygen which can slow down and/or reduce the extent of curing in acrylate or methacrylate terminated prepolymer/monomer systems by acting as a scavenger in free-radical reaction (Decker et al., 1980) and also by quenching excited states. Among the photocurable materials that have been studied, acrylate or methacrylate-functional prepolymers and monomers are the most widely used (Otsubo et al., 1984).

Photocuring has wide application in the paint, adhesive and photo-imaging industries (Roffey, 1982, 1986, 1998) as well as in the dental and medical fields (Kurze, 1994), specifically in composite dental filling (Lovell et al., 2001; Tanoue et al., 1998), preventive treatment for caries (Wilder et al., 1999, 1983), assembly of medical devices (Burger, 2000), and wound dressing (Lee et al., 1992; Szycher et al., 1985, 1986a, 1986b; Trotter, 2002). However, the pharmaceutical industry has yet to use photocuring in commercial applications. Savage and Clevenger explored the use of water-soluble photocurable polymer systems for coating pharmaceutical dosage forms using visible or ultra violet light. Their process included the aqueous coating of hydroxyethyl methacrylate and subsequent photocuring (Savage and Clevenger, 1996a, b). Solventless photocuring was previously investigated for phar-

* Corresponding author at: Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, 69 North Eagleville Road, Storrs, Connecticut 06269, United States. Tel.: +1 860 486 2136; fax: +1 860 486 2076.
*E-mail addresses:* bosesagarika@gmail.com (S. Bose), robin.bogner@uconn.edu (R.H. Bogner).
[1] Current affiliation: Pfizer Inc, 401 N. Middletown Road, Pearl River, NY 10965, United States. Tel.: +1 860 888 9127.

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maceutical coating. Ultraviolet light was used to cure derivatized silicone polymer films on pellets or non-pareil beads in small scale coating equipment; coatings of sufficient integrity were obtained (Wang and Bogner, 1995). However, the silicone films formed a complete and almost perfect barrier to drug diffusion. In an extension of that work, functional photocurable coatings were applied by incorporating different powdered pore-forming agents to the photocured silicone coating matrix. That process involved UV light to cure the acrylate terminated siloxanes (Bose and Bogner, 2006). The yield and process efficiency of the photocurable coating system were 95% and 85%, respectively. The type, particle size and level of the pore-forming agents in the coating as well as the intensity and time of exposure to UV light and initiator concentration were found to be critical for the process (Bose and Bogner, 2006). These parameters were optimized to minimize intra-batch and inter-batch variation of the process.

While the UV photocured coating of siloxane systems was shown to be successful, the toxicity profiles of those siloxanes is unknown at this time. Tetraethyleneglycol dimethacrylate (TEGDMA) and bisphenol A-glycidyl methacrylate (Bis-GMA) are two photocurable monomers that are extensively used in dental composites. Their toxicity is acceptably low and their mechanical strength is in an appropriate range for pharmaceutical coating (Pereira et al., 2005). The current work investigates the feasibility of using visible instead of ultraviolet light, and photocurable monomers, photoinitiators and photo-sensitizers which are generally used in dental practice (Atai et al., 2004; Hussain Latiff et al., 2005; Imazato et al., 2001, 1999; Kim and Jang, 1996; Lu et al., 2004; Mendes et al., 2005; Tarumi et al., 1999) for solventless coating.

## 2. Materials and methods

### 2.1. Materials

Two photocurable monomers, tetraethyleneglycol dimethacrylate (TEGDMA) and bisphenol A-glycidyl methacrylate (Bis-GMA), were obtained from Rohm America (Piscataway, NJ) and ESS Tech (Essington, PA), respectively. Camphorquinone (CQ), a photosensitizer, and 2-(dimethylamino) ethyl methacrylate (DMAEMA), a photoinitiator, were obtained from Aldrich (St Louis, MO). Non-pareil beads (14–18 mesh) containing FD&C#1 as a marker dye were available from Ozone Confectioners (Elmwood Park, NJ). Explotab® (sodium starch glycolate) was obtained from Penwest Pharmaceutical Co. (Patterson, NY). Lactose (spray dried, grade# 315) was available from Foremost (Baraboo, WI). Polyethylene glycol 8000 (PEG) was obtained from Dow Chemical Company (Midland, MI). Talc and sodium chloride were obtained from Fisher Scientific (Fairlawn, NJ). Ac-Di-Sol® (croscarmellose sodium) was obtained from FMC Biopolymer (Newark, DE). All materials were stored as advised by the providers.

### 2.2. Methods

#### 2.2.1. Uncured material

*2.2.1.1. Wetting of solid pore-forming agents by liquid monomer.* The contact angles of the monomer and/or solution (TEGDMA alone and TEGDMA:Bis-GMA 50:50) on each of several pore-forming agents (lactose, Explotab®, Ac-Di-Sol®, PEG, and sodium chloride) and pellets (non-pareil beads) and talc were determined. Compacts of the powders with 10% porosity were prepared using a Carver press (Hydraulic Press, Hydraulic Unit Model # 3912, Carver Inc., Wabach, IN). The porosity of the tablet was calculated from the tablet weight, tablet volume, and thickness and true density of powders. The porosity was controlled at 10% as it was achievable for all the powder compacts. A single drop of liquid monomer was carefully placed on the compact and the contact angle between a drop of liquid monomer and each compact was determined using a magnifier and a goniometer. All experiments were performed in 10 replicates.

The drop penetration method (Hapgood et al., 2002) was also used to evaluate wetting of pore-formers by the liquid monomers. Loosely packed beds of powders (45–150 μm) were leveled in an 85 mm diameter by 18 mm deep Petri dish using a metal spatula. A syringe with a 27.5 gauge needle positioned just above the bed surface delivered a drop of liquid monomer. The time required for the drop to penetrate completely into the porous substrate was recorded. All experiments were performed in 10 replicates.

*2.2.1.2. Viscosities of photocurable monomers.* Viscosities of TEGDMA and mixtures of TEGDMA:Bis-GMA (100:0, 80:20, 70:30, 60:40, 50:50 and 40:60 (w/w)) were determined at room temperature by cone-plate viscometry at a shear rate of $3\,s^{-1}$ (Model# DV-I, Brookfield Engineering Laboratories, Inc., Stoughton, MA). All experiments were performed in triplicate.

#### 2.2.2. Free films

*2.2.2.1. Initiators.* FTIR was used to determine the degree of conversion (i.e., crosslinking) of the coating monomer, TEGDMA, using combinations of two photoinitiators, CQ (0.5–3%, w/v) and DMAEMA (1.5–15%, w/v) using visible light at ~400 nm. The intensity of the light source (Right Touch, Work light, Model # RT-83992, Fountain Valley, CA) was measured using a light meter (Traceable® dual-display light meter, Friendswood, TX). TEGDMA and each proportion of photoinitiator–photosensitizer mixture were mixed well in the dark for 30 min to obtain a clear solution. Films composed of TEGDMA and various combinations of CQ and DMAEMA were cast separately as free films on disposable polyethylene FTIR cards (Model #0020-300, Thermo Electron, Madison, WI) by spreading a drop (5 μl) of the liquid on the card slot. Free films were made without the pore-forming agents due to the difficulty of evenly spreading films with the powdered pore-formers. The film-coated card was placed in a quartz chamber, purged with nitrogen for 3 min, and exposed to a known intensity (82500 lux) of visible light for different exposure times (30–600 s).

The degree of curing (i.e., percent conversion of monomer to polymer) was assessed by measuring the loss of the C=C peak ($1635\,cm^{-1}$) of the acrylate moiety on the TEGDMA using FTIR. The peak height at $1635\,cm^{-1}$ before and after curing provided direct measurement of the extent of curing of the monomer by the equation below. Measurements were made in triplicate.

$$\%\,\text{conversion} = \left(1 - \frac{\text{peak height at } 1635\,cm^{-1} \text{ after curing}}{\text{peak height at } 1635\,cm^{-1} \text{ before curing}}\right) \times 100$$

*2.2.2.2. Film hardness.* The hardness of the films was measured using the Standard Test Method for Film Hardness by Pencil Test (ASTM 3363-00). TEGDMA and Bis-GMA were mixed in several proportions (TEGDMA:Bis-GMA 100:0, 90;10, 80:20, 70:30, 60:40, 50:50 and 40:60 (w/w)). The photosensitizer and photoinitiator, CQ and DMAEMA, at concentrations of 2 and 8 wt% (totaling 10 wt% of the coating solution), respectively, were mixed into the solution of the monomers to prepare the coating liquid. The coating liquid (500 μl) was poured into a glass ring (40 mm diameter) on a glass surface in a quartz chamber, purged with nitrogen for 3 min and exposed to visible light (82500 lux) for 5 min to form a solid film. Pencils (Berol Turquoise) of increasing hardness (6B, 5B, 4B, 3B, 2B, B, HB, F, H, 2H, 3H, 4H, 5H, 6H) were held at a 45° angle and pushed along the photocured film until a pencil was found that did not scratch the film. The hardness number of the last pencil that did not scratch the film was recorded as the scratch hardness.

**Table 1**
Viscosities of TEGDMA and Bis-GMA mixtures at a shear rate of 3 $s^{-1}$ and their respective film quality and hardness (ASTM 3363-00) when cured with 10% (w/w) of 1:4 CQ:DMAEMA for 5 min at 82500 lux intensity of visible light in a nitrogen-purged quartz chamber. Values in parentheses are the standard deviations of three replicates.

| Composition TEGDMA:Bis-GMA | Uncured liquid viscosity (cps) | Hardness of cured films | Film quality |
|---|---|---|---|
| 100:0 | 10.6 (0.3) | 2H | Flexible but weak |
| 90:10 | 19.1 (3.3) | 2H | Flexible but weak |
| 80:20 | 32.4 (1.9) | H | Flexible and improved strength |
| 70:30 | 47.2 (1.2) | 2H | Strong and flexible |
| 60:40 | 102 (7) | 2H/H | Very strong, not flexible |
| 50:50 | 281 (28) | 2H/H | Very strong, not flexible |
| 40:60 | 631 (30) | 2H | Very strong, not flexible |

*2.2.3. Evaluation of the coating on beads*

*2.2.3.1. General description of the coating process.* Dye-containing pellets (non-pareil beads, containing FD&C #1) were used as model pharmaceutical dosage forms to reduce batch size while maintaining an adequate sample population of cores to evaluate process efficiency and coating quality. Five grams of the dye-containing pellets (non-pareil beads) were placed in a mini-coating pan, consisting of the bottom portion of 500 ml Erlenmeyer flask in a rotating drum driven by an all-purpose motor (Erweka, Milford, CT). A Plexiglas chamber was fitted over the coating pan and continually purged with nitrogen at a rate of 0.5 L/min (providing one turnover of the chamber volume each minute) to reduce the presence of oxygen. Through a small port in the chamber, generally 300, 500 or 700 μl of coating liquid consists of 70:30 TEGDMA:Bis-GMA (90% (w/w) and 1:4 CQ:DMAEMA (10% (w/w) was introduced onto the bed of beads and allowed to distribute over the beads for a period called the distribution time of polymer. Next, a powdered pore-forming agent, generally 900, 1200 or 1500 mg, was dusted onto the bed of coated beads within 10–15 s and allowed to distribute for a period called the distribution time of pore-forming agent. The chamber was purged with nitrogen for an additional 3 min. Finally, the beads were exposed to visible light through the front quartz panel of the Plexiglass nitrogen-filled chamber. The intensity of visible light at 5 in. from bed of the beads was 82500 lux. The coating procedure was repeated to produce a number of layers. In all batches described below, the pan rotation speed was set at 18–19 rpm. All batches were prepared in triplicate.

*2.2.3.1.1. Effect of distribution times of monomer and pore-forming agent, and the ratio of the amount of pore-forming agent (S) to volume of liquid monomer (L) on process efficiency and uniformity.* Distribution times of monomer and pore-forming agent were evaluated by coating the non-pareil beads with four layers of coating, each layer consisting of 500 μl of coating liquid consists of 70:30 TEGDMA:Bis-GMA (90% (w/w) and 1:4 CQ:DMAEMA (10% (w/w) and 1200 mg of lactose. Three distribution times of liquid monomer (1, 3 and 5 min) and three distribution times of pore-forming agent (1, 3 and 5 min) were used to determine optimum distribution times.

In another set of batches, lactose (75–106 μm) and coating liquid consists of 70:30 TEGDMA:Bis-GMA (90% (w/w) and 1:4 CQ:DMAEMA (10% (w/w) were applied in four layers onto the beads at three levels (900 mg, 1200 mg and 1500 mg of lactose and 300, 500 and 700 μl of liquid coating solution). Similarly, four other pore-forming agents (Explotab®, Ac-di-sol®, sodium chloride, and PEG) were also applied in various ratios with the same photocurable liquid composition. The particle size for the simple pore-formers (lactose, sodium chloride and PEG) was 75–106 μm. The particle size of the super-disintegrants, Explotab® and Ac-di-sol®, was 45–63 μm. All batches were prepared in triplicate.

Each batch was assessed for yield, coating efficiency and uniformity. *Yield* was calculated as the percentage of the weight of single coated beads to the total weight of coated beads obtained in the process (including doublets, triplets and agglomerates that would be normally rejected from a batch). *Coating efficiency* was a measure of how much of the polymer and pore-forming agent were effectively incorporated during the process. Coating efficiency was calculated by dividing the weight of all coated singlet beads by the weight of all the polymers, pore-forming agents, and beads used in the process.

It was seen from the preliminary studies that with six or more layers of coating, the blue beads became uniformly white. To distinguish any differences in coating uniformity, only four layers of coating were applied to the blue non-pareil beads such that any differences in color uniformity could be distinguished. Uniformity of the coating was measured by image analysis (Kennedy and Niebergall, 1997). Briefly, digital images of each sample were acquired with a 5.1 pixel CCD camera using image analysis software (Image-pro®, Media Cybernetics, Silver Spring, MD). The optical density (using the red channel) of each bead in samples of 200 beads was evaluated. In addition, the diameter and the roundness (perimeter = $\pi \times$ diameter, roundness = perimeter$^2/4 \times \pi \times$ area) of each of 200 beads were determined using Image-pro® software. The inter-bead standard deviations in optical density and diameter as well as average roundness of approximately 200 beads from each batch were utilized as measures of coating uniformity.

*2.2.3.1.2. Effect of viscosity of liquid monomer and particle size of pore-forming agents on process efficiency and coating uniformity.* Seven particle size ranges of the pore-forming agent, lactose (45–63, 75–106, 106–150, 150–180, 180–212, 212–250 and 250–300 μm), and different combinations of TEGDMA and Bis-GMA (TEGDMA:Bis-GMA 100:0, 90:10, 80:20, 70:30, 60:40, 50:50 and 40:60 (w/w)) having wide range of viscosities (Table 1) were used to coat beads. The photocurable coating liquid consisted of 90% (w/w) of different proportions of TEGDMA:Bis-GMA as described above and 10% (w/w) of 1:4 CQ:DMAEMA. Four layers of coating were applied with S/L (i.e., solid pore-former to liquid monomer) ratios of 2.4. All batches were prepared in triplicate. The coating uniformity, yield and coating efficiency of each batch were determined as described in Section 2.2.3.1.1.

*2.2.3.1.3. Effect of initiator concentration, light intensity and exposure time on degree of curing.* Beads were coated with three layers each consisting of 500 μl of liquid monomer mixtures (90% (w/w) of 70:30 TEGDMA:Bis-GMA) and 1200 mg of lactose. Two levels of photosensitizer:photoinitiator (10% and 15% (w/w) at 1:4 ratio CQ:DMAEMA), three levels of light intensity (4100, 37800 and 82500 lux) and six exposure times (5, 10, 15, 20, 30, 45 min) were used for a $2 \times 3 \times 6$ factorial design. After curing, the coating was scraped off samples of beads, finely ground, and analyzed by ATR-FTIR. The ratio of peak height at 1633 $cm^{-1}$ (C–H) to the peak at 1507 $cm^{-1}$ (C=O), the internal standard, was determined. Percent conversion of monomer to polymer was calculated using the ratio before curing and ratio after curing.

$$\%\,\text{conversion} = \left(1 - \frac{\text{ratio of peak height at } 1633\,\text{cm}^{-1} \text{ to at } 1507\,\text{cm}^{-1} \text{ after curing}}{\text{ratio of peak height at } 1633\,\text{cm}^{-1} \text{ to at } 1507\,\text{cm}^{-1} \text{ before curing}}\right) \times 100$$

## 3. Results and discussion

Photocuring has wide applications in the medical, dental and chemical industries, but no current application in pharmaceutical coating. In this paper, the feasibility of a solventless pharmaceutical film coating technique was evaluated to determine the formulation and processing parameters key to optimizing the coating uniformity.

### 3.1. Evaluation of wetting of pore-formers by monomers

Good wetting is essential for (1) adhesion of the liquid monomer to the bead and (2) the incorporation of powdered pore-forming agents into the thin liquid monomer film. The contact angles and penetration times of TEGDMA and 50:50 TEGDMA:Bis-GMA solution on a variety of pharmaceutical powders were measured. Note that the contact angles and penetration times of pure Bis-GMA could not be determined due to its viscosity (~1200 Pa s) (Kalachandra et al., 1993; Morgan et al., 2000; Pereira et al., 2002). The liquid, TEGDMA, had remarkably short penetration times through most materials, while the more viscous 50:50 TEGDMA:Bis-GMA liquid took longer to penetrate. The penetration times and contact angle measurements indicate that a variety of pore-formers can be incorporated into the polymer layers in seconds. In general, these two monomers can wet a wide range of pharmaceutical powders, thus this coating process can be used with various pore-forming agents (Table 2). The pure monomer and monomer mixture had significantly higher drop penetration times through talc indicating that talc may not be suitable as a pore-former in this coating system.

### 3.2. Comparison of initiators

The degree of conversion of liquid TEGDMA to solid polymer was found to be dependent on both the total concentration of initiators and their ratio (Fig. 1). Of all initiator ratios and concentrations studied, the 3% CQ and 12% DMAEMA system yielded the maximum percent conversion (90%) in 10 min (Fig. 1). All 2 wt% CQ combinations with different ratios of DMAEMA (1:3, 1:4 and 1:5) yielded conversions of 79–84%. In general, the 1:4 ratio of CQ:DMAEMA yielded the most rapid and greatest extent of conversion as has been previously reported (Yoshida and Greener, 1993). In all 2% CQ systems (Fig. 1B) and the 3% CQ with 12% DMAEMA (Fig. 1C), there was no significant difference in curing between 3 min and 10 min exposure to light (by Student's $t$-test, $\alpha = 0.05$). The combination of 2% CQ and 8% DMAEMA yielded adequate conversion (83%). The 90% conversion obtained using higher concentrations (3% CQ with 12% or 15% DMAEMA) was not considered to be of practical benefit over that obtained using the lower initiator concentration (2% CQ and 8% DMAEMA). Thus, CQ and DMAEMA at a total concentration of 10% (w/w) in a 1:4 ratio were employed as photosensitizer and photoinitiator in further experiments with visible light curing. The percent conversion achieved (83%) is comparable if not superior to that reported in non-pharmaceutical applications (Atai et al., 2004; Hussain Latiff et al., 2005; Imazato et al., 2001, 1999; Kim and Jang, 1996; Lu et al., 2004; Mendes et al., 2005; Tarumi et al., 1999).

### 3.3. Evaluation of monomer composition on liquid viscosity and film hardness

The ratio of monomers affects both the viscosity of the uncured liquid as well as the properties of the cured film. The viscosities of mixtures of the TEGDMA and Bis-GMA at different proportions are shown in Table 1. Mixtures ranging from 40 to 100 wt% TEGDMA have viscosities (102–11 cps) that would allow them to be easily sprayed in a coating process. Note that mixtures were clear indi-

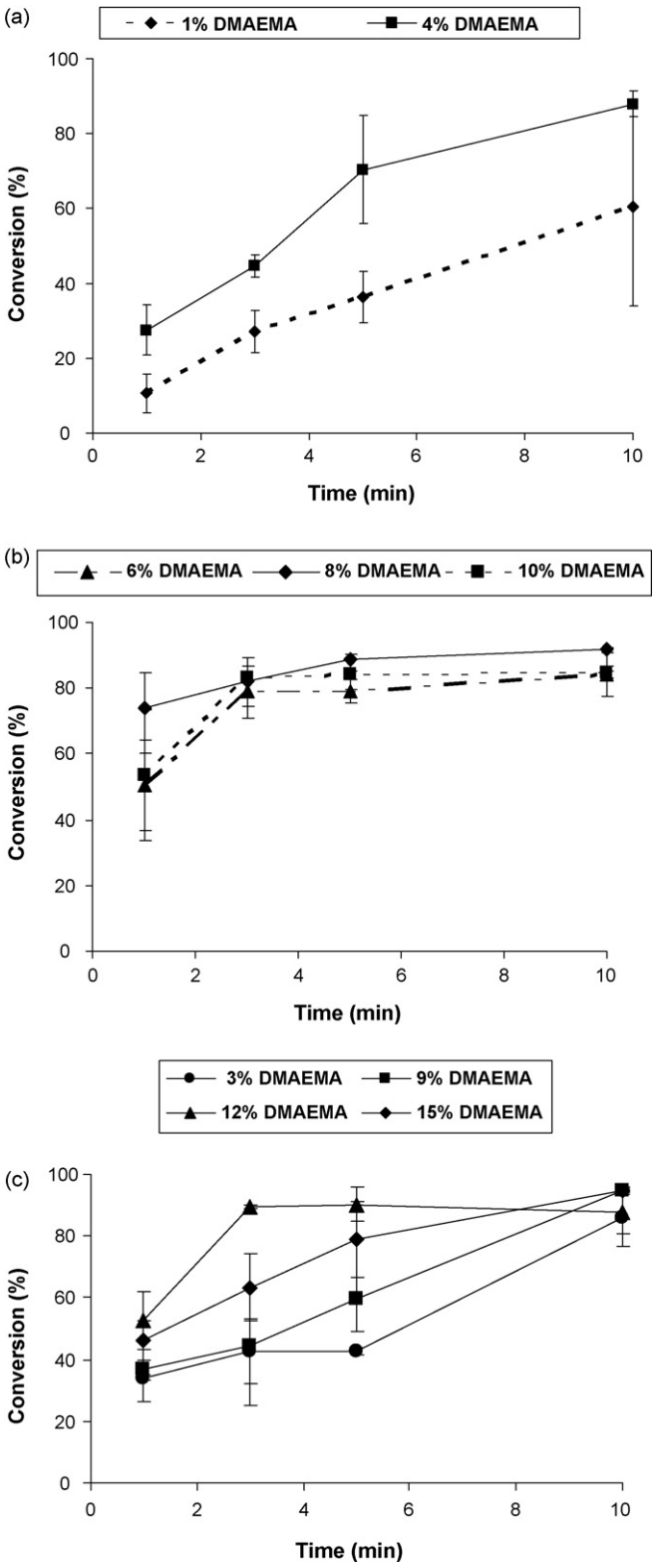


**Fig. 1.** Conversion of TEGDMA monomer to polymer by visible light (82500 lux) using various concentrations of (A) 1%CQ and 1% or 4% DMAEMA; (B) 2% CQ and 6%, 8% or 10% DMAEMA; (C) 3% CQ and 3, 9, 12 or 15% DMAEMA. Percentages are expressed by weight of the total liquid coating solution.

**Table 2**
Contact angle and penetration times of TEGDMA and TEGDMA:Bis-GMA (50:50) on different pore-forming agents, talc and bead forming material. Values in parentheses are the standard deviations of 10 replicates.

| Solid powdered pore-formers | TEGDMA | | TEGDMA:Bis-GMA 50:50 (w/w) | |
|---|---|---|---|---|
| | Penetration time (s) | Contact angle (°) | Penetration time (s) | Contact angle (°) |
| Lactose | 0.7 (0.1) | 19 (4) | 11.8 (0.9) | 26 (5) |
| Sodium Chloride | 0.9 (0.1) | 28 (6) | 21.5 (1.7) | 39 (6) |
| PEG | 1.7 (0.2) | 16 (2) | 38.3 (6.3) | 31 (5) |
| Explotab® | 1.1 (0.1) | 19 (3) | 19.0 (1.3) | 29 (2) |
| Ac-di-sol® | 1.3 (0.2) | 25 (4) | 25.6 (2.3) | 36 (2) |
| Crushed Beads | 9.1 (1.7) | 14 (3) | 217 (57) | 24 (4) |
| Talc | 20.4 (1.6) | 16 (3) | 580 (50) | 22 (5) |

cating that the monomers along with the initiators, 10% (w/w) of 1:4 CQ:DMAEMA were miscible, unlike the photocurable prepolymer system investigated earlier (Bose and Bogner, 2006), which was a dispersion.

The hardness of films composed of 100% TEGDMA and all compositions of TEGDMA and Bis-GMA (with 10% (w/w) 1:4 CQ:DMAEMA), as measured by the pencil test (ASTM 3363-00), was indistinguishable (H and 2H is very close in the range of 6B, 5B, 4B, 3B, 2B, B, HB, F, H, 2H, 3H, 4H, 5H, 6H). By this measure, variation in TEGDMA and Bis-GMA compositions did not affect film hardness in the range explored. However, general observations during routine handling of free films indicated that 70:30 TEGDMA:Bis-GMA yielded films of good mechanical strength and adequate flexibility. Since this composition also has a "sprayable viscosity" (47.2 cps), it was used for subsequent studies.

### 3.4. Evaluation of processing time on coating uniformity

The time allowed for the polymer to distribute uniformly over the beads and the time allowed for distribution and incorporation of powdered pore-forming solids were evaluated as potentially key processing parameters. Three distribution times of monomer (1, 3 and 5 min) and three distribution times of pore-forming agents (1, 3 and 5 min) were evaluated on yield, coating efficiency and uniformity. The optimum times were both the minimum explored (1 min vs. 3 or 5 min) when other conditions such as composition of monomers (TEGDMA:Bis-GMA 70:30), concentration of initiator (10% (w/w) of 1:4 CQ:DMAEMA), type of pore-forming agent (lactose), amount of solid pore-forming agent to volume of liquid monomer ratio (S/L ratio of 2.4), particle size of pore-forming agents (75–106 μm), light intensity (82500 lux) and expose time of light (15 min) were maintained constant (data not shown). Longer distribution times actually decreased the quality of the product as assessed by yield, coating efficiency and coating uniformity. This observation is somewhat counterintuitive, since longer distribution times were thought to provide better distribution of materials. It was found, however, that a longer period between coating and crosslinking allowed more transfer of liquid coating from the beads to the pan, thus reducing the coating on the beads, and reducing overall coating efficiency and uniformity. Thus, similar to the UV-curable silicone system (Bose and Bogner, 2006), distribution times of 1 min were found to be optimal for process efficiency and uniformity while reducing processing time.

### 3.5. Effect of ratio of pore-forming solid (S) to liquid monomer (L) on coating efficiency and uniformity

A potentially key formulation factor for this solventless coating system is the ratio of amount of solid pore-forming agent (S) to the volume of liquid monomer (L). In a UV-curable silicone-based coating system, it was found that an optimum level of powdered pore-forming agents reduced the tackiness of the liquid prepolymer while preventing the presence of excess powder in the coating pan (Bose and Bogner, 2006). In the visible photocuring system, three volumes (300, 500 and 700 μl) of coating liquid (90% (w/w) of 70:30 TEGDMA:Bis-GMA and 10% (w/w) of 1:4 CQ:DMAEMA) and three amounts of pore-forming agent lactose (900, 1200 and 1500 mg) per layer were used for a $3 \times 3$ factorial design to prepare batches with four layers of coating having S/L ratios of 1.3 to 5.0. At two different compositions with the same S/L ratio of 3.0 (300 and 500 μl of liquid monomer and 900 and 1500 mg of powdered pore-forming agent), the coating efficiency was the same (as was the yield). However, both the yield and coating efficiency of the batches coated using the two lowest S/L ratios, 1.3 and 1.7, were significantly lower (Fig. 2A). Thus, two sets of batches with intermediate S/L ratios (1.4 and 1.6 obtained by using 1000 and 1100 mg of pore-forming agents and 700 μl monomer) were prepared to further explore the difference in yield and coating efficiency. The coatings with the intermediate S/L ratios had intermediate values of coating efficiency and yield, showing a clear decline in processibility below an S/L ratio of 1.7. The yield was consistently high when the S/L was 1.7 and above. Coating efficiency was acceptable within the range of S/L ratios 1.7 to 3.0. There was a corresponding increase in the intra-batch standard deviation in diameter and color of the coated beads below an S/L ratio of 1.7 (Fig. 2B and C) indicating poorer uniformity of the coating in this operating range. We also noted a high inter-batch standard deviation in one set of batches with an S/L ratio of 3.0. There was no difference in roundness of the coated beads over the range of S/L ratios (roundness values were between 1.05 to 1.08). Overall, combining all the data, an S/L ratio of 2.4 to 3.0 provided high yield and coating efficiency, and low coating variation.

### 3.6. Evaluation of monomer viscosity and pore-former particle size on coating uniformity

Viscosity plays an important role in adhesion (Simons and Fairbrother, 2000). The effect of viscosity and particle size on adhesion has been addressed in the wet granulation literature. In the granulation process, a critical Stokes number determines the success of adhesion of two particles in the presence of binder solution (Keningley et al., 1997; Rowe, 1989; Simons and Fairbrother, 2000). During wet granulation, when two particles of density $\rho$ and radius $R$ come together with a velocity of $V_0$ (=$2\omega R$) with their surface wet with a layer of binder, a critical Stokes number is defined as

$$\mathrm{St}_{V*} = \frac{16\rho R^2 \omega}{9\mu}$$

where $\rho$ is the pore-former particle density, $R$ is the radius of the particles, $\omega$ is the rotational speed of the equipment, for example, a coating pan in the present system and $\mu$ is the viscosity of the binder. Below the critical Stokes number, colliding particles are expected to adhere during wet granulation (Simons and Fairbrother, 2000). We investigated whether there is a critical Stokes number ($\mathrm{St}_v$) below which powder would

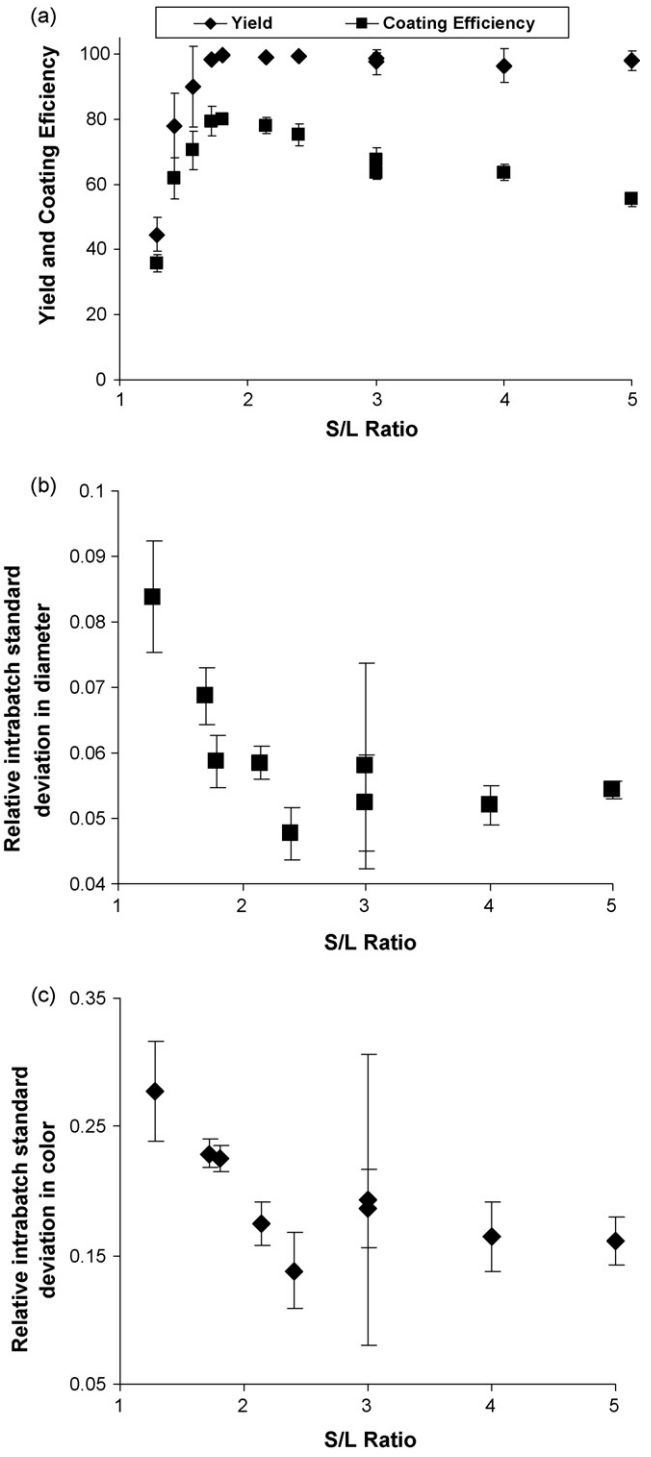


**Fig. 2.** Five grams of non-pareil beads were coated with four layers of liquid monomer (L) (90 wt% 70:30 TEGDMA:Bis-GMA with 10 wt% 1:4 CQ:DMAEMA) and powdered lactose (S) at different S/L ratios. (A) Yield and coating efficiency; (B) relative intra-batch standard deviation of diameter; (C) relative intra-batch standard deviation of color.

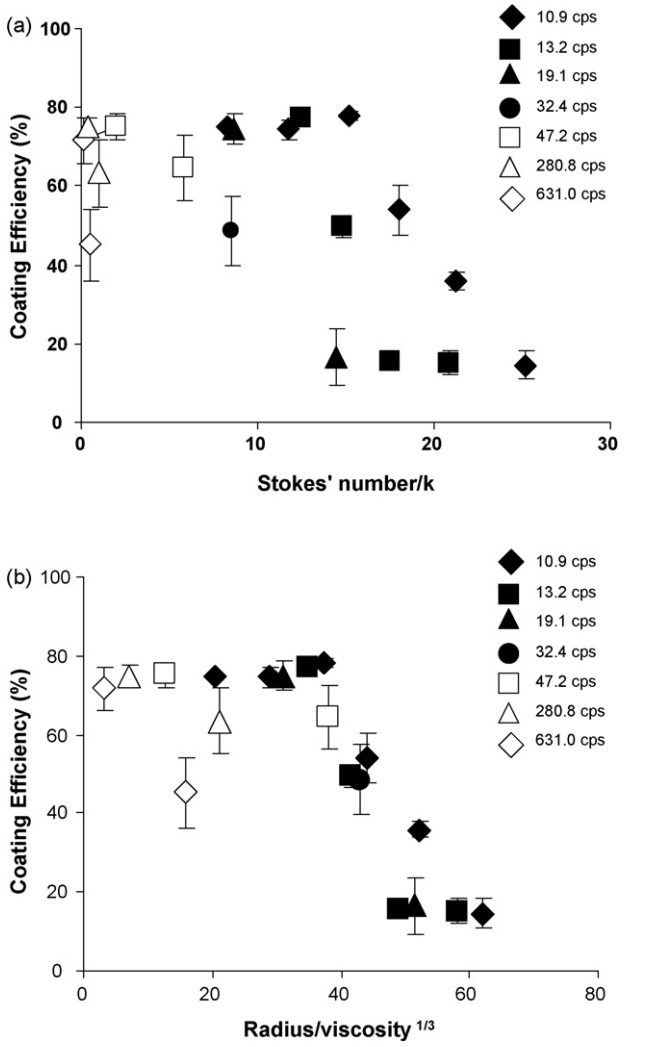


**Fig. 3.** Coating efficiency of five grams of non-pareil beads coated with four layers of liquid monomer (L) (90 wt% 70:30 TEGDMA:Bis-GMA with 10 wt% 1:4 CQ:DMAEMA) and powdered lactose (S) at S/L ratio of 2.4. Coating efficiency is plotted as a function of (A) Stokes number/$k$ and (B) the radius of the particle over the cube root of viscosity.

be well incorporated into the film leading to better coating quality.

Using the form of the critical Stokes number, where $R_A$ is the radius of the bead coated with liquid and $R_B$ is the radius of the powder particles, the critical Stokes number becomes,

$$St_{V*} = \frac{16\rho R_A R_B \omega}{9\mu} = k\frac{R_B}{\mu}$$

Since only the particle size of pore-forming agent and viscosity are varied in this investigation, we report $St_v/k$ in Fig. 3A. The viscosity of the monomer solutions (TEGDMA and Bis-GMA) ranged from 10 to 630 cps (Table 1) and the particle size of the lactose ranged from 45 to 300 μm to obtain a range of $St_v/k$ from 0.07 to 30 (Fig. 3A).

While there is not a clear critical Stokes number in Fig. 3A, we noted a general trend toward greater coating efficiency at $St_v/k$ below 10–15. There was also a trend toward declining coating efficiency for each viscosity. A second analysis was undertaken using radius of pore-forming agent/viscosity$^{1/3}$ instead of the original Stokes number. Using this new parameter, the data collapsed onto a single line (with few exceptions) with a critical value of 37 (Fig. 3B) above which it was not possible to obtain good coating efficiency and acceptable uniformity. Thus, particle size of the pore-forming agents and the viscosity of the monomer were important parameters for the success of the coating process. The data suggest that the process should be operated below a value of radius/viscosity$^{1/3}$ = 37 to obtain optimum coating efficiency and acceptable uniformity (Fig. 3B).

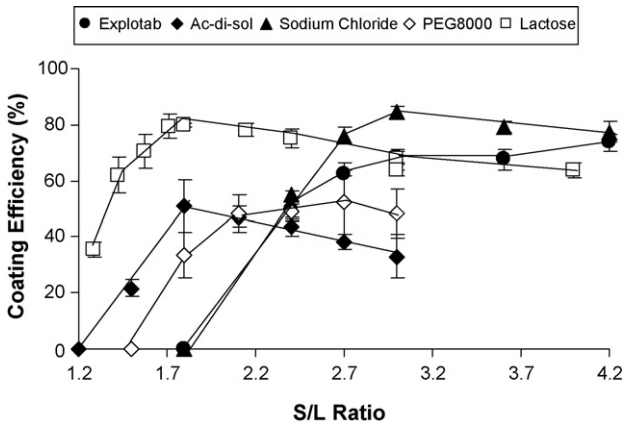


**Fig. 4.** Coating efficiency of five grams of non-pareil beads were coated with four layers of 70:30 TEGDMA:Bis-GMA (2:8 CQ:DMAEMA) liquid monomer (L) and various powdered pore-forming agents (S) with different S/L ratios.

### 3.7. Evaluation of coating uniformity using alternate pore-forming agents

Sodium chloride and PEG were also used as simple pore-formers, whereas Explotab® and Ac-di-sol®, two super-disintegrants, were explored as swellable pore-forming agents in the photocurable coating. The particle size ranges of the simple pore-formers and the super-disintegrants used were 75–106 and 45–63 μm, respectively.

For Ac-di-sol® and PEG, the yield and coating efficiency were low for all S/L ratios and thus, it was difficult to make batches of coated beads with Ac-di-sol® and PEG as pore-forming agents (Fig. 4). The surfaces of the coatings in which Ac-di-sol® was incorporated were rough and uneven having loose powder on the surface. A similar observation was made when PEG was incorporated as a pore-forming agent. It was difficult to separate the loose powder from the coated beads to perform image analysis as a reliable measure of coating uniformity. Similarly, there was high color variation when Ac-di-sol® was incorporated in the siloxane-based systems (Bose and Bogner, 2006) and PEG coated beads had defects in silicone-based systems leading to higher release. Thus, Ac-di-sol® and PEG are not considered preferred pore-formers for either photocurable coating system.

Good coating efficiency was obtained with lactose in the lower range of S/L ratios (1.8–3.0). For sodium chloride and Explotab®, higher S/L ratios were required for good coating efficiency when compared to lactose (Fig. 4). The intra- and inter-batch variations in color and diameter were determined for batches using the midpoint of the optimum S/L ratio range (Table 3). Sodium chloride, lactose and Explotab® had comparable intra-batch variation in diameter. Similarly, intra-batch %RSD of color intensity ranged from 14% to 16% indicating comparable color variations within each batch regardless of pore-former. The roundness of the coated beads ranged from 1.05 to 1.07 for all the batches using all pore-forming agents. The intra-batch %RSD of diameter and color in Table 3 are comparable to corresponding results from the siloxane-based coating (Bose and Bogner, 2006).

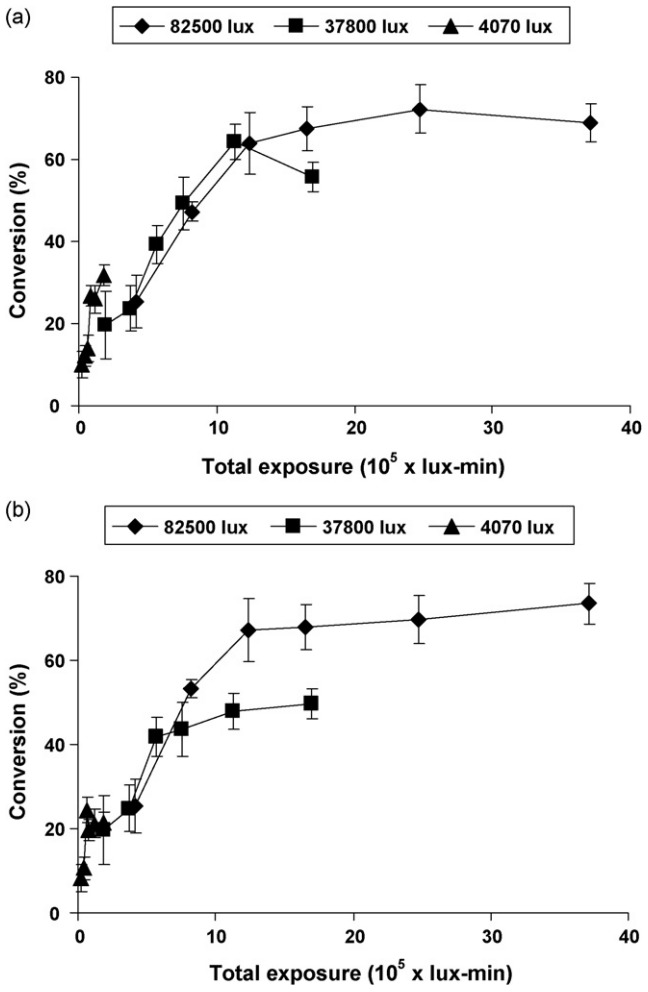


**Fig. 5.** Effect of light intensity and total exposure to the percent conversion of monomer to polymer using (A) 10% (w/w) 1:4 CQ:DMAEMA; (B) 15% (w/w) 1:4 CQ:DMAEMA.

### 3.8. Evaluation of level of initiator, light intensity and exposure time on degree of curing and mechanical strength of the coating

An evaluation of initiators in free films was described earlier in the text. In contrast to the free films, coatings on beads do not have

**Table 3**
Intra-batch and inter-batch percent relative standard deviations in diameter, color as well as roundness of batches of coated beads (5 layers) prepared using different pore forming agents (simple pore-formers and super-disintegrants) at the midpoints of their optimum S/L ratios ranges (as determined from Fig. 4). Intra-batch %RSD is defined as the relative standard deviations within one batch of coated beads. Inter-batch %RSD is defined as the relative standard deviations of the means of three batches (batch-to-batch) of coated beads. The values of intra-batch and inter-batch %RSD in diameter of uncoated beads were 7 and 0.33, respectively, where the values of intra-batch and inter-batch %RSD in color of uncoated beads were 20 and 4, respectively. The roundness values of uncoated beads were 1.01 with standard deviation of 0.01.

| Pore-formers | Diameter | | Color intensity[a] | | Roundness[b] |
|---|---|---|---|---|---|
| | Intra-batch % RSD | Inter-batch % RSD | Intra-batch % RSD | Inter-batch % RSD | |
| Sodium chloride (S/L 3.6) | 5 | 0.6 | 14 | 2 | 1.05 (0.00) |
| Lactose (S/L 2.4) | 5 | 3.8 | 14 | 12 | 1.06 (0.01) |
| Explotab® (S/L 3.0) | 6 | 1.0 | 16 | 11 | 1.06 (0.01) |

[a] On a 0–256 scale on the red channel.
[b] Roundness = perimeter$^2/4\pi \times$ area; standard deviations are in parenthesis.

constant exposure to light due to their curved surfaces and cascading motion in the rotating coating pan. In addition, the free films previously evaluated did not contain pore-forming agents whereas pore-forming agents were part of the coating on the beads. Thus, sets of batches were prepared to determine the effect of light intensity, duration of light exposure, and concentration of photoinitiator on the degree of curing on coatings that were applied by a pharmaceutically relevant process on pellets (non-pareil beads).

According to Fig. 5, exposure times up to 15 min significantly increased the percent conversion (by *t*-test and ANOVA, $\alpha = 0.05$). When the exposure time was extended from 15 min to 45 min, there was no further increase in conversion regardless of the % of initiator. Conversion also increased with increasing light intensity at both initiator concentrations. However, the higher initiator concentration did not result in higher conversion.

Analysis by ANOVA showed that conversion of the monomers to polymer film depends on total exposure (intensity x exposure time), as well as on light intensity and time, separately (analyzed by ANOVA, $\alpha = 0.05$). The data in Fig. 5 suggest that total exposure is the key parameter, particularly at the 10% initiator concentration. This result is in contrast to the results obtained from siloxane-based system cured with UV light, where the total exposure was not important but the exposure time and more importantly intensity of the UV light controlled the degree of conversion (Bose and Bogner, 2006).

## 4. Conclusion

The results presented extend previous research on solventless photocurable coatings to systems using materials of known low toxicity (i.e., TEGDMA, Bis-GMA, CQ and DMAEMA). The design space for manufacturability of this alternate coating technology was delineated. It was found that (1) the ratio of the amount of solid (S) pore-forming agent to volume of liquid (L) monomer, (2) particle size of the pore-forming agent, (3) viscosity of the monomer mixture, (4) type of pore-former, (4) concentration of initiator and (5) total exposure of light were critical formulation and processing parameters. Solid-to-liquid (S/L) ratio and Stokes number or a related parameter (radius/viscosity$^{1/3}$) of the process were key determinants for the success or failure of a batch and is dependent on the pore-former and its particle size. A photosensitizer-photoinitiator combination at 10% of 1:4 CQ:DMAEMA with a light intensity of 82500 lux for 15 min yielded approximately 70% conversion of monomer to polymer which is comparable to similar systems in medical and dental applications (Atai et al., 2004; Hussain Latiff et al., 2005; Imazato et al., 2001, 1999; Kim and Jang, 1996; Lu et al., 2004; Mendes et al., 2005; Tarumi et al., 1999). In general, the data suggest that solventless photocuring is a feasible coating technique for pharmaceutical applications. A modified version of traditional coating pans can be used and the light source can be place in front of the pan.

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