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Solvent-free film coating using a novel photocurable polymer

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Abstract

Commercially available film coating polymers are applied with aqueous or organic solvent that must be removed from the coating. In contrast, the results herein presented demonstrate the feasibility of coating without solvent. A liquid silicone-based polymer formulation which can be crosslinked upon ultraviolet irradiation was applied to non-pareil beads to form a relatively impermeable coating. Irradiation exposure and filler content were varied. Bead aggregation and film coating integrity were determined. Film integrity was assessed by marker dye which leaked through defects in the impermeable film coating. Scanning electron micrographs showed smooth continuous coatings with no striations within or between layers of coating. Bead aggregation was reduced by the presence of filler and by an increase in irradiation exposure. Coating integrity increased with an increase in the number of layers of coating. These preliminary results demonstrate the feasibility of coating pharmaceutical cores using a solvent-free photocurable polymer.

Keywords: Film coating; Photocurable polymer

1. Introduction

Solvent-based coatings have been widely used in the pharmaceutical industry to produce elegant dosage forms or achieve controlled drug release. The presence of either organic or aqueous solvents in coating systems can affect the properties of coating and the quality of final products. In particular, residual solvent in coatings and moisture penetration into tablet cores have been questioned (Banker and Peck, 1981).

Elimination of solvent from coating systems has been studied as a means of eliminating the problems associated with solvent-based coatings. DeLange (1984) discussed powder coating using thermal plastic polymers. Powder coated cores were heated above the melting temperature of the polymer to form polymer melt coatings. Appelgren and Eskilson (1990) reported a continuous melt coating technique which applied the polymer melt directly onto cores to form a coating which was solidified upon cooling. These two methods represent physical approaches to achieve solvent-free coatings. The coating materials do not undergo chemical reactions, such as crosslinking, and their chemical structures are not altered

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after coating. However, high temperatures are usually applied to melt the polymers. In contrast, photocuring provides a chemical approach to form coatings at room temperature or below with an extremely rapid rate (Yang, 1993).

Photocuring is essentially a photopolymerization reaction in which functional moieties on photocurable materials react to form a crosslinked network upon absorption of photons. The majority of photocuring methods utilize free radical polymerization which are free of by-products (Roffey, 1982). Photocuring systems consist of three major components: (1) ultraviolet or visible light sources; (2) photocurable materials which are specially functionalized liquid monomers or polymers; and (3) additives such as initiators, sensitizers or catalysts (Pappas, 1985).

The primary component in a photocuring system is the photocurable film-former – a polymer or monomer. Photocurable polydimethylsiloxane is widely used as a photocuring material due to its good thermal stability and extraordinary flexibility (Jacobine and Nakos, 1992). In addition, photocurable siloxanes are used in transdermal drug delivery systems (Thomas and Pfister, 1991), composite dental fillings (American Dental Association, 1985), and other medical products (Ambrogi and Tsang, 1992). Two classes of photocurable siloxanes are acrylic acid derivatives and ene-thiols. Acrylic siloxanes are prone to inhibition by oxygen and moisture present in the atmosphere. However, ene-thiol systems are not affected by either oxygen or moisture (Jacobine and Nakos, 1992). This characteristic allows the use of such photocurables in open systems such as pan coaters. In addition, it was previously shown that the ene-thiol system cures faster and more completely than acrylate siloxanes. The ene-thiol siloxane forms a film of high integrity within 2 min under a photointensity of 16 W/cm^2. The photocured films were characterized by water vapor transmission rates comparable to commercially available coating materials (Wang and Bogner, 1995).

The objective of this research was to determine the feasibility of photocuring as a pharmaceutical coating technique by evaluating the processibility of a photocurable formulation in a laboratory-scale apparatus with the characteristics of a traditional pan coater. In this article, norbornene-endcapped polydimethylsiloxane (NB-PDMS) was investigated for its potential application as a solvent-free film-coating material for non-pareil beads. Due to its impermeability to organic salts, NB-PDMS is intended to be a stable matrix for pore-forming excipients, rather than having pharmaceutical release characteristics (i.e., immediate, enteric or controlled release) of its own. The purpose of the research described herein is to determine the feasibility of applying such a photocurable silicone onto a bed of pharmaceutical cores. Parameters such as irradiation exposure and presence of filler were varied. The resulting degree of aggregation and microscopic appearance of the coatings were monitored. In addition, the release of a marker dye was used as a measure of coating integrity.

2. Experimental

2.1. Materials

Norbornenylpolydimethylsiloxane (NB-PDMS) with an average molecular weight of 12000 was preformulated with 1% (w/w) thiol crosslinker and 2% 2-hydroxy-2-methyl-1-phenylpropan-1-one, an initiator (Loctite Corp., Newington, CT). The corresponding structures of these components are shown in Fig. 1. The viscosity of the formulated preparation was 640 cps as measured

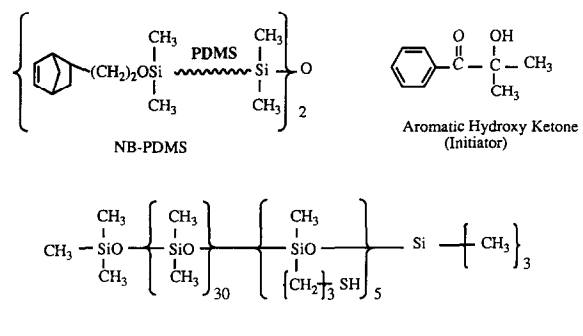

Fig. 1. Chemical structures of the prepolymer, NB-PDMS, and its initiator and crosslinking agent.

by cone-plate viscometry at a shear rate of 0.005 s^{-1}. This preparation was stored in the dark at 6 ± 2°C until use. TiO_2 (98% rutile, Aldrich, Milwaukee, WI) was passed through a 100 mesh screen and used as a filler.

2.2. Coating nonpareil beads using photocuring

A laboratory-scale coating pan for small sample sizes was fabricated from the bottom 3 inches of a 500 ml volumetric flask which was placed in an open drum rotating at 40 rpm. 5 g of 14–18-mesh non-pareil beads which contain FD and C no. 1 as a marker dye (Ozone Confections, Elmwood Park, NJ) were loaded into the glass coating pan. Upon addition of 0.2 g of the NB-PDMS formulations (unfilled and filled with 20% TiO_2), the beads were allowed to roll in the coating pan for 3 min to evenly distribute the coating material. Photo-irradiation was then applied at an intensity of 13 W/cm^2 for a predetermined time (1, 3 or 6 min) while dry nitrogen was streamed into the coating pan. At the end of the photo-irradiation interval, approx. 100 beads were removed from the coating pan for analysis of aggregation and dye release. The remainder of the beads in the coating pan were processed for five additional cycles to produce six layers of coating. Samples were withdrawn and analyzed after each layer of coating was applied and cured.

2.3. Analysis of coating deposition and bead aggregation

The numbers of singlet and aggregate beads from a 100 bead sample were counted after each layer of coating was applied and cured. From the counted singlets, 50 were weighed in groups of 10 to record the weight increase due to the deposition of coating material. To quantify the degree of bead aggregation during photocuring in this system, the percentage of singlet coated beads was calculated based on Eq. 1:

$$\%S = \frac{N_1}{N_1 + 2N_2 + 3N_3 \ldots + nN_n} \quad (1)$$

where $\%S$ represents the percentage of single coated beads, N_1, N_2, N_3, and N_n denote the corresponding number of singlets, doublets, triplets and aggregates, and the coefficients 2, 3 and n are used to obtain $\%S$ based on total weight rather than on number. The % aggregation of coated beads was determined from Eq. 2:

$$\%\text{ aggregation} = 1 - \%S \quad (2)$$

2.4. Release of marker dye

FD&C Blue no. 1 was used as a marker for coating integrity due to its inability to detectably permeate NB-PDMS free films over a 24 h period. Each sample of 50 singlet beads from the aggregation study was loaded in a wire mesh basket. The basket was suspended 1 cm above the bottom of a glass vial (7.0 cm tall and 3.2 cm in diameter). Doubly distilled water (5.0 ml) was added to the vial and stirred using a magnetic stirrer located at the bottom center of the vial. Each vial containing 50 beads with either 1, 2, 3, 4, 5, or 6 layers of coatings was placed in a water bath maintained at 37 ± 0.5°C. At each sampling time, 1.0 ml of solution was withdrawn and analyzed; the medium was replaced with 1.0 ml of fresh doubly distilled water. The release of marker dye from the coated beads was monitored at 630 nm (Lambda 3A, UV spectrometer, Perkin Elmer, Greenwich, CT) and expressed as a percentage of dye released from the corresponding uncoated beads.

2.5. Scanning electron microscopy studies

The texture and thickness of beads with six layers of coating were examined using field emission scanning electron microscopy (Model HP50B, Coates and Welter, Nannametric, Sunnyvale, CA). Photomicrographs of the surface and cross-section of coated beads were examined for integrity, uniformity of thickness and texture.

2.6. Infrared spectroscopic measurement of curing

Filled and unfilled NB-PDMS coatings were peeled from the nonpareil beads and examined for any residual C = C moieties using FTIR spectrometry (Bio-Rad, Cambridge, MA). The char-

acteristic C = C peak was monitored in the region of 1600–1650 cm^{-1}. The detection of residual C = C moieties was used as an indicator of incomplete curing (Yang, 1993). IR spectra were collected for unfilled coatings photo-irradiated for 1, 3, or 6 min per layer.

3. Results

3.1. Coating integrity

The average total weight of 10 coated singlet beads was plotted as a function of the number of coating layers as shown in Fig. 2. The weight of the coated beads increased steadily with increasing number of coating layers. Filled and unfilled coatings showed a very similar pattern of weight increase. This suggested a uniform deposition of the coating material onto the beads with each coating application. The characteristic continuity and uniformity of the photocured NB-PDMS coatings can be seen in the scanning electron photomicrograph in Fig. 3. There were no obvious pores in the coating and the layers of coating appeared to have merged in the absence of plasticizers or heat which are frequently applied in pharmaceutical coating systems.

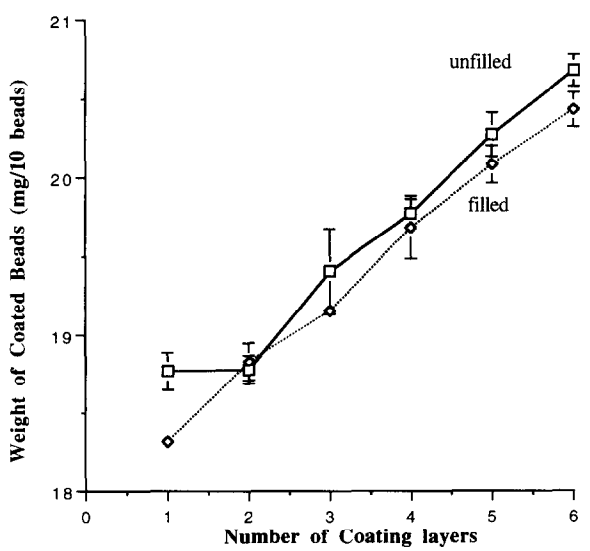

Fig. 2. Weight increase of samples of 10 coated beads as a function of the number of layers of coating. Data shown are mean and standard deviation ($n = 5$).

The degree of coating integrity was further tested by monitoring the release of a marker dye from the coated beads. It was determined in a separate permeation experiment that photocured NB-PDMS free films were impermeable to FD&C Blue no. 1. Thus, the release of FD&C Blue no. 1 was employed as a measure of defects in the film coating. Any marker dye detected in the dissolution medium indicated that there was incomplete coverage of the polymer coating or rupture of the coating during the release study.

A representative dye release profile is shown in Fig. 4. The marker dye was measured as a percentage of dye released from uncoated beads. Uncoated beads released 100% of the dye within 15 min. In addition, a release study showed that uncured coatings also released 100% of the marker dye within 15 min. However, with increasing layers of cured NB-PDMS, the dye release was slowed and the extent of release over 24 h was reduced. The slowing of the release may be due to a decrease in the porosity of the coating due to increased coverage. The reduction in release suggests that the integrity of the coating improved with an increase in the number of coating layers.

There was a large batch-to-batch variability in the marker dye release profiles such as that shown in Fig. 4. Due to the difficulty of adequately describing such variability, the two parameters were chosen to describe the marker dye release profiles: (1) the time for 20% of dye to be released, $t_{20\%}$ and (2) the percent of dye released over 24 h, E_{24}. These parameters correspond to a rate and an extent of dye release. Fig. 5 shows the values of $t_{20\%}$ and E_{24} for beads coated with filled and unfilled NB-PDMS and irradiated for 3 min per layer as a function of coating layer as well as the standard deviations of the parameters. The increase in $t_{20\%}$ and decrease in E_{24} with increasing number of coating layers are additional evidence for an increase in coating integrity. However, the presence of filler did not affect the integrity of the coating as assessed by release of marker dye.

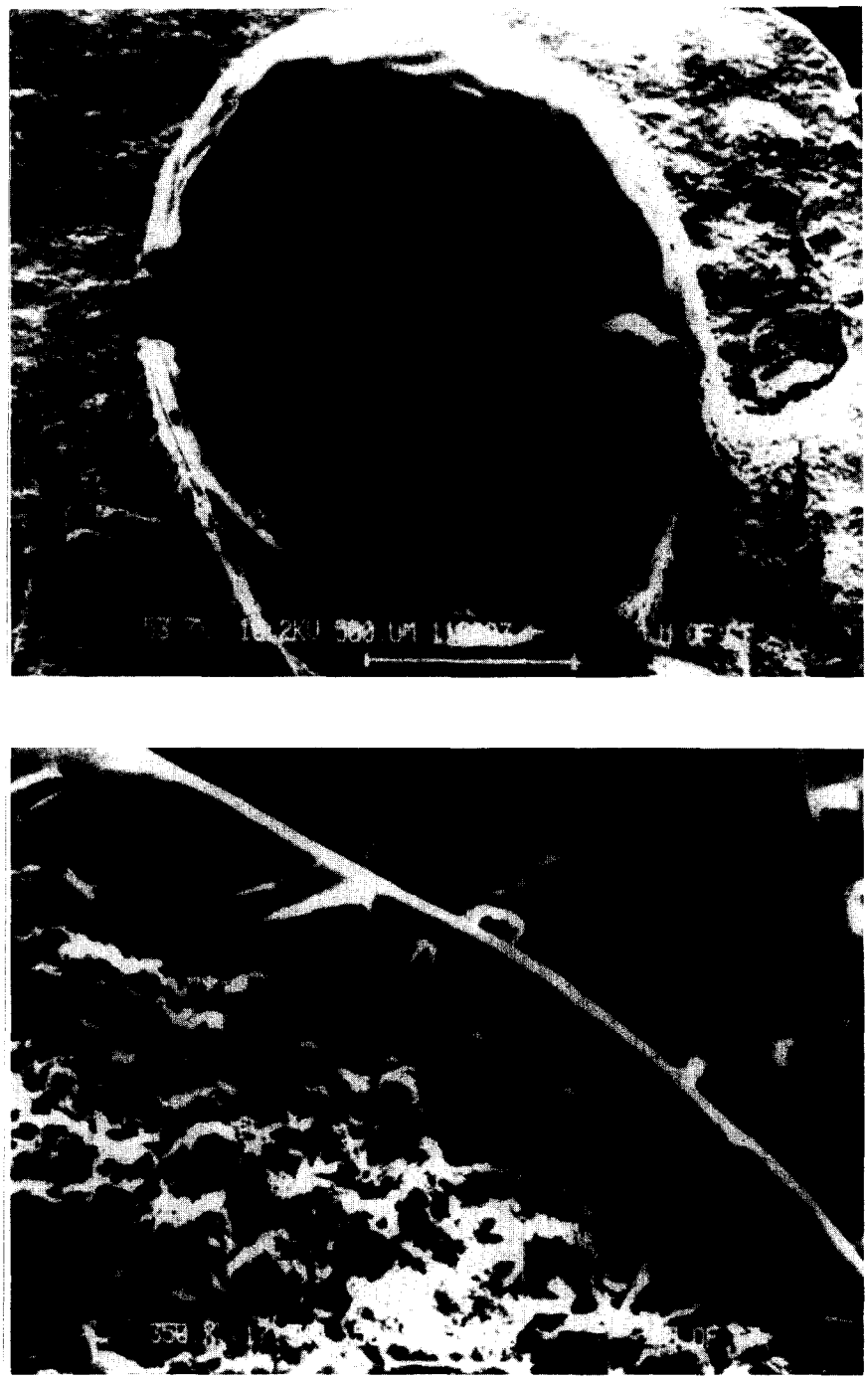

Fig. 3. Scanning electron micrographs of the surface and cross-section of a bead coated with six layers of unfilled NB-PDMS and irradiated for 3 min per layer of coating.

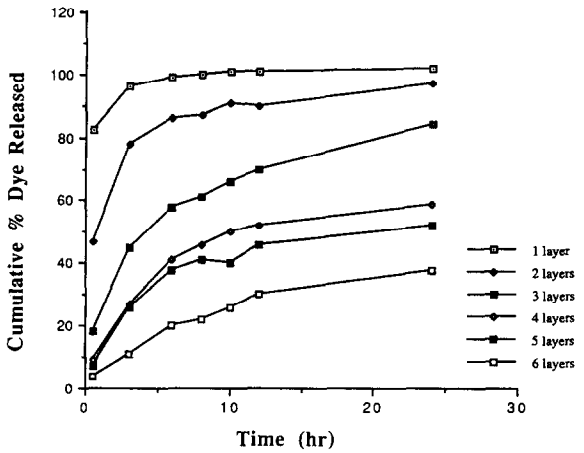

Fig. 4. Representative profile of marker dye release from a sample of 50 beads coated with six layers of unfilled NB-PDMS and irradiated for 3 min per layer of coating.

Table 1
Measurements of beads coated with six layers of filled and unfilled NB-PDMS irradiated for 1, 3 and 6 min per layer

Parameter	Irradiation time per layer					
	Unfilled NB-PDMS			Filled NB-PDMS		
	1 min	3 min	6 min	1 min	3 min	6 min
t_{205} (h) [a]	3.8	5.6	6.3	3.8	4.8	3.7
	(0.5)	(1.7)	(1.4)	(0.8)	(0.9)	(0.7)
E_{24} (%) [b]	48.7	44.4	43.3	45.3	45.3	48.9
	(0.8)	(5.4)	(4.9)	(8.0)	(1.7)	(4.3)
Aggregation (%) [c]	39.3	37.4	25.7	41.2	11.0	14.2
	(1.9)	(1.5)	(2.6)	(1.3)	(0.8)	(3.1)

[a] Time for 20% of the dye to be released from a sample of 50 beads. [b] Extent of dye released after 24 h. [c] Percent of aggregated beads (Eq. 2).

The rate of dye release, $t_{20\%}$, was affected by the period for which each coating layer was irradiated (1, 3 or 6 min) as shown in Table 1. For the unfilled NB-PDMS, there was a trend toward longer times to release 20% of the marker dye as the irradiation period increased. The higher radiation dose (i.e., irradiation intensity times exposure time) received at the longer irradiation times would be expected to result in a more complete cure. However, IR spectra of coatings peeled from beads irradiated for 1, 3 or 6 min per coating layer all showed no residual C = C. Thus, it was concluded that unfilled coatings were completely cured by 1 min of irradiation per layer.

For the filled NB-PDMS, the beads irradiated for 3 min (rather than 1 or 6 min) per coating

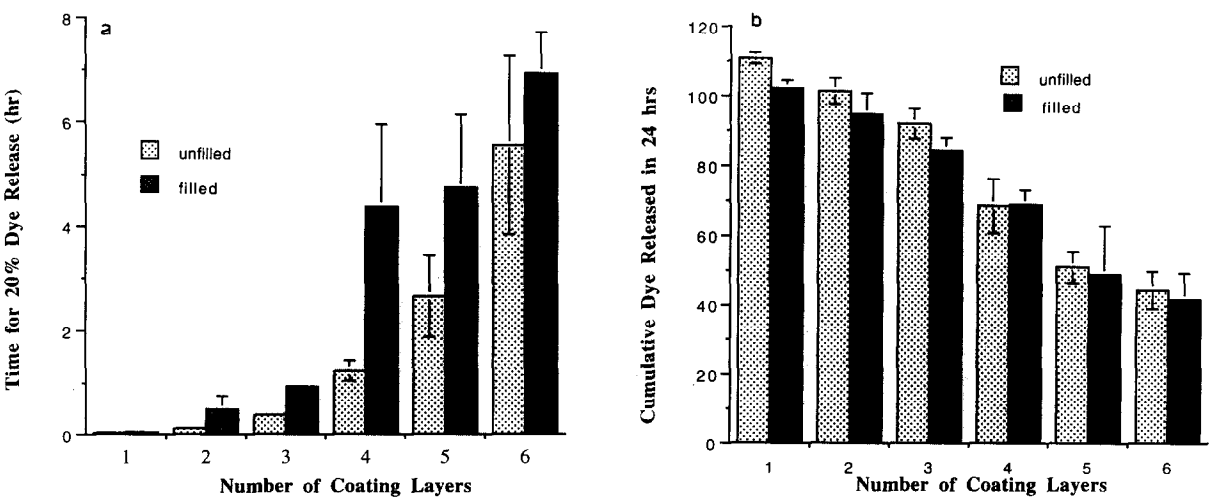

Fig. 5. (a) Time for 20% of the marker dye to be released, $t_{20\%}$, from samples of 50 filled and unfilled NB-PDMS coated beads irradiated for 3 min. Bars represent standard deviations ($n = 3$). (b) Percent of marker dye to be released within 24 h, E_{24}, from samples of 50 filled and unfilled NB-PDMS coated beads irradiated for 3 min. Bars represent standard deviations ($n = 3$).

layer exhibited significantly higher values for $t_{20\%}$ ($p > 0.05$). While it was expected that 3 min of irradiation per layer would produce a coating of greater integrity than those exposed to 1 min of irradiation per layer, the reasons for the decrease in integrity indicated by a shorter $t_{20\%}$ for coatings irradiated for 6 min per layer were not immediately obvious; this will be discussed later in light of the aggregation results. In addition, it was not possible to obtain IR spectra of the filled coatings due to their opacity. Moreover, there was no difference in the extent of dye released over a 24 h period, E_{24}, for either filled or unfilled coatings irradiation for 1, 3, or 6 min per layer (Table 1). Thus, while radiation dose has some effect on the coatings, it appears that the most significant parameter affecting coating integrity is the number of layers of coating.

3.2. Aggregation of coated beads

Aggregated beads are not considered to be a useful product. Their presence decreases coating efficiency. In addition, aggregation is a measure of the tackiness of the coating. Thus, the degree of bead aggregation was determined throughout the coating process. The degree of bead aggregation does not appear to vary with the number of layers of coating (Fig. 6). However, irradiation period was a significant factor in the degree of bead aggregation. For the unfilled NB-PDMS coatings, there appeared to be fewer aggregated beads when the irradiation period was 3 or 6 min per layer as opposed to 1 min per layer as shown in Table 1. Due to the large variation in the data, the difference was not statistically significant ($p < 0.05$).

For beads coated with filled NB-PDMS, the degree of aggregation for beads irradiated for 3 and 6 min per layer of coating was significantly lower than that for 1 min of irradiation ($p < 0.05$). Furthermore, the incorporation of filler reduced the degree of bead aggregation from that of the beads coated with unfilled NB-PDMS (Table 1).

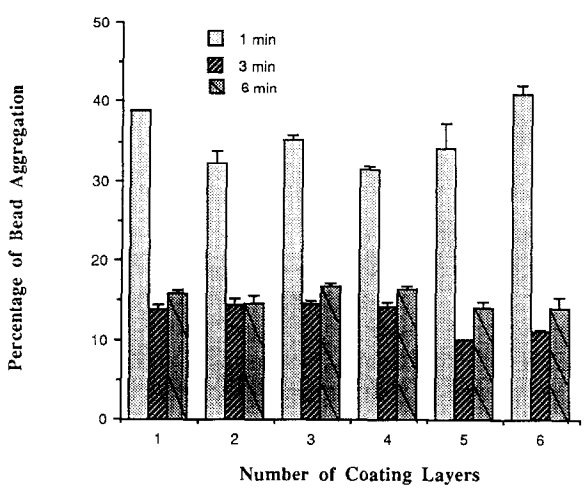

Fig. 6. Degree of bead aggregation as a function of the number of layers of filled coatings irradiated for 1, 3 and 6 min per layer. Bars represent standard deviations ($n = 3$).

4. Discussion

The coated beads were visually inspected during the release studies. The release of the marker dye appeared to occur by two mechanisms. First, the marker dye was released from existing defects in some of the coated beads. This mechanism was more apparent for beads with 1–4 layers of coating. Second, beads with coatings containing no defects swelled as water permeated through the coatings. Eventually, the coatings on some of the swollen beads ruptured due to the additional stress of swelling. This mechanism was more apparent for beads with 5–6 layers of coating. Still many swollen beads remained intact for the 24 h period of the release study.

Due to its intended use as a stable matrix for pore-forming excipients, the release of the marker dye is used an indication of a lack of integrity of NB-PDMS coatings without such excipients. A similar test of film integrity is found in the USP test for enteric coatings in which the release of the coated drug in simulated gastric fluid must not exceed 10% of the total dose in a 2 h test period (USP XXII, 1989). Although not tested under such conditions, the beads coated with six layers of NB-PDMS under the conditions described would barely pass this USP test for integrity. It is believed that the imperfect film in-

tegrity was the result of the variation in coating thickness across the surface of the beads. The lack of homogeneity of the uncoated bead surface resulted in some of that variation. Another factor that had the potential to decrease the uniformity of the coating thickness was adhesion and subsequent separation of two or more tacky coated beads as they rolled in the mini-pan coater that was devised for this research. By this process, one bead picks up coating from another bead, leaving one bead with a small lump in its coating and the other bead with a pit in its coating. These inhomogeneities cause stress concentration at the points where thin coating meets thick coating. During swelling, it is expected that these are the points of rupture. At each sampling time the beads were visually inspected. It was noted that some beads became swollen by the dissolution medium and eventually ruptured. Due to the large number of beads (50) in each dissolution cell, the rupture of an individual coating did not result in a burst or sudden increase of dye present in the dissolution medium at a single time point. However, the combined mechanisms of dye leaching out from existing defects and the eventual rupture of individual coatings resulted in a prolonged release of the marker dye from the coated beads. This indicates a reduction in coating integrity over time.

In order to improve film integrity by reducing tackiness, two parameters were investigated – the presence of filler and the effect of irradiation time. The presence of filler did not reduce aggregation of the coated beads which were irradiated for 1 min per layer of coating, but did significantly reduce aggregation of the coated beads irradiated for 3 and 6 min per layer (Table 1). The inability of the filler to reduce the aggregation of beads irradiated for 1 min per layer of coating was probably due to incomplete curing through the partially opaque films. Nevertheless, the decrease in aggregation of filled, coated beads irradiated for 3 min per layer correlated well with an increase in the time for 20% of marker dye to be released from these coatings (Table 1). Thus, it appears that a decrease in the degree of aggregation correlates with an increase in integrity as assessed by marker dye release. This is not true for beads coated with filled NB-PDMS and irradiated for 6 min per layer of coating where the extended exposure to irradiation appears to have a detrimental effect on the integrity of the coatings. The doubling of the radiation dose from 3 to 6 min per layer is expected to result in a localized elevated temperature at the bead surface. For partially cured coatings, the elevated temperature can cause an increase in tackiness resulting in the adhesion and separation leaving defects in the coating. While not statistically significant, the small increase in aggregation at 6 min of irradiation per layer supports such a mechanism. Thus, within the range of experimental conditions explored in this phase of research, filled coatings exposed to 3 min of irradiation per coating layer yield film coatings of the highest integrity.

The research described in this report demonstrates that photocuring can be used in a laboratory device approximating the conditions of traditional pan coating equipment to successfully coat nonpareil beads. The film coatings obtained are of adequate integrity as assessed by scanning electron microscopy and release of a marker dye. These coatings have no evidence of pores or striations seen in many solvent based film coatings. It should be noted that the NB-PDMS by itself is not suitable as a functional pharmaceutical coating. In order to prepare functional coatings (e.g., enteric, immediate or controlled release coatings), excipients including polymer blends or copolymer systems must be added to the silicone matrix. Such an approach has been explored in aqueous-based silicone coatings (Li and Peck, 1991).

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