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The Effects of Heat and Desiccation Treatment on the Controlled Release Properties of Aqueous Silicone Latex Coated Tablets

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ABSTRACT

An aqueous based polymeric coating system, polydimethyl-siloxane elastomer latex, was employed to coat acetaminophen tablets. Drug release characteristics due to this polymer coating were monitored by in-vitro dissolution tests. It was found that heat treatment of the coating and the desiccation pretreatment significantly changed the drug release profiles compared to untreated, coated tablets. The slowest drug release rate was obtained by desiccating the coated tablets for 24 hours or more followed by heat treatment at 40°C for at least 4.5 hours. Rupturing of the coating layer during dissolution testing was observed only if the curing process was not utilized. As expected, drug released at a given time was inversely proportional to the coating thickness.

INTRODUCTION

Polyorganosiloxane chemistry has been evaluated for more than 100 years. It has been extensively reviewed and discussed in a recently published textbook [1]. Dow Corning has utilized polyorganosiloxane chemistry to develop an aqueous based polymeric coating system for the pharmaceutical industry. This potential

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controlled release film coating system is composed of an emulsion polymerized and crosslinked product of hydroxyendblocked polydimethylsiloxane (PDMS) and an alkoxysilane [2]. Some of the properties of polydimethylsiloxane include good thermal stability, low surface energy, a solubility parameter of approximately 7.5 $\sqrt{cal/cm^3}$ [1], and a glass transition temperature of -123°C [3]. PDMS has previously been characterized as free films [4] and as a coating system [5, 6]. Due to the poor mechanical strength of PDMS, a colloidal silica dispersion containing 4 nm particles is added to the polymer coating suspension to strengthen the coating [1, 2]. Since it has been widely reported that silastic type membranes are impermeable to ions [7], it is necessary to add a pore forming agent to the coating system. The pore forming agent will increase the coating layer permeability to the penetrating species of interest. The purpose of this work is to evaluate the utility of this coating material on single unit dosage forms and to evaluate various curing treatment modifications such as desiccation pretreatment, heat treatment (curing) temperature, and the length of heat treatment on drug release.

EXPERIMENTAL

Materials

The silicone elastomer latex used in this study was supplied by Dow Corning Company, Midland, MI. The latex suspension has a mean particle size of 250 nm, pH of 7-8 and a total solids content of approximately 52% (w/w). The colloidal silica solution, trade name of Nalcoag 1115, was obtained from Nalco Chemical Company, Chicago, IL. This solution contains approximately 15% (w/w) of solids content having a mean particle size of 4 nm and a solution pH of 10.5. The polyethylene glycol 8000 (PEG 8000) was NF grade and obtained from Union Carbide Co., Danbury, CT. The tablet core is composed of acetaminophen, USP, microcrystalline cellulose, NF and magnesium stearate, NF. Acetaminophen and magnesium stearate were supplied by Mallinckrodt, Raleigh, NC and Mallinckrodt, St. Louis, MO, respectively. Microcrystalline cellulose, Avicel PH-102 type, was obtained from FMC, Philadelphia, PA.

Granulation and Tabletting

A 3:1 ratio of acetaminophen and microcrystalline cellulose was blended in a Collette Gral-10 mixer (Collette, Chicago, IL) for 2 minutes and wet granulated by spraying purified water at a spray rate of 25 gm/min for 17 minutes to obtain a wet mass of appropriate texture. After screening the wet granules through a #10 mesh screen, the granules were dried in a 50°C oven for 1 day and milled through a #20 mesh screen. Additional microcrystalline cellulose was then dry blended with the granules to obtain the final formulation which had 30% of the total microcrystalline cellulose added extragranularly. Magnesium stearate (0.5% w/w) was mixed with the powder blend in a P-K blender for 2 minutes before the final blend was compressed into tablets using 5/16" round, deep concave punches on a Stokes F-3 tablet press (Pennwalt, Warminster, PA). The final weight and

hardness for the tablets were 460 mg (containing 310 mg of active) and 8 kp, respectively.

Coating Process

The method to prepare the coating suspension involved: 1) dissolving the appropriate amount of PEG 8000 in purified water, and 2) mixing the PEG 8000 solution with a mixture of silicone elastomer latex and Nalcoag 1115 silica in a stainless steel beaker. The silicone and silica solids ratio was 2:1 in the final suspension. The final suspension contained 25% w/w solids (35% w/w of the total solids was PEG 8000). The high level of PEG 8000 was chosen because preliminary work in these laboratories showed long lag times would occur at lower PEG 8000 levels. The coating suspension was continuously stirred and pumped via a MasterFlex^{R} peristaltic pump (Cole Parmer Instruments, Chicago, IL) to the Vector-Freund Model HCT-30 Mini Hi-Coater (Vector Corp., Marion, IA). The coating conditions consisted of a pan rotation speed of 20 rpm, an inlet air temperature of 90^{o} C, and an outlet air temperature of 45^{o} C. Low spray rate (e.g. 2 gm/min) was required during the first 30 minutes and increased to 6 gm/min during the remainder of the coating process. Tablets were coated to a 19% weight gain, however some tablets were removed from the coating pan at various times during the coating process so the effect of various coating levels on drug release could be evaluated.

Heat and Desiccation Treatments of the Coated Tablets

The coated tablets were divided into three groups to evaluate the effects of curing conditions on drug release through the polymer coating. The groups included untreated, heat treated, and desiccation pretreated plus heat treated tablets. The desiccation pretreatment was completed by placing the tablets in a desiccator containing Drierite (W.A. Hammond Drierite Co., Xenia, OH), applying house vacuum, and leaving the tablets at room temperature for 6, 24 or 65 hours. Weight losses before and after desiccation were recorded. The heat treatment of the tablets was accomplished by placing several tablets in a petri dish and storing them in the chamber at a specified temperature (e.g. 40, 50, 60 or 80^{o} C). Tablets were removed from the chamber for dissolution testing after a period of 1, 4.5, 8, 24, 48, 72 or 96 hours.

Dissolution Testing

Drug release characteristics of the uncured and/or cured coated tablets were monitored using a dissolution apparatus (Hanson, Northridge, CA) interfaced to an HP-8451A diode array spectrophotometer (Hewlett-Packard, Palo Alto, CA). The USP XXI Apparatus II (paddle method) with a stirring speed of 60 rpm was employed [8]. Each tablet was placed in a glass vessel containing 900 ml of purified, deaerated water maintained at 37^{o}C. The amount of acetaminophen released from each tablet was determined by comparing the UV absorbance at 244 nm against a standard.

RESULTS AND DISCUSSION

Several factors will affect drug release from polymer coated, single unit dosage forms. The more fundamental parameters include the membrane surface area and thickness, drug solubility, and the apparent diffusion coefficient of the drug substance through the polymeric film. However, in the case of dosage forms coated with the newly developed water-based polymeric dispersions, subtle processing and storage conditions may also override the aforementioned factors to some degree. For instance some previous work demonstrated the effects of heating (curing) time and temperature, storage time and temperature, and an overcoat [9-11] on drug release. The effect of some of these factors are discussed below for the polydimethylsiloxane/silica coating system.

Effect of Coating Level on Drug Release

Figure 1 illustrates the dramatic differences in drug release profiles among the tablets with various coating levels. The uncoated tablets disintegrated within 15 minutes and totally dissolved within 45 minutes. The 8% coated tablets broke into two open halves at the circumference during dissolution testing, presumably due to the forces exerted on the silicone/silica film from the tablet core. Hence a significantly faster release rate was observed for the tablets covered with 8% coating compared to tablets coated to 19%. Since both 8% and 19% coated tablets had been cured at 60° C for 96 hours, the fracturing of the 8% coated tablets indicated that 8% coating was not strong enough to maintain the integrity of the dosage form in water. The high percentage of PEG 8000, its affinity for the hydrophilic silica [4], and the inherent lack of tensile strength of polydimethylsiloxane undoubtedly contributed to this observation. Therefore, tablets with 19% coating were chosen to evaluate the effects of curing conditions on drug release and thus determine the optimum curing conditions for this type of controlled release coating system. Dissolution testing was also performed on the uncoated tablet cores cured at 80° C for 96 hours as the control for heat treatment. The results demonstrated that heat treatment did not affect the dissolution behavior of the core.

Effect of Curing on Drug Release From Tablets With 19% w/w Coating

Curing time and temperature as well as high temperature storage conditions are known to affect the coalescence phenomenon for latex films sprayed from an aqueous coating system. Vanderhoff and his co-workers [12] have described the coalescence phenomenon of latex particles. Figure 2 demonstrates that heat treatment significantly decreased the drug release from the tablets compared to the uncured tablets. It was observed that the coating on some uncured tablets either partially or completely ruptured at the tablet circumference during dissolution testing. The dosage form remained intact in the dissolution medium in the situation where the coating only partially ruptured. Because rupture of each uncured, coated tablet did not occur at the same time, large standard deviations (ranged from 0.5 to 9.9, n=12) for the percent released data for the

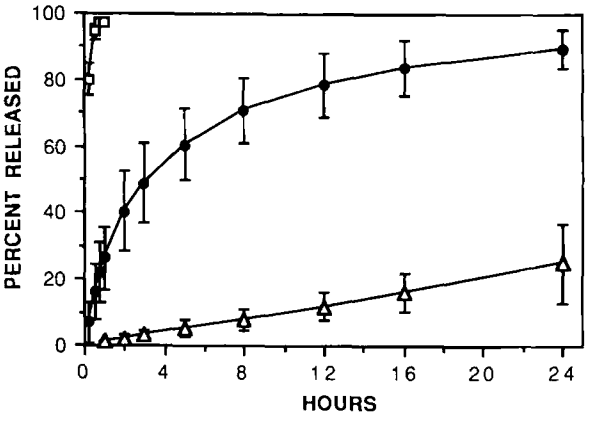

Figure 1.
Acetaminophen release profiles showing the effect of coating level on drug release. Key: uncoated, uncured tablets (□ , n=12)*; tablets coated with 8% weight gain cured at 60° C for 96 hours (● , n=6); tablets coated with 19% weight gain cured at 60° C for 96 hours (△ , n=6). *Standard error bars are within the symbol.

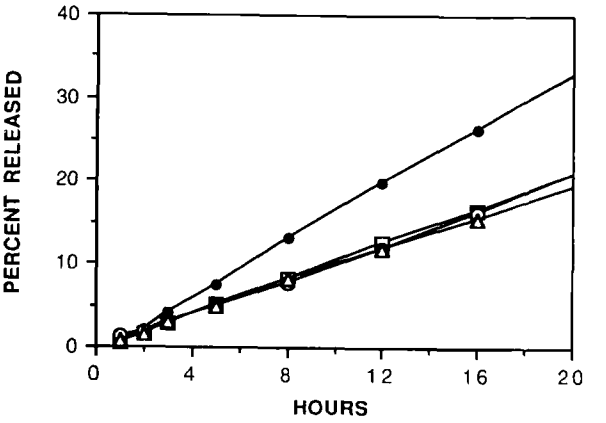

Figure 2.
Effect of curing on acetaminophen release from tablets with 19% coating. Key: uncured tablets (● , n=12); tablets cured at 40° C for 24 hours (□ , n=12); tablets cured at 60° C for 96 hours (○ , n=6); tablets cured at 80° C for 1 hour (△ , n=6). Standard error bars were omitted for clarity. See text for the range of standard deviations.

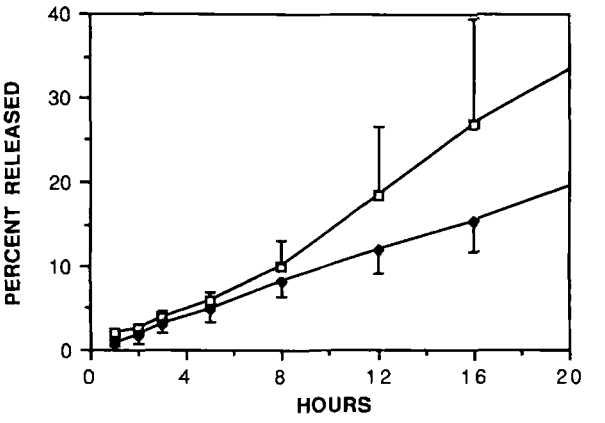

Figure 3.
Effect of curing time on acetaminophen release from tablets with 19% coating cured at 80° C. Key: tablets cured for 96 hours (□ , n=6)*; tablets cured for 1 hour (● , n=6). *Large standard errors were due to the breaking of four tablets during dissolution testing.

uncured tablets were obtained. All cured tablets remained intact during dissolution testing in water and the standard deviations only ranged from 0.4 to 6.1. The impact of heat treatment on this polymer system in reducing the release rate and standard deviation is a surprising result because the glass transition temperature of this polymer has been reported to be well below room temperature [3,13]. These curing effects may be due to the removal of enough water that coalescence can continue.

It was also observed that similar release profiles were obtained when the coated tablets were cured at 40° C, 60° C or 80° C for 24 hours, 96 hours or 1 hour, respectively. The consistency in drug release implies that complete coalescence could be achieved by heating the tablets at 80° C for 1 hour or at lower temperatures for 24 hours. Since 1 hour at 80° C was so effective in slowing the release of acetaminophen from the coated tablet core, it was of interest to see if more coalescence and subsequent slowing of drug release would occur when the coated tablets were subjected to the same heat treatment for 96 hours. As discussed previously, heat treatment did not affect the characteristics of the tablet core. However the additional curing of the tablets at 80° C appeared to weaken the coating strength because the tablet coating fractured in 4 out of 6 tablets approximately 8 hours after commencement of the dissolution test. The ruptured tablets resulted in a release profile that was significantly faster than tablets cured for one hour at 80° C (Figure 3). It could be speculated that the excess curing removes too much water from the polymeric film, which leads to a lack of plasticizer in the film. A change in the color of the tablets from opaque white to

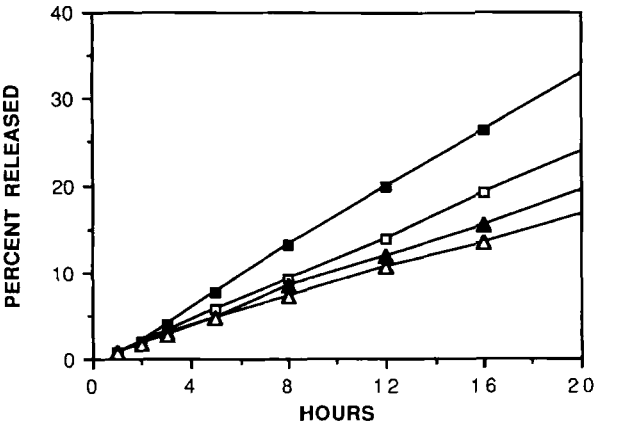

Figure 4.
Effect of 65 hours desiccation pretreatment on acetaminophen release from tablets coated with 19% polymer. Key: uncured tablets without desiccation (■ , n=12); uncured tablets with desiccation (□ , n=6); tablets cured at 80° C for 1 hour without desiccation (▲ , n=6); tablets cured at 80° C for 1 hour preceeded by desiccation pretreatment (△ , n=6). Standard error bars were omitted for clarity, but are included in the text.

dark brown also occurred, possibly due to oxidative degradation of PEG 8000. Because PEG 8000 is susceptible to oxidative degradation in environments such as air, it is suggested that exposure of PEG 8000 to elevated temperatures and/or oxygen be minimized [14]. Alternatively, addition of a commercially available antioxidant can also deter oxidative degradation.

One other major consequence of using PEG 8000 as a pore former is that it has a melting range of 60° to 63° C [15]. Curing coated tablets at a temperature of 60°C or above may effectively melt the PEG 8000 out of the coating shell thereby leaving a silicone/silica shell, which would dramatically reduce the dosage form's ability to release drug. Some PEG 8000 was observed remaining on the petri dish after curing the tablets at 80° C. However, if it is assumed that the elevated curing temperature reduces the level of pore former due to melting, the 40° C cured tablets should give a different release profile compared to the tablets cured above the melting point of PEG 8000. This means that the release rate from the tablets cured at 60° C should have been slower due to loss of PEG 8000 and concomitant closure of the empty domain due to fusion of the silicone latex particles. However, since there was no difference in release rates between tablets cured at less than 60° C and those greater than or equal to 60° C, this implies that very little PEG 8000 is lost resulting in film coalescence around the immiscible PEG 8000 domains.

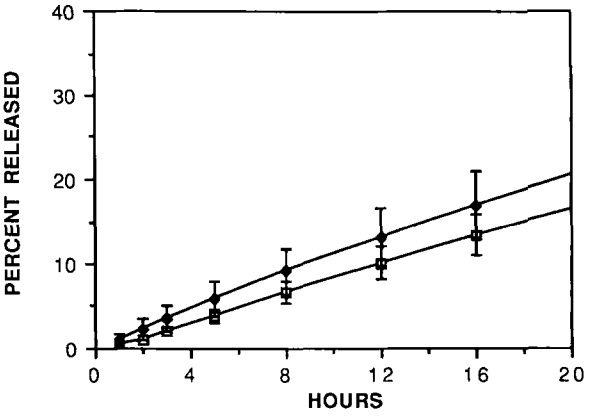

Figure 5.
Effect of 24 hours desiccation pretreatment preceeding curing at 40° C for 4.5 hours on acetaminophen release from 19% polymer coated tablets. Key: undesiccated tablets (◆ , n=6); desiccated tablets (□ , n=6).

Effect of Desiccation on Drug Release From Tablets With 19% w/w Coating

Because coalescence is a function of latex particle deformation and moisture removal, the feasibility of desiccation was studied in enhancing the film-forming process. Desiccation may also be useful for those compounds which can not withstand excessive thermal stress. A desiccation pretreatment phase of 65 hours was evaluated and shown to slow drug release for both cured and uncured coated tablets (Figure 4). Although still unacceptable, a significant decrease in the frequency of ruptured coatings for desiccated, uncured tablets (1 out of 6), compared to the uncured tablets without desiccation pretreatment (7 out of 12) was observed. This also resulted in a slower average release rate and narrower standard deviation among desiccated tablets. For instance, the standard deviations for uncured, undesiccated tablets were approximately 1.5-fold higher than the desiccated, uncured tablets. For the cured tablets, additional desiccation pretreatment continued to show the trend where drug release is decreased, i.e. from 15.5% to 13.5% at the 16-hour time point, however, the magnitude of the decrease is not significant. The standard deviation among 6 tablets were similar for desiccated and undesiccated tablets and ranged from 0.4 to 4.2, which is less than half the value observed for the uncured, undesiccated tablets. A 0.5% weight loss was observed after desiccation treatment.

For the tablets cured at 40° C for only 4.5 hours, the addition of 24 hours desiccation pretreatment also slowed the drug release (Figure 5) and the release profiles were similar to those of the tablets cured at 80° C for one hour with 65 hours of desiccation pretreatment. Therefore, a long desiccation pretreatment phase of 65 hours before curing is not necessary, and the same effect will result

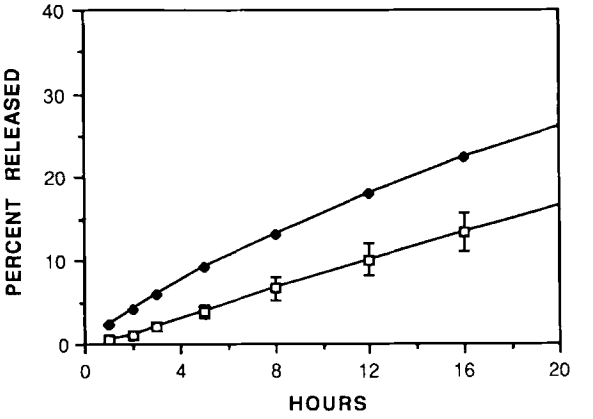

Figure 6.
Acetaminophen release profiles for the tablets pretreated with 24 hours desiccation before curing at 40° C. Key: tablets cured for 1 hour (◆ , n=6); tablets cured for 4.5 hours (□ , n=6). Standard deviations were wide (i.e. ranged from 4 to 20) for the upper curve due to the rupture of one coated tablet. Error bars left off the upper curve for clarity.

from 24 hours of desiccation. Additionally, three out of 6 tablets partially cracked at the circumference when there was no desiccation pretreatment and the fracturing of the coating was totally avoided by incorporating 24 hours of desiccation pretreatment before curing at 40° C for 4.5 hours. Six hours of desiccation did not improve the coating strength as evidenced by one tablet completely rupturing and one tablet showing a small fissure during dissolution testing of six tablets.

Another study was performed to further evaluate if sufficient curing could be obtained by heat treatment at 40° C for only one hour in combination of 24 hours of desiccation pretreatment. It was found that one out of six tablets ruptured during the dissolution test which led to a considerably faster average release rate than those tablets cured for 4.5 hours at 40° C (Figure 6). It is therefore suggested that tablets be desiccated for 24 hours followed by curing at 40° C for at least 4.5 hours.

CONCLUSION

This work has favorably shown the utility of the new emulsion polymerized and crosslinked PDMS aqueous coating system. Coating level, heat treatment and desiccation pretreatment significantly decreased the drug release rates and enhanced the integrity of the coating. However, these parameters must be

carefully optimized to prevent the occurrence of either dose dumping due to rupture of the coating after immersion into either biological fluids or the dissolution medium. One advantage of the present coating system is that no tackiness is observed during the coating process which is unlike the characteristics of other aqueous latex dispersions. The most notable observation with respect to the tablet coating's physical appearance is the unique rubbery texture. Furthermore the coating can be subjected to high temperatures and does not require an overcoat.

REFERENCES

1. I. Yilgor and J.E. McGrath, Polysiloxane Containing Copolymers: A Survey of Recent Developments, in Advances in Polymer Science: Polysiloxane Copolymers/Anionic Polymerization, Volume 86, Springer-Verlag, New York, NY, 1988.

2. Dow Corning technical information presented to Syntex Research, October 24, 1988.

3. W. Noll, Chemistry and Technology of Silicones, Academic Press, New York, NY, 1986.

4. L.C. Li and G.E. Peck, Drug Dev. Ind. Pharm., 15 (1), 65-95 (1989).

5. L.C. Li and G.E. Peck, Drug Dev. Ind. Pharm., 15 (4), 499-531 (1989).

6. L.C. Li and G.E. Peck, Drug Dev. Ind. Pharm., 15 (12), 1943-1968 (1989).

7. R.J. Kostelnik, "Polymeric Delivery Systems", Gordon and Breach Science Publishers, New York, NY, 1978.

8. USP XXII/NF XVII, United States Pharmacopeial Convention, Inc., Rockville, MD, Mack Publishing Co., Easton PA, 1989, pp. 1580.

9. F.W. Goodhart, M.R. Harris, K.S. Murthy, and R.U. Nesbitt, Pharm. Technol., 8 (4), 64-71 (1984).

10. R. Chang, C.H. Hsiao, and J.R. Robinson, Pharm. Technol. 11 (3), 56-68 (1987).

11. I. Ghebre-Sellassie, U. Iyer, D. Kubert, and M. B. Fawzi, Pharm. Technol., 12 (9), 96-106 (1988).

12. J.W. Vanderhoff, H.L. Tarkowski, M.C. Jenkis, and E.B. Bradford, J. Macromol. Chem., 1, 361, 1966.

13. W. Hofmann, Kunststoffe German Plastics, 78 (2), 14-20 (1988).

14. Carbowax^{R} Polyethylene Glycols, Union Carbide Corporation, Industrial Chemicals Division, Danbury, CT, 1986, page 4.

15. Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, Washington, DC, 1986, page 210.