Drug Development and Industrial Pharmacy, 22(3), 269–274 (1996)

Development and Characterization of an Oral Controlled-Release Delivery System for Melatonin

Beom-Jin Lee,[1] Keith A. Parrott,[2] James W. Ayres,[2] and Robert L. Sack[3]

[1]College of Pharmacy, Kangwon National University, Chuncheon, Korea
[2]College of Pharmacy, Oregon State University, Corvallis, OR
[3]Department of Psychiatry, School of Medicine, Oregon Health Sciences University, Portland, OR

ABSTRACT

Sugar spheres loaded with melatonin (MT) were coated with Aquacoat® to control the release rate of MT. Dissolution of MT was evaluated using the USP basket method. With 18–20 mesh beads, $T_{50\%}$ (time to release 50% of drug) for 5%, 10%, and 20% coatings was 10 min, 35 min, and 60 min, respectively. A desired release pattern over 8 hours was obtained with 20% coating on 8–10 mesh beads. $T_{50\%}$ for 5%, 10%, and 20% coatings was about 1, 2, and 4 hours, respectively. MT in 20% coated beads was quite stable during storage at room temperature with less than 5% MT degraded during 6 months of storage. Dissolution profiles from 8–10 mesh beads with a 20% coating were unchanged after 6 months of storage at room temperature. Administration of the dosage form to human subjects maintained MT plasma concentrations over 100 pg/ml for approximately 8 hours.

INTRODUCTION

Melatonin (MT) is an indole amide neurohormone (1). It is primarily secreted by the pineal gland in a circadian rhythm (2). Exogenous MT has been used as a circadian rhythm synchronizer in humans to treat a variety of circadian rhythm disorders including sleep disorders, jet lag, shift work syndrome, and seasonal depression; it may also help blind and elderly people with desynchronized rhythms (3–5). It may be desirable to develop controlled-release dosage forms that deliver MT over 8 hours so that the normal endogenous plasma profile of MT may be reestablished in selected individuals whose MT plasma profile differs from that found in normal subjects.

Application of aqueous polymeric film coatings to drug-loaded nonpareils (sugar spheres, NF) is a common method of developing controlled-release dosage

forms (6,7). Aqueous polymeric ethylcellulose suspension (Aquacoat®) has replaced the conventional organic solvent-based coating methods because of the potential toxicity and high costs associated with organic solvents (8,9). Aquacoat® is an ethylcellulose dispersion stabilized by sodium lauryl sulfate and cetyl alcohol (9). Plasticizers must be added to these polymeric suspensions prior to their use. Plasticizers provide flexibility for the coating polymer by lowering its glass transition temperature, promoting film coalescence, and making the polymer more susceptible to deformation. Diethyl phthalate, dibutyl sebacate, and triethyl citrate are commonly used as plasticizers (8,9).

The fluid bed process is increasingly popular for coating of drug-loaded particles such as granules, beads, and sugar spheres (10,11). Fluid-bed coating utilizes three basic approaches to spray coating materials: top, tangential, or bottom spray patterns (Wurster). The fluidized bed process using bottom spraying with a Wurster air-suspension column provides the best conditions for coalescence of small polymeric particles, coating efficiency, homogeneous drug disposition, and reproducible release characteristics (7,11,12). Drug release rate from a polymer coated system is sensitive to various parameters such as coating thickness, coating morphology, amount of additives and plasticizers, physicochemical properties of drugs, and polymeric components. Therefore, optimizing processing and formulation parameters is required to ensure desired release rates of drugs (12–14).

The purpose of this study was to develop an oral controlled-release delivery system that releases MT over an 8 hr period. Release rates of MT from coated beads were investigated by varying the sugar pellet size and the amount of polymer coating. Stability of MT in the delivery system and the release rate of MT from the coated beads after storage was also determined.

MATERIALS AND METHODS

Materials

Melatonin (MT) was obtained from Regis Chemical Co. (Morton Grove, IL). Core sugar spheres (USP/NF) as a substrate for MT loading were from Paulaur Co. (Robbinsville, NJ). Polyvinylpyrrolidone (average molecular weight 40,000) and hydroxypropylcellulose (average molecular weight 300,000) were from Aldrich Chemical Co. (Milwaukee, WI). Aquacoat® (polymeric ethylcellulose suspension: type ECD-30) containing 30% solids was provided courtesy of FMC Corp. (Philadelphia, PA). Sebatic acid dibutyl ester was from Sigma Chem. Co. (St. Louis, MO) and triethyl citrate was from Aldrich Chemical Co. (Milwaukee, WI). All other chemicals were of reagent grade and were used without further purification.

Equipment

The apparatus for MT loading on sugar spheres and applying the polymeric film coating consisted of a laboratory scale spray coater having a Wurster column (2 inches × 7 inches, STREA-1, Aeromatic Inc., Columbia, MD) inside a clear plexiglass chamber mounted on a fluid-bed dryer (Lab-Line/P.R.L. Hi-Speed Fluid Bed Dryer, Lab-Line Instruments Inc., Melrose Park, IL). A peristaltic pump was used to deliver solutions to the spray nozzle. The entire equipment was located in a ventilating hood. Typical processing conditions for MT loading and coating of MT-loaded beads are given in Table 1.

Preparation of MT-Loaded Beads

A mixture of MT (1.2 g) and polyvinylpyrrolidone (0.24g) and hydroxypropyl cellulose (0.12 g) as binders in 200 ml of ethanol was applied to 300 grams of prewarmed sugar beads (retained on either an 18–20 or an 8–10 mesh screen) in a fluid-bed coating chamber at 40°C with a continuous fluidizing air supply. The solution was delivered at 4 ml/min using a peristatic pump.

Table 1

Typical Processing Conditions for Coating of MT-Loaded Beads (STREA-1, Aeromatic)

Wurster insert	Bottom spray
Nozzle size	0.8 mm
Inlet temperature[a]	50°C
Atomization air	12–15 psi
Fluidization air blower	50–70% of full capacity
Flow rate[b]	1 ml/min and 4 m/min

[a]40°C was used for the preparation of MT-loaded beads.
[b]4 ml/min was used for the preparation of MT-loaded beads. Peristaltic pump was manually switched between "on" and "off" as necessary to control clumping of beads during the coating process.

Coating Process

Dibutyl sebacate (4.5 g) and triethyl citrate (4.5 g) as plasticizers were added to 100 g of Aquacoat® suspension. The Aquacoat® suspension was then diluted with deionized water (w/w, 1:1) to give the final coating suspension. The coating suspension was stirred for at least 2 hours prior to application to ensure that plasticizers were well mixed with the coating suspension. It was also continuously stirred throughout the coating process. The coating suspension was applied to 90 g of MT-loaded beads with a continuous air supply at a rate of 1 ml/min for 10 minutes and then 4 ml/min, using a peristaltic pump, to achieve the desired coating. A theoretical coat, based on the solids content of Aquacoat®, of 5%, 10%, or 20% was achieved by applying 31.4 g, 62.7 g, or 125.4 g of coating solution, respectively (see Table 2). Although some solids from the coating suspension are lost during the coating process, coatings are designated as 5%, 10%, or 20% for convenience. The final coated beads were dried in the coating chamber for 30 minutes and then further air dried in a hood.

HPLC Analysis of MT

MT concentration in solution was determined using a HPLC system (Water Associates, Milford, MA) consisting of a delivery pump (M-600A), an automatic sample injector (WISP 712B), a reversed-phase (C18, 4 μm) radial compression column, a Model 441 absorbance detector with 229 nm light source, and a C-R3A Chromatopac Integrator (Shimadzu Corp, Kyoto, Japan). Mobile phase consisted of 50% (v/v) methanol in 0.01 M sodium acetate buffer (pH 4.7). The flow rate was 1.1 ml/min. Methylparaben (16.7 μg/ml) was used as an internal standard. The standard calibration curve was constructed by plotting the ratio of MT peak area/internal standard peak area versus known MT concentrations ranging in concentration from 0.04 to 0.5 μg/ml.

Table 2

Preparation of Coating Suspension and Coated MT Beads

Ingredient	Coating Suspension Quantity (g)	Coating Suspension % (w/w)
Aquacoat®[a]	100.0	47.85
Dibutyl sebarate	4.5	2.15
Triethyl acetate	4.5	2.15
Water	100.0	47.85

MT Beads	Coated M-T Beads: Coating Suspension (g)	Solids[b] (g)	% Coat (g)
90	31.4	4.5	5
90	62.7	9.0	10
90	125.4	18.0	20

[a]30% solids, w/w.
[b]From Aquacoat®

Assay for MT Content from Beads

About 2 g of MT-loaded or -coated beads were ground into a fine powder using a mortar and pestle. About 100 mg of powder was accurately weighed and transferred to 1 ml of 95% (v/v) ethanol. The suspension was agitated and centrifuged at 10,000 g for 10 min. The supernatant was removed and the pellet resuspended with 1 ml of 95% ethanol. This step was repeated three times. The supernatants were then combined and diluted with deionized water. MT concentration was determined by HPLC.

In Vitro Dissolution

In vitro dissolution of each formulation was performed in triplicate using the USP dissolution apparatus I (Basket method) at 37 ± 0.5°C. The stirring rate was 50 rpm except when the effect of the stirring rate on the release rate of MT was evaluated. Dissolution medium for the first 2 hr was 900 ml of enzyme-free simulated gastric fluid (pH 1.4 ± 0.1) followed by enzyme-free simulated intestinal fluid (pH 7.4 ± 0.1). Dissolution samples were collected at 0.25, 0.5, 0.75, 1.0, 1.5, and 2 hr (in gastric fluid), and 3, 4, 5, 6, 8, 12, and 24 hr (in intestinal fluid) with replacement of equal volume with temperature equilibrated media. MT concentrations in dissolution samples were determined by HPLC.

Stability of MT in Coated Beads

Uncoated and Aquacoat® coated MT beads were placed in polyethylene containers and stored at room temperature (24 ± 2°C) and protected from light to evaluate drug stability. MT content of the beads after storage for 6 and 9 months was determined in duplicate

according to the procedure described previously. Dissolution of the 20% coated beads (8–10 mesh) after 6 months of storage was also determined.

RESULTS AND DISCUSSION

The amount of MT assayed from beads is summarized in Table 3. Because some MT was lost to the coating chamber wall, supply tube, Wurster column, and through exhaust from the chamber during processing, the content of MT assayed was about 80% of total MT applied.

In Vitro Dissolution

Dissolution profiles of MT from 18–20 mesh beads coated with Aquacoat® are shown in Figure 1. Most MT was released in simulated gastric fluid, and the desired controlled release was not achieved. Dissolution profiles of MT from 8–10 mesh beads coated with Aquacoat® are shown in Figure 2. A desired controlled-release pattern was observed over 8 hr at 20% coating. $T_{50\%}$ (time to release 50% of drug) of MT from 18–20 mesh and 8–10 mesh coated beads is compared in Figure 3. As coating amounts are increased, $T_{50\%}$ of MT is increased, as expected. $T_{50\%}$ was about 4 hr for the 20% coating of 8–10 mesh beads that provided the controlled release over 8 hr.

Dissolution profiles of MT from 20% coated beads (8–10 mesh) as a function of stirring speed are compared in Figure 4. No statistically significant change of MT release rate was observed in 20% coated beads (8–10 mesh) as stirring speed increased from 50 to 100 rpm.

Table 3

Amount of MT (mg per gram of bead) Assayed in Beads

Size	Theoretical % Coating	Amount (mg/g bead)
80–10 mesh	0	3.26 ± 0.11
	5	2.71 ± 0.07
	10	2.70 ± 0.09
	20	2.49 ± 0.10
18–20 mesh	0	3.50 ± 0.10
	5	3.50 ± 0.05
	10	3.40 ± 0.03
	20	3.05 ± 0.12

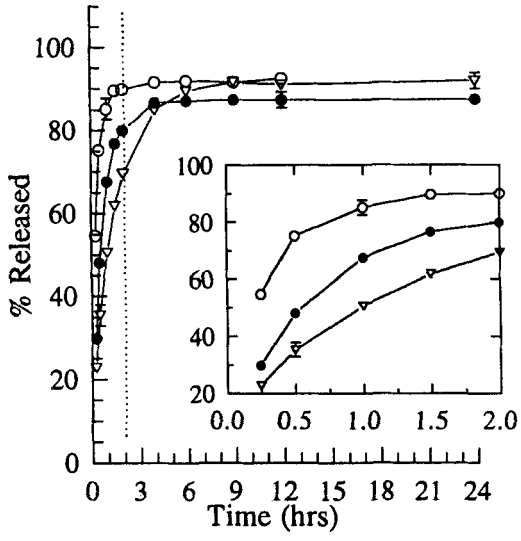

Figure 1. Dissolution profiles of MT from 18–20 mesh beads coated with Aquacoat®. Coatings: ○ 5%, ● 10%, and ▽ 20%. Each point represents the mean ± standard deviation except where the standard deviation is too small to show.

Stability of MT from Beads

The amount of MT determined per gram of beads and the percentage of intact MT from coated beads after storage at room temperature for up to 9 months is given in Table 4.

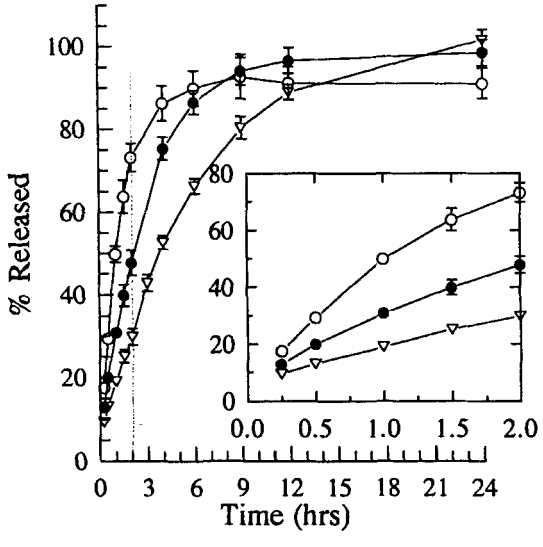

Figure 2. Dissolution profiles of MT from 8–10 mesh beads coated with Aquacoat®. Coatings: ○ 5%, ● 10%, and ▽ 20%. Each point represents the mean ± standard deviation except where the standard deviation is too small to show.

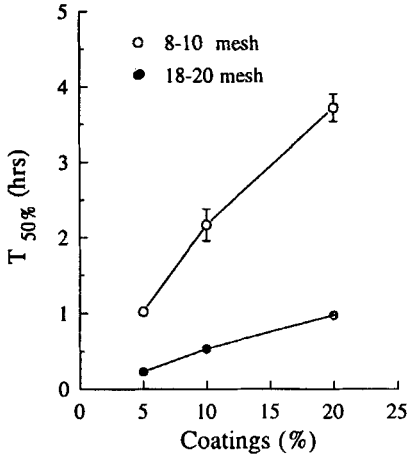

Figure 3. Time for 50% MT dissolution ($T_{50\%}$) as a function of coatings in coated beads. Each point represents the mean ± standard deviation except where the standard deviation is too small to show.

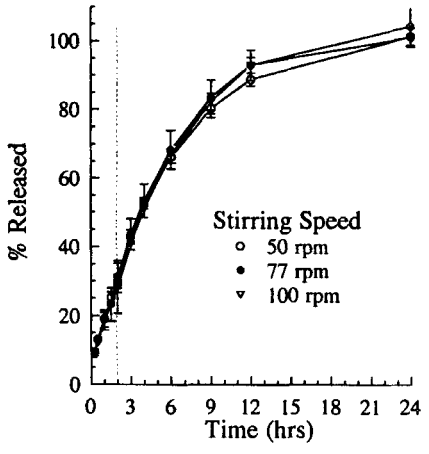

Figure 4. Dissolution profiles of MT from 8–10 mesh coated beads with 20% coatings at three different stirring speeds. Each point represents the mean ± standard deviation except where the standard deviation is too small to show.

Dissolution of MT from the 20% Aquacoat® coated beads (8–10 mesh) after 6 months of storage was relatively unchanged (see Figure 5).

CONCLUSIONS

Desired controlled release over 8 hr was not observed with the 18–20 mesh coated beads at 5%, 10%, or 20% coatings. However, 8–10 mesh beads coated with 20% Aquacoat® showed the desired controlled release over 8 hr. Stirring speed at three different settings (50, 77, and 100 rpm) did not affect the in vitro release rate of MT from the 20% coated beads (8–10 mesh). MT from coated beads was slowly degraded at room temperature but the dissolution profile of MT from 20% coated beads (8–10 mesh) was unchanged after 6 months of storage. Administration of the dosage form to human subjects (melatonin dose 0.5 mg) produced peak plasma MT concentrations of approximately 600 pg/ml that

Table 4

Amount of MT (mg per gram of bead) in Coated Beads After Storage at Room Temperature (24 ± 2°C)

Size	Coating (%)	Time (month) 0	6	9
8–10 mesh	0	3.26 ± 0.11	2.91 ± 0.07 (10.6)[a]	2.84 ± 0.05 (12.9)
	5	2.71 ± 0.07	2.55 ± 0.03 (5.90)	2.32 ± 0.04 (14.1)
	10	2.70 ± 0.09	2.65 ± 0.08 (4.41)	2.43 ± 0.04 (9.76)
	20	2.49 ± 0.10	2.35 ± 0.03 (5.48)	2.11 ± 0.06 (15.3)
18–20 mesh	0	3.50 ± 0.10	2.98 ± 0.07 (14.8)	2.92 ± 0.04 (16.4)
	5	3.50 ± 0.05	2.94 ± 0.01 (16.1)	2.58 ± 0.05 (26.4)
	10	3.40 ± 0.03	2.76 ± 0.03 (18.8)	2.68 ± 0.05 (21.3)
	20	3.05 ± 0.12	2.61 ± 0.20 (14.4)	2.51 ± 0.03 (17.7)

[a]Numbers in parentheses indicate the percentage of MT degraded based on initial amount of MT

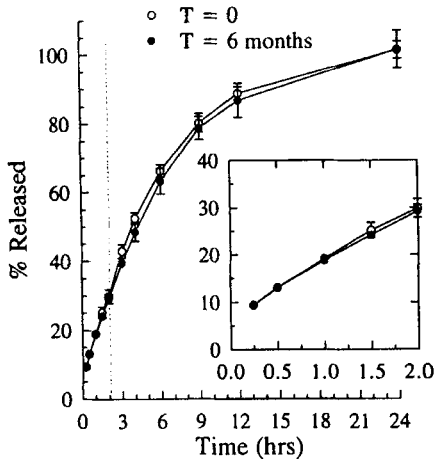

Figure 5. Comparison of dissolution profiles of MT from 8–10 mesh coated beads with 20% coatings after 6 months of storage at room temperature. Each point represents the mean ± standard deviation except where the standard deviation is too small to show.

were maintained at approximately 100 pg/ml over 8 hr (15).

ACKNOWLEDGMENT

This work was partially supported by the Gustavus and Louise Pfeiffer Research Foundation. The authors thank Wanda Parrott, Faculty Research Assistant, Oregon State University, for editorial assistance and Carol Roberts, College of Pharmacy, for her patience and assistance in preparation of this manuscript. This work was presented as a poster at the 1993 American Association of Pharmaceutical Scientists Western Regional meeting held in Reno, Nevada.

REFERENCES

1. A. B. Lerner, J. D. Case, and R. V. Heinzelman, J. Am. Chem. Soc., 81, 6084 (1959).
2. F. Waldhauser and M. Dietzel, Ann. New York Acad. Sci., 453, 205–214 (1985).
3. A. Miles, D. R. S. Philbrick, and C. Thompson, Melatonin, Clinical Perspectives, Oxford University Press, New York, 1988.
4. L. J. Petterborg, B. E. Thalen, B. F. Kjellman, and L. Wetterberg, Brain Res. Bull., 27(2), 181 (1991).
5. R. L. Sack, A. J. Lewy, M. L. Blood, J. Stevenson, and L. D. Keith, J. Biol. Rhythm, 6(3), 249 (1991).
6. I. M. Jackson, S. Robert, P. Timmins, and H. Sen, Pharm. Tech., Feb., 50–56 (1990).
7. G. S. Rekhi, R. W. Mendes, S. C. Porter, and S. S. Jambhekar, Pharm. Tech., March, 112 (1989).
8. I. Ghebre-Sellassie, U. Iyer, D. Kubert, and M. B. Fawzi, Pharm. Tech., Sep., 96 (1988).
9. Aquacoat® Manual, FMC Corp., Philadelphia, PA.
10. A. M. Mehta, M. J. Valazza, and S. E. Abele, Pharm. Tech., April, 46 (1986).
11. A. M. Mehta, Pharm. Tech., Feb., 46 (1988).
12. M. Hossain and J. W. Ayres, Pharm. Tech., Oct., 72 (1990).
13. H. M. Abdou, Dissolution, Bioavailability and Bioequivalence, Mack Publishing Company, Easton, PA, 1989.
14. B. H. Lippold, B. K. Sutter, and B. C. Lippold, Int. J. Pharm., 54, 15 (1989).
15. B-J Lee, K. A. Parrott, J. W. Ayres, and R. L. Sack, Int. J. Pharm., 124, 119 (1995).