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Diffusion of a Freely Water-Soluble Drug in Aqueous Enteric-Coated Pellets

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ABSTRACT The effects of filler used in the pellet cores (ie, waxy cornstarch or lactose) and the enteric film coat thickness on the diffusion and dissolution of a freely soluble drug were studied. Two kinds of pellet cores containing riboflavin sodium phosphate as a model drug, microcrystalline cellulose (MCC) as a basic filler, and waxy cornstarch or lactose as a cofiller were film coated (theoretically weight increase 20% or 30%) with an aqueous dispersion of cellulose acetate phthalate (CAP). The diffusion of riboflavin sodium phosphate in aqueous enteric-coated pellets was investigated using noninvasive confocal laser scanning microscopy (CLSM). The in vitro release tests were performed using a USP apparatus I (basket method). Diffusion of drug from the core to the film coat was found to be greater with lactose-containing pellets than with waxy cornstarch-containing pellets. The dissolution test showed that 30% enteric-coated waxy cornstarch pellets had a good acidic resistance in 0.1 N HCl solution for at least 1 hour, while the other enteric pellet formulations failed the test. The waxy cornstarch-containing enteric pellets dissolved at SIF in less than 10 minutes. Confocal images of film-coated pellets showed that waxy cornstarch-containing pellets had less drug dissolved than respective lactose-containing pellets. The observations were further confirmed by measurement of fluorescence intensity of riboflavin sodium phosphate in the film coat. The dissolution test was consistent with the confocal microscopy results. In conclusion, waxy cornstarch as a cofiller in the pellet cores minimizes premature drug diffusion from the core into the film coat layer.

Key Words: aqueous enteric coating, pellets, diffusion, waxy cornstarch, gastric resistance, confocal laser scanning microscopy (CLSM)

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INTRODUCTION

Enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. Polymers for enteric coating can be applied to solid dosage forms (ie, granules, pellets, or tablets) from aqueous latex or pseudolatex dispersions, aqueous solutions of alkali salts, or organic solvent solutions. The most commonly used pH-sensitive enteric polymers today include cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP), and methacrylic acid copolymers.

A problem associated with enteric-coated formulations made of aqueous disperse systems or solutions may be the lack of resistance against gastric fluid. Enteric films prepared from organic-solvent-based solutions have showed considerably lower permeability to a basic drug, theophylline, than films prepared from aqueous latex and pseudolatex dispersions [1]. It has been reported that the diffusion of a water-soluble drug was faster through films prepared from ammoniated aqueous solutions than through films prepared from organic-solvent-

based (acetone) solutions [2]. More recently, as different aqueous enteric coating systems were evaluated, tablets coated with aqueous enteric dispersions exhibited good performance in the United States Pharmacopeia (USP) dissolution test when a water-insoluble drug was used [3]. With a water-soluble substance, however, enteric-coated tablets did not pass the USP test unless the tablet cores were insulated by subcoating barriers or were coated with double amounts of the coating. Also, a number of other studies [3,4] have shown that the enteric-coated formulations made of aqueous film-coating systems gave poor gastric fluid resistance.

According to the literature, dissolution of a small amount of drug from the core tablet to the aqueous film may occur during the coating process. The higher release rates of coated pellets were attributed primarily to drug diffusion into the film layer during the coating process [5,6]. The undesired presence of a drug or an excipient in an applied film coating substantially alters the mechanical adhesion and permeation characteristics of the coating [7]. If the active ingredients are freely water soluble, they may dissolve in the spray mist during the coating process, resulting in active ingredients being included in the film. Although a suitable method to prevent this phenomenon completely has not yet been found, a fairly effective method is to keep the droplet size of the spray mist small and to use a low spray rate [8]. Visualization of drug diffusion could be performed by using, for example, the confocal laser scanning microscopy (CLSM) technique.

CLSM is widely used in cell biology and in medicine but, so far, to a minor extent in pharmaceutical solid dosage form research [9-12]. CLSM offers several advantages: (1) it allows information to be collected from a defined optical section; (2) it virtually eliminates out-of-focus fluorescence, which results in an increase in contrast, clarity, and detection; and (3) it circumvents artifacts by permitting immediate investigation of the sample, thereby avoiding any fixation procedure.

In this study, the effects of a cofiller used in the pellet core (ie, waxy cornstarch or lactose) and the effects of enteric film-coat thickness on drug diffusion and dissolution properties were studied. The diffusion of the drug was investigated by CLSM, visualizing the distribution of the autofluorescent drug in the aqueous enteric film.

MATERIALS AND METHODS

Materials

Riboflavin sodium phosphate (European Pharmacopoeia) was used as a model of freely water-soluble drug. Microcrystalline cellulose, MCC (Emcocel®, type 90M, E. Mendell, Nastola, Finland) and waxy cornstarch (Amioca®, National Starch and Chemical GmbH, Neustadt, Germany) were used as excipients in pellets. In other pellets, lactose monohydrate (Pharmatose®, type 80M, DMV International, Veghel, Netherlands) was used as a reference cofiller instead of waxy cornstarch. Purified water was used as a granulation liquid. The aqueous enteric coating solution contained cellulose acetate phthalate, CAP, (Aquateric, FMC Corporation, Philadelphia, PA), triacetin (Fluka Chemie AG, Buchs, Switzerland), Tween 80 (Fluka Chemie AG, Buchs, Switzerland), and purified water.

Preparation of Pellets

The composition of core pellets was as follows: For waxy cornstarch as cofiller, riboflavin sodium phosphate 0.1%, microcrystalline cellulose 70.6%, waxy cornstarch 29.3%; for lactose as cofiller, riboflavin sodium phosphate 0.1%, microcrystalline cellulose 70.6%, lactose 29.3%. Pellets were made with the extrusion/spheronization technique (NICA M6L mixer/granulator; NICA E170 extruder; NICA S320 spheronizer; NICA System AB, Mölndal, Sweden). The pellets were prepared in batches of 2.5 kg. The speed of the powder feeder was 35 rpm and the speed of the liquid input pump was 195 rpm for formulation I and 158 rpm for formulation II. The spheronization times for formulations I and II were 6 minutes and 2 minutes, respectively. The pellets were dried for 24 hours in a drying oven at 32°C. The dried pellets were sieved manually, and

those between 0.71 mm and 1 mm in diameter were selected for subsequent film coating.

Film Coating of Pellets

The composition of the aqueous enteric coating dispersion was as follows: Aquateric 11%, triacetin 3.9%, Tween 0.10%, and purified water 85%. The pellets were coated using an Aeromatic air-suspension film coater (Areomatic Strea-1, Aeromatic AG, Muttenz, Switzerland). Each coating batch comprised 300-g pellets. Pellet cores were preheated for 10 minutes. The inlet air temperature was adjusted to 40 ± 2 °C and the outlet air temperature to 30 ± 2°C for the Aquateric film coating. The pneumatic spraying pressure was 1.6 bar, and the air flow rate was 100 m3/h. The pump rate of the coating solution was 3.4 g/min until a 2% increase in coating weight was obtained, then proceeding at a pump rate of 6.8 g/min to complete the coating run. After spraying, the same elevated temperature was maintained for an additional 10 minutes in the drying phase to avoid the sticking problem. The pellets were then dried in an oven at 60°C for 2 hours. The theoretical amounts of coating were 20% wt/wt and 30% wt/wt of the total weight of the pellets for formulations I and II, respectively.

Dissolution Tests

The in vitro release tests were performed using a USP (U.S.A. Pharmacopoeia, 1995) apparatus I (basket method). The dissolution medium was 500 mL of 0.1 N hydrochloride acid and simulated intestinal fluid (SIF) without enzyme (pH 7.4, USP) maintained at 37 ± 0.5°C. The basket rotation speed was kept at 100 rpm. Samples were assayed by UV spectrophotometry (PERKIN ELMER, Bodenseewerk, Perkin-Elmer GmbH, Uberlingen, Germany) at 444 nm for riboflavin sodium phosphate.

Confocal Laser Scanning Microscopy (CLSM) and Image Analysis

Observations were made with a Bio-Rad Lasersharp MRC-1024 (Bio-Rad, Hemel Hempstead, UK) attached to a microscope (Axiovert 135M, ZEISS, Germany) using a Zeiss Plan-Neofluar 10x/0.30 NA air lens. A 488-nm line of a krypton-Argon laser and a laser power of 0.15 mW were used. The iris, black, gain control, and all other settings were kept constant during all experiments. Kalman for N = 6 frames per Z level was set prior to initiation of Z series. Images were recorded at intervals of 5 μm in the Z direction. The figures were maximum projection.

Each stack of pictures was evaluated using an image analysis system (ImageSpace, Molecular Dynamics, Inc, Sunnyvale, USA). The image was measured by determination of fluorescence intensity of riboflavin sodium phosphate in the film. The measurements were made in triplicate. Exactly the same size of image was determined for images at different sections. The 3-D plots were obtained by using intensity values on a section.

RESULTS

Dissolution Tests

To investigate the enteric properties of the film-coated pellets, a dissolution test was performed in 0.1 N HCl for 1 hour, and subsequently in SIF. The results showed that the 30% enteric-coated waxy cornstarch pellets had a good acidic resistance in 0.1 N HCl solution for at least 1 hour, while the other enteric pellet formulations studied failed the test (Figures 1 and 2). The waxy cornstarch-containing enteric pellets dissolved in SIF in less than 10 minutes. Figure 2 shows that neither the 20% nor the 30% enteric-coated lactose pellets gave acidic resistance. As regards pellet cores, waxy cornstarch-containing pellets released the drug slower than respective lactose pellets.

Confocal Images and Image Analysis

The CLSM images of uncoated (Figure 3A) and coated (Figure 3B) waxy cornstarch pellets were shown in Figure 3. The pellets appeared to have a smooth surface (Figure 3A). In the film-coated waxy cornstarch pellets (Figure 3B), appreciable

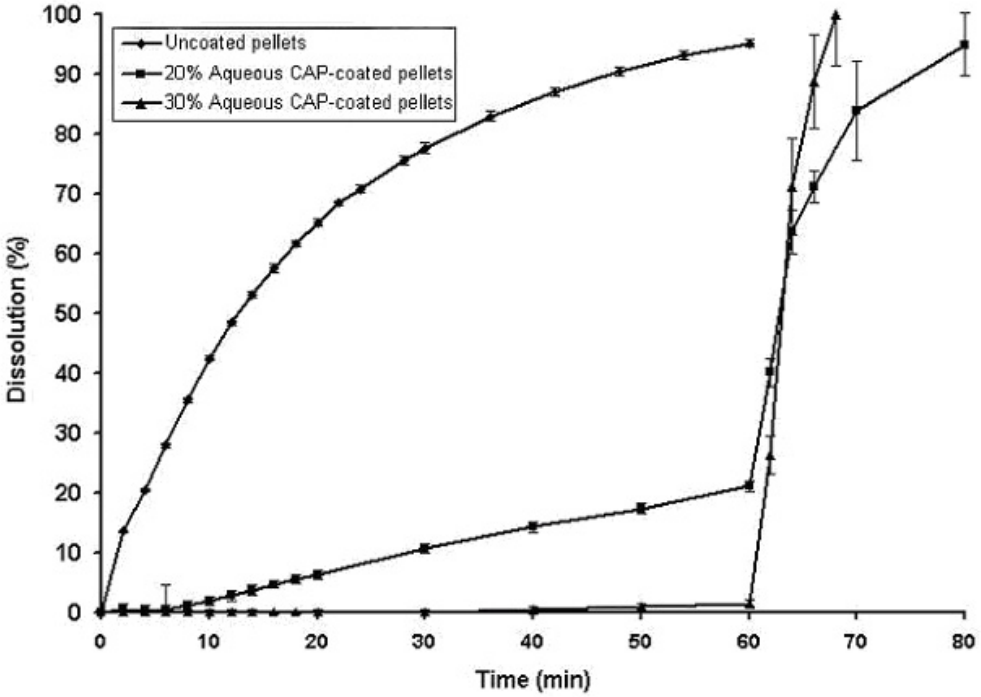

Figure 1. Dissolution profiles of riboflavin sodium phosphate pellets containing waxy cornstarch as a cofiller in the core (n=6).

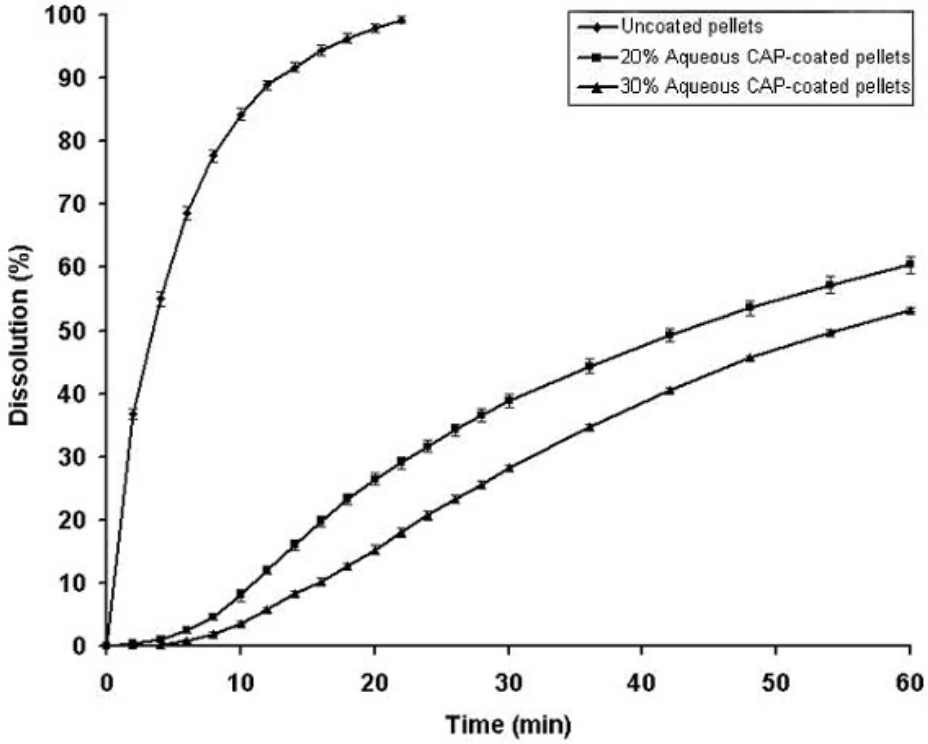

Figure 2. Dissolution profiles of riboflavin sodium phosphate pellets containing lactose as a cofiller in the core (n=6).

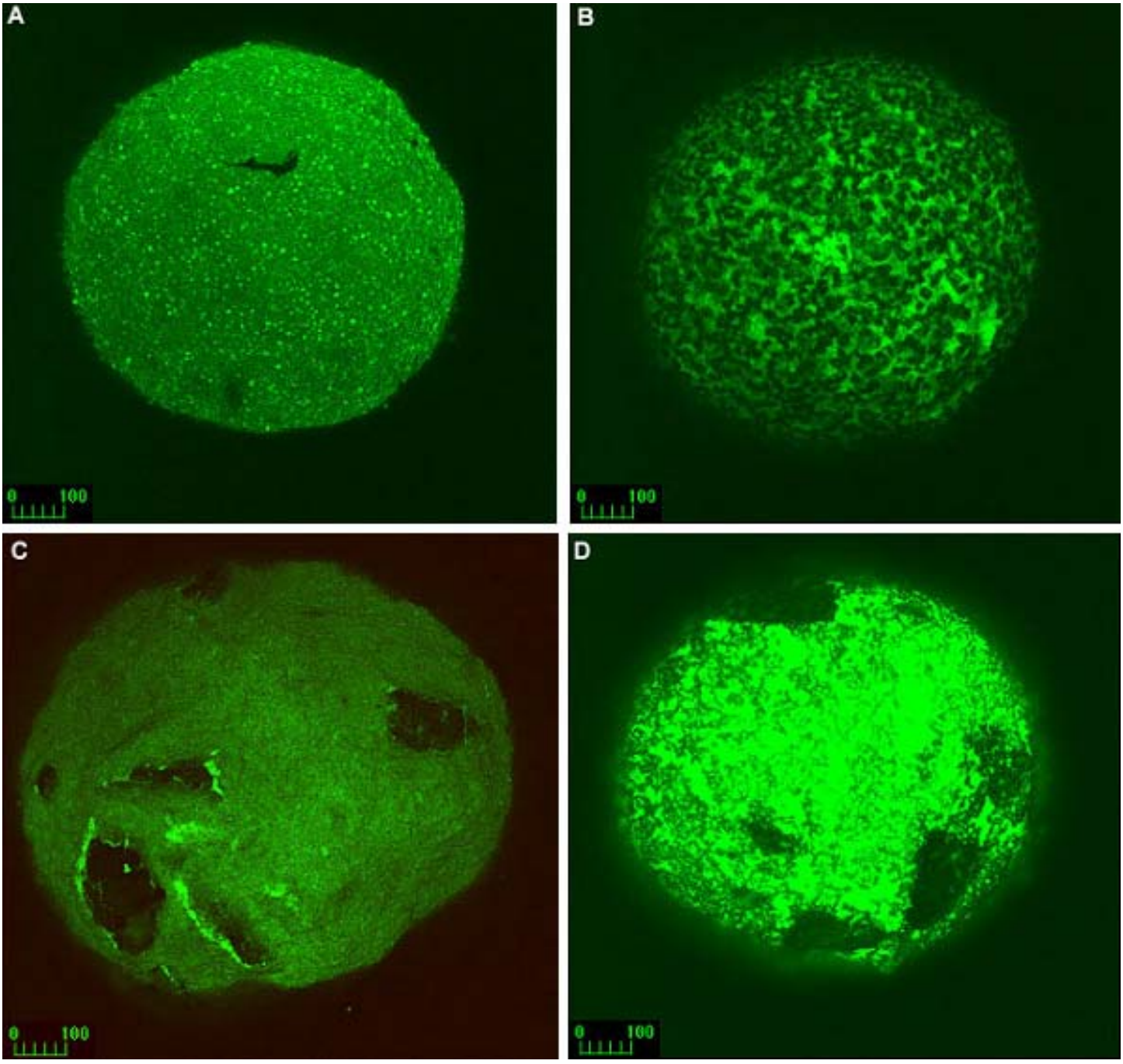

Figure 3. Confocal images of an uncoated (A) and coated (B) riboflavin sodium phosphate pellet containing waxy cornstarch as a cofiller and an uncoated (C) and coated (D) riboflavin sodium phosphate pellet containing lactose as a cofiller.

coalescence of the polymeric spheres was formed on the pellet surface (dark network areas). No riboflavin sodium phosphate (ie, drug diffusion) could be seen surrounding the pellet core. The respective uncoated lactose pellets had a rougher surface (Figure 3C). In the film-coated lactose pellets (Figure 3D) the film was not formed by well-defined and discrete polymeric beads. Some riboflavin sodium phosphate was found to have diffused to the film coat of the pellets. CLSM images showed relatively large nonfluorescence areas in the lactose pellets (Figure 3C and 3D).

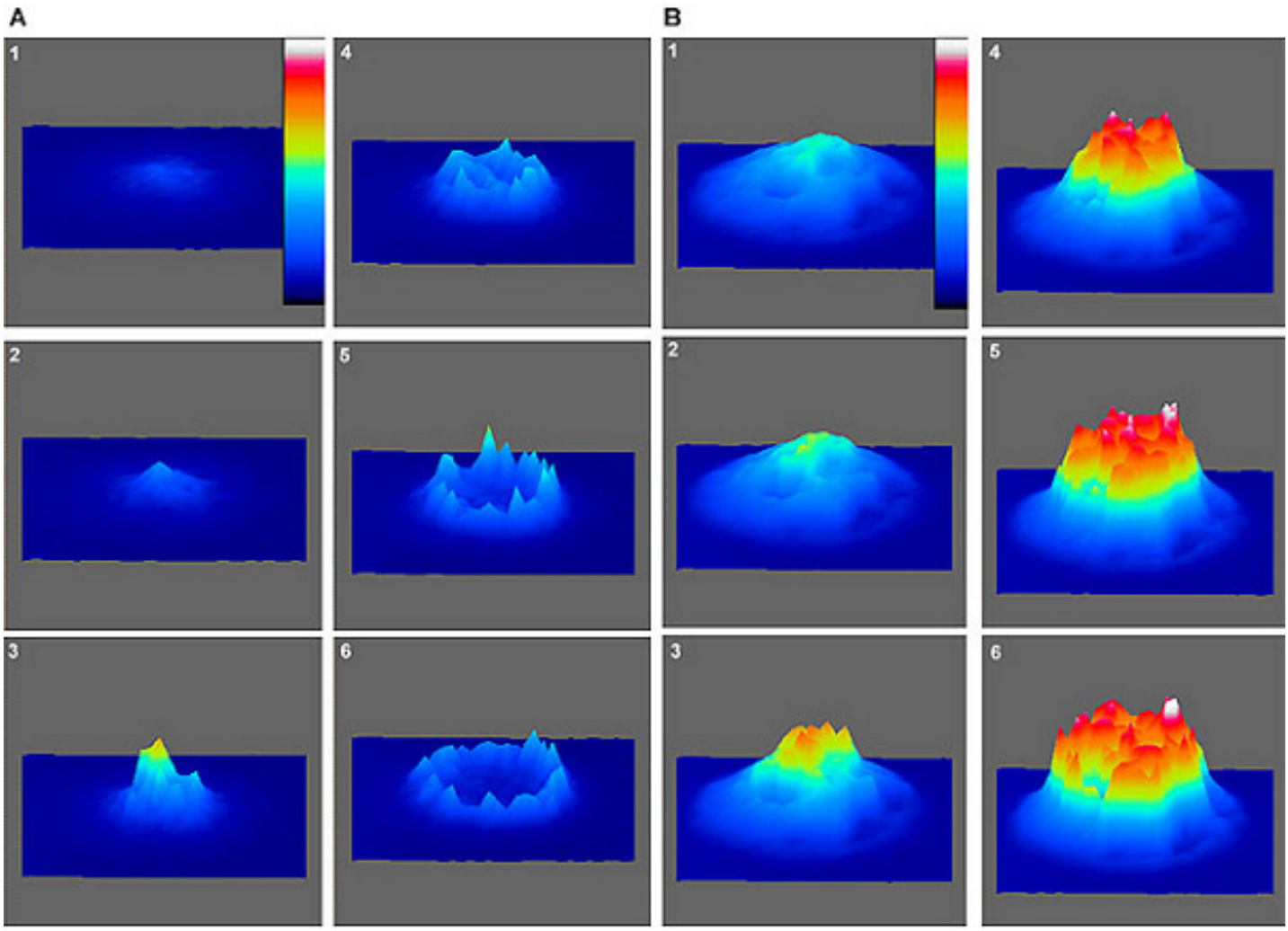

Figure 4. The 3-D plots of enteric-coated pellets from surface of film coat to pellet core (1-6). A: waxy cornstarch pellet, B: lactose pellet.

To confirm the observations on CLSM images, the 3-D plots were taken from different sections (Figure 4) from film coat to pellet core, and the fluorescence intensity of riboflavin sodium phosphate in the sections was quantified (Figure 5). As seen in Figures 4 and 5, the higher fluorescence intensity in the film coat of the lactose pellets provides evidence of a greater extent of diffusion than that observed with the pellets containing waxy cornstarch as a cofiller.

DISCUSSION

Clear differences were found in dissolution between the waxy cornstarch- and lactose-containing pellet cores (Figures 1 and 2). According to Junnila et al [13], the pellets containing lactose as a cofiller with MCC are larger in diameter than those containing waxy cornstarch. Furthermore, the release rate of drug from the pellets has been reported to be rather proportional to their surface area [14]. Waxy cornstarch contains almost entirely amylopectin, with no amylose. Amylopectin is a branched D-glucose (alpha 1-6) chain. This chain also contains alpha 1-4, 1 of the 2 polysaccharides that make up a starch. The branched structure of waxy cornstarch with all its

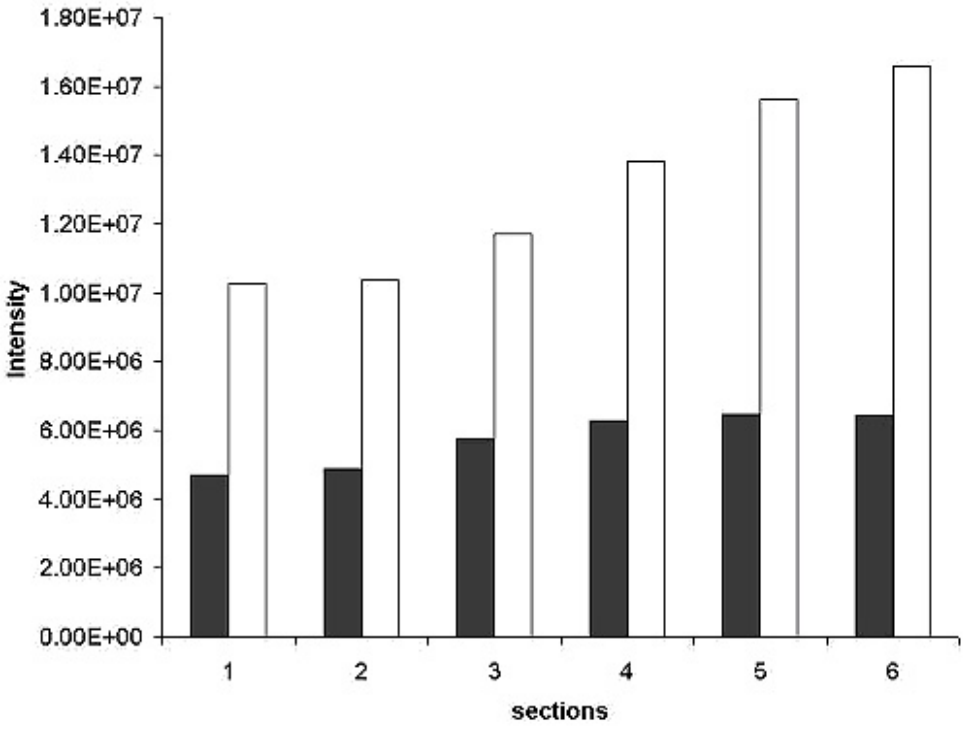

Figure 5. Fluorescence intensity of riboflavin sodium phosphate quantified from the film coat to the pellet core. Key: (■) waxy cornstarch pellets, (□) lactose pellets.

attached chains yielded a large molecule and gave steric hindrance. Obviously, this large branched molecule of waxy cornstarch is able to better control premature riboflavin sodium phosphate release from the enteric-coated pellets than lactose as a cofiller (lactose is additionally more water soluble than waxy cornstarch). The reasons mentioned above explain why lactose-containing pellet cores dissolved faster and, consequently, were poorer candidates for substrates for enteric coating than respective waxy cornstarch pellets. Both the particle size of the excipients and the solubility of drug have been shown to be important for the release properties of the pellets as well [15].

The CLSM technique seems to show clear differences in the surface morphology and structure between the waxy cornstarch- and lactose-containing pellets. The apparent differences could be explained by the fact that in CLSM the confocal mode can only visualize fluorescent materials. Materials without fluorescence cannot be detected. Therefore, nonfluorescence areas in the lactose pellets were assumed to be undissolved lactose crystals existing on the pellet surface, making the pellets apparently more irregular in the CLSM images than the respective pellets containing waxy cornstarch.

The high fluorescence intensity of drug observed in lactose-containing pellets might contribute to more drug dissolving and diffusion to the film than waxy cornstarch-containing pellets (Figures 4 and 5). Drug molecules diffusing from the drug layer into the film layer seriously interfere with the film formulation mechanism of the dispersion. Yang and Ghebre-Sellassie [6] reported that a significant amount of drug may dissolve in the coating formulation and reduce the surface tension of the liquid, which is essential for the development of the capillary pressure needed for the deformation of the polymeric spheres. As a result of this, the film deposited on the substrate may become less continuous and, eventually, lead to relatively high release rates. Drug molecules may also interpose them-

selves between adjacent polymer spheres and dissolve during dissolution to generate a porous and more permeable coating material that subsequently releases the drug at high rates. Furthermore, irregular lactose pellets can form uneven film after coating. This may also result in a high release rate as shown in the dissolution test.

In conclusion, waxy cornstarch used as a cofiller in the pellet cores evidently can prevent drug diffusion from the core into the film coat layer. Diffusion of a water-soluble drug and excipient (ie, lactose) can result in coating failure and, subsequently, premature dissolution of enteric-coated pellets in an acidic environment. Both the cofiller in the pellet core and the coating load can affect the enteric properties of aqueous CAP-coated pellets. Diffusion of an autofluorescent water-soluble drug in enteric-coated pellet formulations can be visualized by CLSM.

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