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Research Article

Ultrasound-assisted powder-coating technique to improve content uniformity of low-dose solid dosage forms

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ABSTRACT. An ultrasound-assisted powder-coating technique was used to produce a homogeneous powder formulation of a low-dose active pharmaceutical ingredient (API). The powdered particles of microcrystalline cellulose (MCC; Avicel® PH-200) were coated with a 4% m/V aqueous solution of riboflavin sodium phosphate, producing a uniform drug layer on the particle surfaces. It was possible to regulate the amount of API in the treated powder. The thickness of the API layer on the surface of the MCC particles increased near linearly as the number of coating cycles increased, allowing a precise control of the drug content. The tablets (n=950) prepared from the coated powder showed significantly improved weight and content uniformity in comparison with the reference tablets compressed from a physical binary powder mixture. This was due to the coated formulation remaining uniform during the entire tabletting process, whereas the physical mixture of the powders was subject to segregation. In conclusion, the ultrasound-assisted technique presented here is an effective tool for homogeneous drug coating of powders of irregular particle shape and broad particle size distribution, improving content uniformity of low-dose API in tablets, and consequently, ensuring the safe delivery of a potent active substance to patients.

KEY WORDS: content uniformity; homogeneity; low-dose API; powder coating; ultrasound.

INTRODUCTION

Homogeneous distribution of the active pharmaceutical ingredient (API) is a major concern in the preparation of low-dose solid dosage forms. The uniform distribution of highly potent API in the preformulation, and preservation of content uniformity during further processing, are essential for obtaining the correct effect in the final product. Inadequate content uniformity of the formulation can lead to a fluctuation in the dose. Single-dose ineffectiveness can be a consequence of insufficient API, while an overdose can cause toxic side effects. Both situations possess health risk to patients.

It is well known that direct compression is a cost-effective method for tablet manufacturing because it requires fewer unit operations. In addition, it avoids stability problems during formulation due to the absence of moisture and heat during the process (1). However, direct compression has some disadvantages such as segregation of the physical mixture, as well as cohesion of drug substances during mixing and tabletting (2,3). It is of most concern if a low-dose drug with a narrow therapeutic index and high toxicity is in use. Because of that, an intermediate wet or dry granulation of the mixture is usually done to increase the bulk density of powder and distribute the API uniformly (4–8). Nevertheless, granulation is a complicated processing stage that involves several steps and adds extra costs to tablet manufacture. In addition, it causes a marked increase in the particle size of the mixture, which can affect the dissolution characteristics of the API.

Several other approaches have been used to improve content uniformity of low-dose solid dosage forms, avoiding the costly and time-consuming granulation step. Geometric dry blending of API and triturated excipient using various mixers has been used to produce a homogeneous formulation of a highly potent drug (9). In a US patent (10), ordered mixing of micronized steroidal compounds and the excipients was performed to design low-dose solid dosage forms. However, in this case, only carefully preselected diluents with superior binding properties and very low demixing potentials could be successfully used to obtain a sufficiently homogeneous mixture. In another work, a very potent medical compound was deposited onto the surface of the excipient by dissolving the drug in an organic solvent such as chloroform, mixing the solution obtained with carrier particles, and drying the mixture (11). The structured system was successfully obtained, but the use of unsafe volatile liquids is highly criticized nowadays. Spray-drying of an alcoholic suspension containing dissolved API and dispersed adjuvant particles was carried out to produce a preformulation with the drug substance adhering to the surface of the carrier particles (12). This admixture can be further dry blended with directly

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compressible excipients to produce solid dosage forms of a uniform content, avoiding demixing and sizing effects.

The goal of the present study was to develop a homogeneous powder formulation of a low-dose API in order to improve content uniformity of single-dose forms. The main idea was to thoroughly coat the excipient powder with a model drug and to produce a uniform layer of API on the surface of the carriers, avoiding granulation of the mixture. The coarse grade microcrystalline cellulose (MCC) dispersed by a vibratory feeder was treated with an aqueous mist of riboflavin sodium phosphate (RSP) solution nebulized by an ultrasound-assisted technique. Lubricant-free tablets made of both the drug-coated powder and the respective physical mixture of the ingredients were compared for content variation as a function of the tabletting time.

MATERIALS AND METHODS

Materials

Riboflavin sodium phosphate, riboflavin 5′-monophosphate sodium salt (Ph. Eur., Fluka Analytical, Sigma-Aldrich, France) was used as a freely water soluble model drug. MCC (Avicel® PH-200, FMC, Ireland) was utilized as a directly compressible self-lubricating (3,13) carrier polymer (Fig. 1). Purified water was used as a solvent.

Coating Procedure

The method for coating of powders has been described in our earlier work (14) and the schematic diagram is presented in Fig. 2. A mist of 4% (m/V) riboflavin solution generated by an ultrasound nebulizer (Ultrasonic Nebulizer NE-U17, Ultra Air, Omron, The Netherlands) was applied onto the coarse grade MCC, which was dispersed by a vibratory feeder (Laborette 24, Germany). Due to the open setup of the technique, some loss of API occurred during the entire coating procedure. The amount of MCC powder was 350.0 g. A total of 30 coating cycles were done with the same solid material. The supplying rate of the powder was 9.7±0.6 g/min, whereas the feeding rate of the RSP solution was 1.1±0.2 ml/min. The average duration of one cycle was 35 min. No stirring of the surface-covered cellulose was performed. A metal spoon was used to turn over the powdered mass. Representative samples of 5 g were withdrawn every 5th cycle. All experimental procedures were performed in a dim room to minimize the destructive effect of light on the riboflavin salt. The API solution was covered with foil and stored at 4°C. After the last coating round, the processed powder as well as the collected six samples and the original raw substances (RSP and MCC) were left for 24 h to equilibrate in the ambient environment (19±1% relative humidity and 21.5±0.5°C) prior to testing. An infrared moisture analyzer (Sartorius MA 100, Sartorius AG, Germany) was used to determine the moisture content of the powders based on loss of weight at 105°C. The measurements of the water activity of the samples were made by using an AquaLab water activity meter (AquaLab 3 TE, Decagon Devices, Inc. Washington, DC, USA). Both tests were conducted in triplicate. The results on moisture content and water activity are summarized in Table I.

Riboflavin Content of the Coated Powders

To determine the coating efficiency of the described procedure, the withdrawn samples were analyzed for RSP content. Two hundred fifty milligrams of the treated powder from each sample was suspended in 100 mL of water. The absorbance of the filtered solution was measured at 444 nm using a UV/VIS spectrophotometer (Pharmacia Ultrospec III, Pegasus Scientific Inc., Rockville, MD, USA). Three parallel measurements were made for each powder sample. To build up the standard curve, 200 mg of RSP and 2,300 mg of MCC (both powders were equilibrated in the ambient environment) were used to prepare 0.2 mg/mL stock solution of RSP in water. The regression model gives the following equation (Eq. 1):

$$Y = 23.365X + 0.008 \quad (1)$$

where Y is the absorbance and X is the concentration (mg/mL). The coefficient of determination of the linear regression (R^2) is 0.9999.

Physical Mixture of RSP and MCC

A physical mixture of RSP and MCC was prepared to compare formulations. To calculate the exact amount of API required to get a binary mix with the same RSP content as in

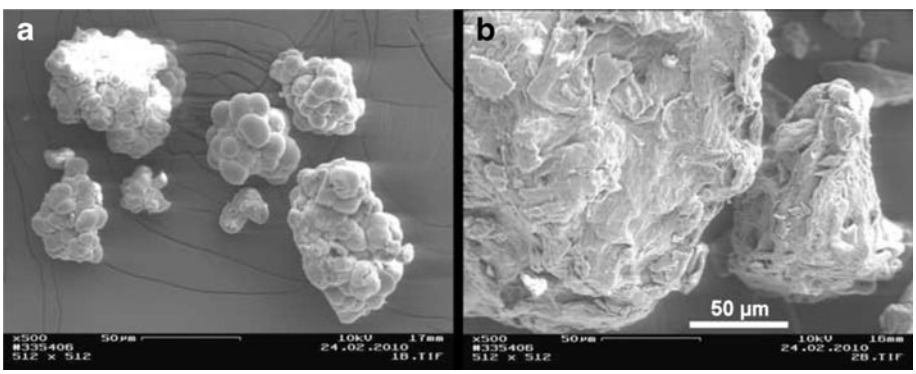

Fig. 1. The scanning electron micrographs of raw riboflavin sodium phosphate, RSP (**a**) and microcrystalline cellulose, MCC (**b**) at a magnification of ×500

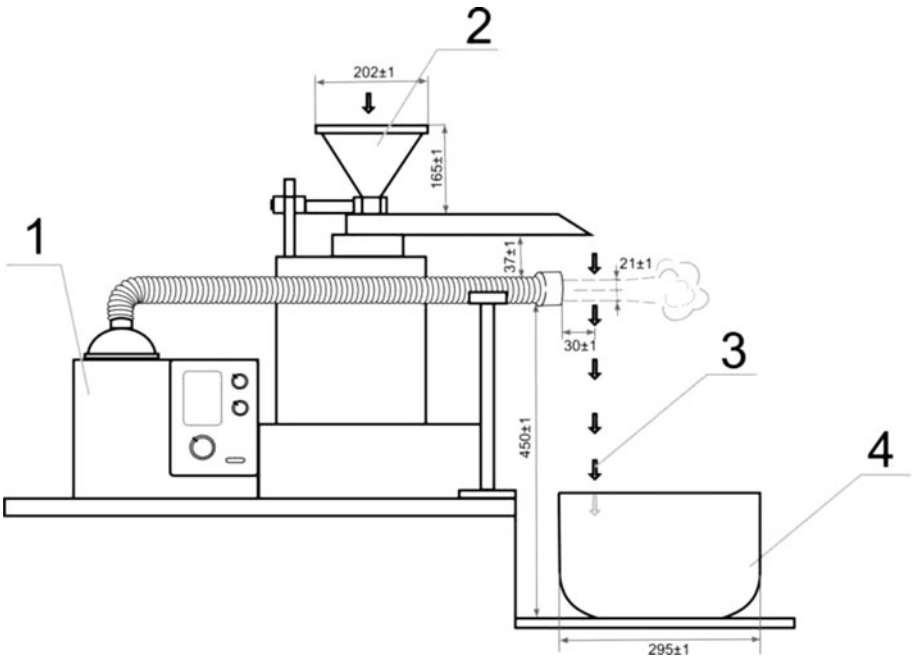

Fig. 2. Schematic diagram of the coating technique: *1*, ultrasound nebulizer, *2*, vibrating feeder, *3*, carrier powder, and *4*, collector (the dimensions of the system are given in millimeters)

the coated powder, the latter (250 mg of powder in 100 mL of water) was assayed at 444 nm (n=11).

The total mass of the basic mixture was 310 g. The powder components were placed in the glass jar with RSP being loaded in the middle of MCC powder. The mixer was approximately two thirds full. The powders were mixed with a rotation speed of 46 rpm in a Turbula blender (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). After 30 min, which was a sufficient time for uniform distribution of API within a formulation (15), a homogeneous mixture as determined by visual observation was obtained. The physical mixture was assessed for content uniformity of RSP (250 mg of powder in 100 mL of water, n=11) by taking samples from different locations of the blender. The standard deviation (SD) and the relative standard deviation (S_{rel}) were calculated.

Analysis of Particle Size

An automatic sieve shaker (Fritsch analysette, Germany) was used to measure the particle size distributions of the powders using the following sieves: 45, 71, 90, 125, 180, 250, 355, and 500 μm. The sample size was 5 g. A stacked set of the sieves was shaken for 5 min with an amplitude setting value of 6.

Table I. Moisture Content and Water Activity of the Raw Microcrystalline Cellulose (MCC) and the Maximally (30 Cycles) Coated Powder before and after Stabilization at 19±1% Relative Humidity and 21.5±0.5°C (Data are Presented as Means±Standard Deviations, n=3)

Sample	Before stabilization		After stabilization	
	IR (%)	α_w	IR (%)	α_w
MCC	4.1±0.2	0.307±0.006	2.8±0.1	0.135±0.001
Coated MCC	7.3±0.4	0.623±0.061	2.7±0.1	0.135±0.001

Tabletting

Tablet compression was performed in the climate-controlled room (51±2% relative humidity and 26±2°C). Before tabletting, both coated powder and physically mixed powder were stored in the above meant acclimatization environment for 15 h to create a stabilizing water sorption layer on the particle surfaces. Lubricant-free tablets were compressed from both powders by using an instrumented single punch tabletting machine (Korsch EK-0, Erweka Apparatebau, Berlin, Germany) equipped with flat-faced 9 mm punches. The compression force used was 2.3 kN for both formulations. The batch size was 950 tablets with a speed of 37 tablets per minute. The device was set up to produce tablets with a target weight of 250 mg and a target crushing strength of 90 N. The same settings were used for coated as for physically mixed powders. The tablets were collected sequentially one by one into the plastic tubes: 100 tablets per tube. The probable differences between the two batches were analyzed.

Homogeneity of Coated Powder and Physical Mixture after Tabletting

Segregation, layering and separation of the mixture can take place during the transfer and compression of the blend, especially when the physicochemical properties and the size characteristics of the materials in the mixture are different (2). In order to check the homogeneity of both formulations after tabletting, the powders remaining in the hopper of the tabletting machine were analyzed quantitatively for riboflavin content at 444 nm (250 mg of powder in 100 mL of water).

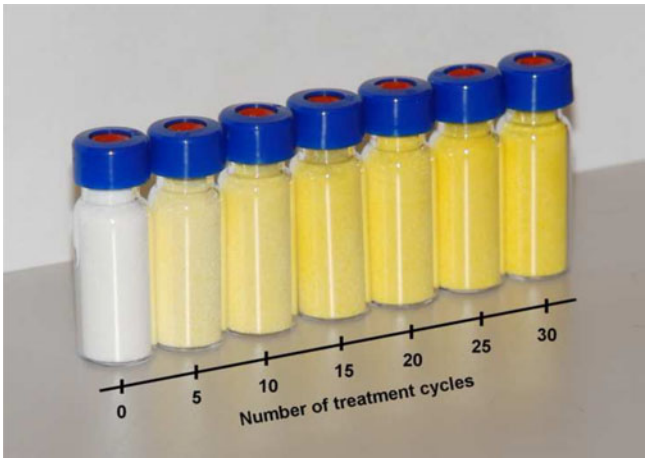

Fig. 3. The increase in the color intensity of riboflavin sodium phosphate-treated powders as the number of coating cycles increased

Analysis of Tablets

Weight and Content Variation

To analyse the homogeneity of mass and content of low-dose forms and observe the differences in these parameters with tabletting time, the first ten tablets in series from each sequential tube were weighed one by one and assayed. The content variation was determined by disintegrating every tablet individually in 100 mL of purified water and measuring the absorbance of the filtered solution spectrophotometrically at 444 nm. A total of 100 tablets from each batch were analyzed.

Crushing Strength

Surface coating of the MCC particles with the API could have an impact on the mechanical properties of tablets prepared from this powder. Therefore, the crushing strength of tablets (n=100) was measured by using a crushing strength device (Schleuniger-2E, Dr. K. Schleuniger&Co, Germany).

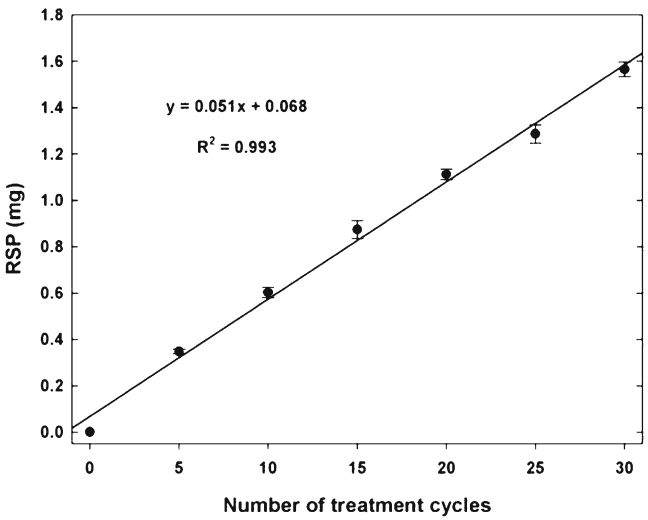

Fig. 4. Coating efficiency of the process, expressed as the amount of riboflavin sodium phosphate (*RSP*) attached to the surface of 250 mg of the progressively coated powder samples. *Error bars*, mean± standard deviation (n=3)

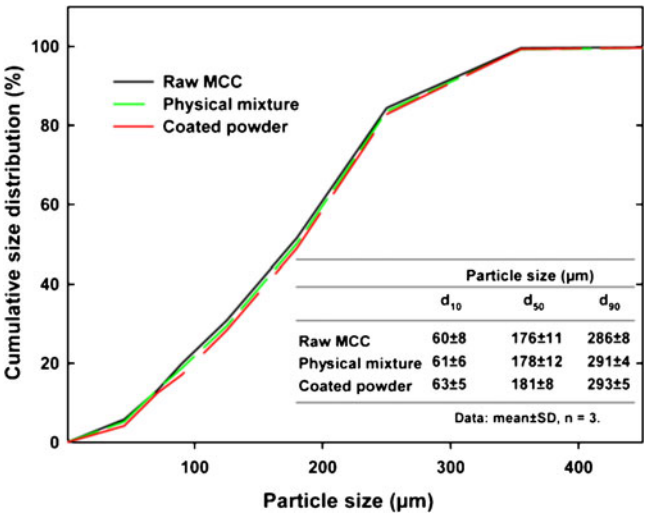

Fig. 5. The cumulative particle size distribution of the raw microcrystalline cellulose (*MCC*), the coated powder and the physical mixture of powders measured by sieve analysis (data are presented as means, n=3)

Morphology of Powders and Tablets

Scanning Electron Microscopy

The morphological properties of the powdered particles were investigated using scanning electron microscope (SEM; Zeiss DSM 962, Carl Zeiss, Oberkochen, Germany). Before scanning, the samples were coated with platinum using a vacuum evaporator. SEM images were acquired at an accelerated voltage of 10 kV using magnification of ×500.

Inverted Fluorescence Microscopy

RSP is autofluorescent (16) and therefore, inverted fluorescence microscope (Olympus IX71/IX51, Olympus optical co., LTD, Japan) was used to determine the homogeneity of the API surface coating of the cellulose particles. In addition, it was used to visualize the distribution of API within the binary mixture. The images were obtained at a magnification of 20x using AnalySIS 3.2 software. The excitation filter used was 470–490 nm and the barrier filter was 515 nm with an exposure time of 588 msec. All other settings were kept constant during all observations.

Table II. Properties of Tablets Prepared from the Coated Powder and the Physical Mixture of Powders (Data are Presented as Means± Standard Deviations (Relative Standard Deviations), n=100)

	Weight (mg)	Amount of API (mg)	Amount of API (%)
Tablets, coated powder	252.4±0.9 (0.4)	1.54±0.03 (1.8)	0.61±0.01 (1.7)
Tablets, physical mixture of powders	247.0±1.3 (0.5)	1.41±0.09 (6.5)	0.57±0.04 (6.5)

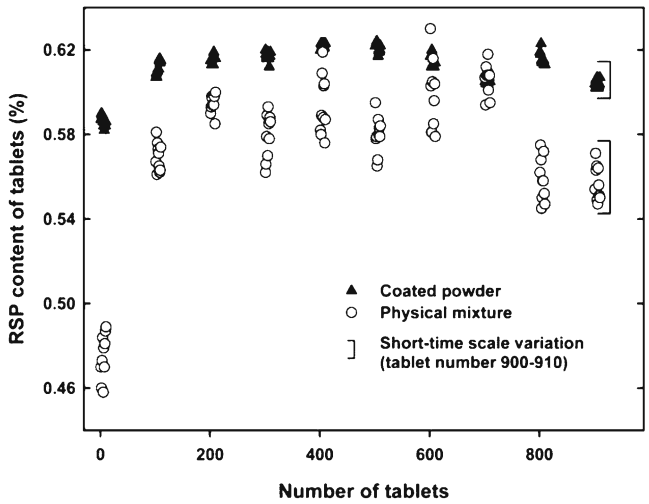

Fig. 6. The content variation of tablets prepared from the coated powder and the physical mixture of powders as a function of the number of tablets compressed (n=100)

Stereomicroscopy and Digital Imaging

Stereomicroscope (Leica M26, Germany) in connection with a digital camera (DC) was used to acquire color images of prepared powders and tablets at a magnification of ×0.63. The powdered samples were photographed using another DC (Casio EX-F1, Japan).

RESULTS AND DISCUSSION

Coating Efficiency

RSP coating produced an ultra-thin yellow layer on the surface of the polymer carriers. The color's intensity increased as the coating proceeded (Fig. 3). A quantitative analysis of the surface-treated powders, taken at predetermined intervals during the coating procedure, revealed a near linear increase in the thickness of the drug layer (Fig. 4). This means that the amount of the surface-attached active substance can be controlled easily during the coating process. The small SD in the results revealed that the coating was homogeneous, as nearly every single particle was treated with a mist of RSP solution, preventing the formation of "dead zones" in the processed powder.

Particle Size

The increase in the moisture content of the powder during treatment could have a negative effect on the particle size distribution and cause agglomeration of the surface-coated powder. Particle size characteristics remained almost unchanged, revealing an absence of granule formation (Fig. 5). The d_{50} for all samples was in the range of 179± 9 μm, which is in agreement with the literature value of 180 μm for the mean particle size of Avicel® PH-200 (13). The differences in the cumulative curves of the raw MCC and API-coated cellulose were inside the error limits. A slight increase in the particle size of the processed powder is most likely due to a thin RSP layer on the surface of the MCC particles. In addition, the recollection of the coated powder and refilling the vibrating feeder could provoke elimination of dust as a consequence of the open setup of the technique. Some fine particles could be captured as well by the stream of mist and eliminated from the bulk of powder. Obviously, all these factors together caused an overall increase in the particle size of the API-coated powder.

The Content Variation of Coated and Physically Mixed Powders

The average amount of riboflavin was 1.48±0.04 mg per 250 mg of coated powder (S_{rel}=2.8%). This value was used to calculate the amount of riboflavin salt needed to be added to MCC to get a physical mixture with the same quantity of the active ingredient for both formulations. Thus 1.8 g of RSP and 308.2 g of Avicel were blended together. However, we obtained a basic mixture with a lower amount of riboflavin: 1.31±0.08 mg per 250 mg of powder (S_{rel}=5.7%). To determine where the API powder was lost, the empty mixing jar was rinsed with water and the suspension obtained was filtered and analyzed for riboflavin content. It appeared that 35.86 mg of API was stuck to the walls and to the cork of the bottle. However, this was still not enough to explain the entire decrease in the content of API in the physical mixture of powders. This observation and a higher SD in riboflavin

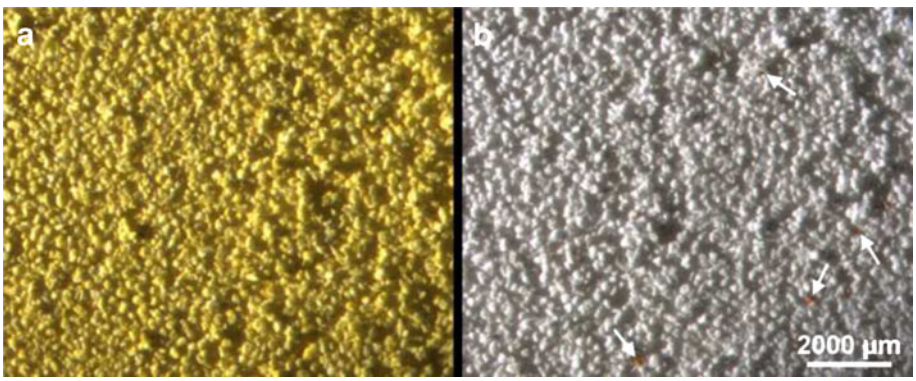

Fig. 7. Stereomicrographs of the coated powder (**a**) and the physical mixture of powders (**b**) before tabletting. *Arrows* in (**b**) point to riboflavin sodium phosphate particles (*small orange spots on the image*)

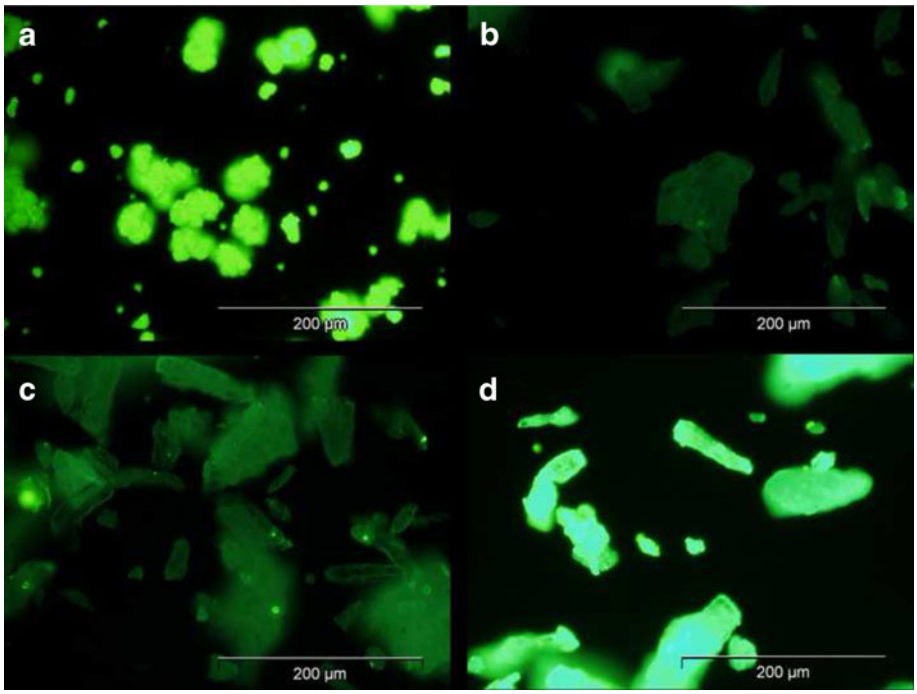

Fig. 8. The inverted fluorescence microscope images of raw riboflavin sodium phosphate, RSP (**a**), microcrystalline cellulose (**b**), the physical mixture of powders (**c**), and the surface-coated powder (**d**)

content within the physical system in comparison with the coated powder could indicate that the basic mixture was not completely homogeneous and that areas of high and low drug content were formed.

Tablet Properties

Tablets from both formulations were compressed without addition of any lubricant. It was found that API coating of MCC powder did not change the mechanical properties of tablets significantly in comparison with tablets prepared from the physical mixture: 94±3 N and 90±3 N, respectively.

Weight and Content Variation

The maximum percentage deviations of the individual weights from the average weight of the tablets prepared from the coated powder and the physical mixture of powders were 0.8% and 1.5%, respectively. The average mass of the tablets made from the coated powder was slightly higher, indicating

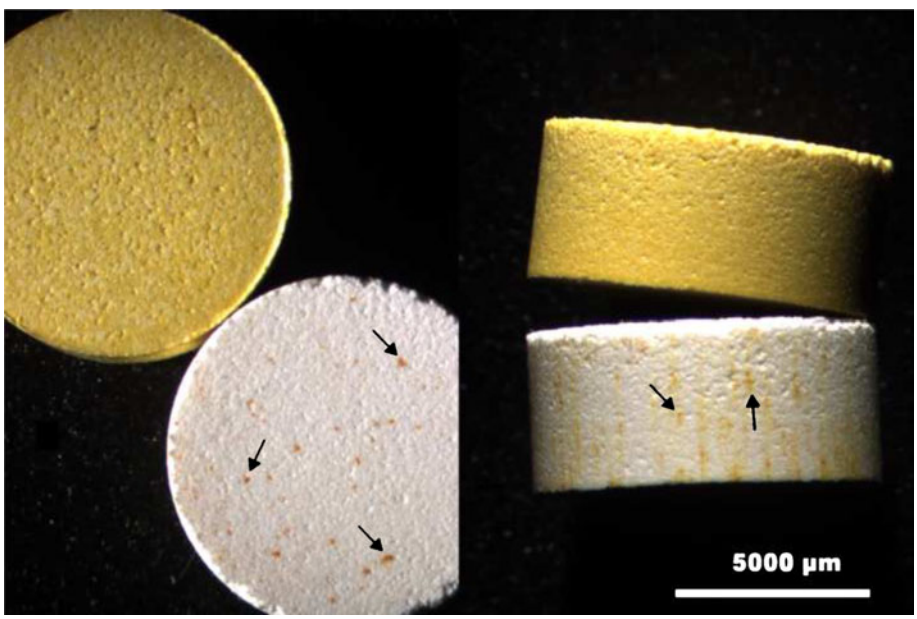

Fig. 9. Stereomicrographs of tablets prepared from the surface-coated powder (*yellow tablets*) and physical mixture of powders (*white tablets with yellow-orange spots*). *Arrows* point to poorly mixed riboflavin sodium phosphate particles (*small yellow-orange spots*)

denser packing of the powder during tablet compression (Table II). The S_{rel} in weight variation of these compacts was smaller and consequently, the uniformity of weight was higher.

The content variation was clearly less for the surface-treated material, where the drug coating gave rise to an even distribution of API within the powder (Fig. 6). The API content in individual tablets ($n=100$) was between 95.4% and 102.6% for the tablets prepared from the coated powder, and 80.4–109.5% for the tablets made from the basic mixture. S_{rel} was almost four times higher for the directly compressed compacts of the physical mixture than for the tablets prepared from the RSP-coated formulation, indicating a smaller long-time scale variation in the latter preparation (Table II). Additionally, the short-time scale variation within the first ten compacts from each subsequent series was better for tablets prepared from the surface-coated powder than for tablets prepared from the physical mix (Fig. 6). Obviously, segregation of the physical mixture occurred during tabletting, since the hopper's strong vibration could provoke separation of the binary formulation. This caused an increase in the content variation of the reference tablets.

Before compression by transferring the physical mixture of low-dose API to the tabletting machine, the coarser cellulose particles, due to their gravity and superior flow properties, could enter the hopper first, causing a decrease in the content of RSP at the beginning of the process (Fig. 6). After tabletting, visual observation of the powder remaining in the hopper revealed orange stripes of the API within the physical mixture, indicating formation of "hot" and "cold" spots. Analysis of the representative samples of the coated powder and the physical mixture after tabletting confirmed the visual examination of preparations: 1.51±0.05 mg API per 250 mg of the coated powder (S_{rel}=3.5%) and 1.18±0.22 mg per 250 mg of the mixed powder ($Srel$=18.8%). Before and after tabletting, the S_{rel} of the API content within the binary mixture increased 3.3 times, whereas the S_{rel} of the coated formulation increased 1.3 times.

Appearance of Powders and Tablets

RSP coating produced a uniform drug layer on the surface of the carrier particles (Figs. 7 and 8). The direct compression formulation appeared to be a random mixture, where API agglomerates of spherical particles were still observable. The cohesive nature of RSP related to its small particle size (Fig. 1) prevented the homogeneous dispersion of API species within the physical system.

The observation of tablet surfaces revealed a uniform distribution of the active substance in the drug-coated formulation, whereas the surface of the directly compressed tablets appeared to be unevenly spotty (Fig. 9). Interestingly, the areas of the dissolved RSP were present on the lateral sides of the directly compressed tablets. Evidently, under a high compression pressure, the water contained in the formulation was released from the tablets' sides and dissolved the API, forming stripes with high concentration of RSP. As well, the mechanical compression was probably responsible for the negligible color variation on the surface of the tablets prepared from the coated powder. This could apparently be due to the rupture of the RSP film that produced slightly lightened regions on the surface of the tablets. Nevertheless, the overall appearance of the compacts prepared from coated powder looks much more homogeneous than the exterior of the directly compressed tablets of the physical mixture.

CONCLUSIONS

By using the ultrasound-assisted coating technique presented here, it was possible to make a homogeneous powder formulation of a low-dose API that remained uniform during the entire tabletting process. The amount of API in the treated powder can be regulated precisely, as the coating procedure produces a uniform drug layer on the particle surface. Lubricant-free tablets prepared from the coated powder showed significantly improved weight and content uniformity in comparison with the tablets compressed from the physical mixture of the powders. The ultrasound-assisted technique is an effective tool for obtaining a homogeneous drug coating of powders of irregular particle shape and broad particle size distribution in order to increase content uniformity of low-dose API in tablets. This ensures the safe delivery of a potent active substance to patients.

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