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Pellet Starters in Layering Technique Using Concentrated Drug Solution

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Characteristics of inert starters in drug solution layering are important for successful active pellet formation. Four types of starters composed of sucrose or microcrystalline cellulose (MCC) or lactose and MCC were compared in our study. The active pellets were prepared using Wurster type apparatus. Yield and pellet quality parameters were determined. The highest yield (85.66–89.41%) was obtained for cores composed of MCC due to their insolubility in water (the drug solvent) and good mechanical properties. On the contrary, soluble and brittle sucrose cores dissolved partially during the process forming undesirable agglomerates and giving lower yield (76.2%). All pellet samples showed good flow properties and drug content from 82.4 to 94.5% of the theoretical drug amount.

Keywords pellets; concentrated drug solution layering; nonpareils; sucrose; microcrystalline cellulose

INTRODUCTION

Pellets are primarily produced for manufacturing of oral controlled-release dosage forms with gastroresistant or sustained-release properties. They posses many advantages when compared with single solid oral dosage forms, for example, providing the flexibility in dosage form design, minimizing the local irritation of gastrointestinal tract, and combining incompatible drugs or drugs with different release pattern in the same dosage form. In addition, pellets have nearly spherical shape, ideal for the application of a film coating. Pellets can be prepared using several technologies, the most used ones are layering of drug solution or suspension on inactive cores, and extrusion/spheronization of a plastic mass composed of a drug and suitable excipients (Kristensen & Schaefer, 1996; Vetchý & Rabišková, 2002).

The layering process usually begins with inert spherical cores (starters, nonpareils). They provide the solid surface on which one or more layers of the active ingredient are deposited. The drug in the form of its aqueous or alternatively organic solution (suspension) is sprayed on the carrier beads until the pellets of desired size or drug content are achieved. The solids content of the drug solution is almost irrelevant when producing very low potency pellets, but is a major economic factor when making high-dose products. Typically, a solution containing at least 40% of solids can produce pellets of 50% potency within few hours (Jones, 1989). Inert starters are traditionally formed from pharmaceutically acceptable substances, such as lactose, sucrose, and starch (e.g., Suglets®, Nu-Pareil PG®). Recently, microcrystalline cellulose (MCC) starters (e.g., Cellets®, Celphere®) have been introduced and used for experiments (Eichler, 2002). As they do not dissolve in water, they can be advantageous especially when high amount of a drug in water solution should be applied.

Although there are many papers describing properties of pellets prepared by the drug solution or suspension layering, there is no article focused exclusively on the comparison of the inactive seeds, and to our best knowledge, the evaluation of their influence on the shape, drug contents, or mechanical and flow properties of the resulting product has not been reported. That is why the aim of this experimental study was to investigate the influence of the inactive starter type used for high amount of the concentrated drug solution layering on the production process itself as well as on the properties of obtained pellets. Three commercially available starters (sugar and MCC cores) and starters composed of lactose and MCC (LM cores) prepared in our laboratory by rotoagglomeration were tested. Concentrated water solution (i.e., 50%, wt/wt) of the model drug diltiazem hydrochloride (DHCl) was sprayed on all kinds of inactive seeds mentioned above to achieve approximately 50% drug loading. The layering process was performed in the fluid bed equipment with Wurster column insert. The course of layering process has been observed, and pellet properties were evaluated in order to find the optimal cores for concentrated aqueous drug solution layering process.

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MATERIALS AND METHODS

Materials

Sugar spheres of the size 0.5–0.6 mm (Mendel, Rosenberg, Germany) and MCC spheres of the size 0.5–0.71 mm (Celphere® CP 507, Asahi Kasei Kogyo, Osaka, Japan) and 0.5–0.7 mm (Cellets® 500, Syntapharm, Duesseldorf, Germany) were used as commercially available starters. In order to prepare lactose/MCC cores, α-lactose monohydrate 200 Mesh (Cerapharm, Vienna, Austria), Avicel® PH 101 (Mingtai Chemical Co., Ltd., Bah-Der City, Taiwan), and purified water as wetting agent were used. The solution for drug layering was composed of DHCl (kindly donated by Zentiva, Prague, Czech Republic), povidone (Kollidon® 25, Basf, Ludwigshafen, Germany) as a binder, and purified water as a solvent. All substances were of pharmaceutical grade.

Preparation of Commercially Unavailable Nonpareils

Three hundred and fifty grams of MCC and 650 g of lactose were mixed for 5 min in a Stephan mixer (UMC 5, Hameln, Germany). One kilogram of powder blend was loaded into the inner bowl of the rotoprocessor (MP 1, Aeromatic Fielder, Bubendorf, Switzerland). The rotor disc was operated at 160–1,360 rpm depending on the step of the process, and water was sprayed into the container at the optimal, experimentally determined rate, i.e., 30 g/min, with the aid of a peristaltic pump using 0.8×10^5 Pa of atomization pressure (Vetchý & Rabišková, 2002). Once all the water was sprayed, spheronization was performed at the rotor speed of 1,800 rpm for 2 min. After completion of the pellet formation, the pellets were dried at 50°C by lifting the inner wall of rotoprocessor. Required pellet size fraction 0.5–0.8 mm was separated on sieves of appropriate apertures. The manufacturing process was repeated six times, and nonpareils of the size 0.50–0.80 mm were separated and used for the layering experiments.

Preparation of Active Pellets

The solution intended for the drug layering was composed of 1,000 g of DHCl, 60 g of povidone, and 2,000 g of distilled water. About 1,000 g of inactive cores were charged into the process chamber of a bottom-spray fluid bed unit of Multiprocessor (MP 1, Aeromatic Fielder) and heated up. When the product temperature reached 45°C, the layering solution was sprayed onto the starters with the aid of the 0.8-mm diameter spray nozzle and peristaltic pump using 170 kPa of atomization pressure. The inlet air temperature was 65°C, and product temperature was 45°C. At the beginning, the spray rate was kept at 10 g/min. After the addition of 1,000 g of the liquid, the spray rate was increased to 20 g/min. When the next 500 g of solution were applied, the spray rate reached the final rate of 30 g/min. Once all the drug solution was sprayed, pellets were dried at temperature 80°C. The layering process was repeated two times for each type of nonpareils. Theoretical content of DHCl in active pellets was 48.5% (wt/wt). The process conditions are summarized in Table 1.

TABLE 1
The Layering Process Conditions

	Heating	Layering	Drying
Inlet temperature (°C)	80	65	80
Product temperature (°C)	45	45	45
Air flow (m^3/h)	100	250	250
Spray air pressure	–	170 kPa	–
Blow-back interval (s)	60	20	60

Characterization of Starters and Resulting Pellets

Particle size and size distribution of both starters and prepared pellets were determined by a sieve analysis for each batch. The set of stainless steel sieves with apertures in the range of 0.5–1.0 mm and a sieve shaker (type AS 200, Retsch, Haan, Germany) were used. Particles smaller than 0.5 mm were considered as a dust and particles bigger than 1.0 mm as agglomerates and were excluded from the total yield. The results were expressed as a percentage of weight retained on each sieve. Based on the results of sieve analysis, the particle mean diameter (mm) was calculated according to formula given by Haznos and coworkers (Haznos, Langer, & Gyamathy, 1992).

The particle shape, surface morphology, and internal structure were examined using a JEOL JSM-6700F scanning electron microscope (JEOL Ltd., Tokyo, Japan). Samples were mounted on a cylindrical stub using a double-sided sticky tape. The samples were coated with an approximately 70 nm thick gold layer in a SCD 030 sputter coater (Balzers Union Ltd., Balzers, Liechtenstein) and observed under the microscope operating at 5.0 kV.

The image analysis was employed in order to evaluate the sphericity (*S*) of cores and pellets. The image analysis of 200 pellets was performed using an optical microscope (DN 45, Lambda, Prague, Czech Republic) and CCD camera (Alphaphot, Nicon, Tokyo, Japan) linked to the computer operated by Leco IA 32 software (Leco Instruments, St. Joseph, USA). Pellet sphericity was calculated according to the following equation (Sienkiewicz, Pereira, Rudnic, Lausier, & Rhodes, 1997):

$$S = \frac{4p \times \text{area}}{\text{perimeter}^2} \quad (1)$$

The hardness of used starters and prepared pellets was tested on the C 50 Tablet Hardness Tester (Engineering Systems, Nottingham, UK) equipped with a C5 cell for pellet evaluation. The hardness of 10 randomly selected particles of each sample was evaluated.

For friability testing, 10 g of dust free particles (pellets or starters) were precisely weighed, put into the friabilator Roche (type TAR 10, Erweka, Heusenstamm, Germany) with stainless steel drum along with 200 pieces of 4 mm glass beads and rotated for 10 min at 20 rpm (Vertommen & Kinget, 1997).

The friability was expressed as a percentage of the weight loss after agitation. The measurement was repeated three times.

The pycnometric density (i.e., the apparent density) was determined with helium pycnometer (Pycnomatic—ATC, Porotec GmbH, Germany) according to Ph. Eur. recommendations.

The Hausner ratio (HR) was expressed as a ratio of tapped and bulk densities measured after 1,250 taps in a settling apparatus (type SVM 102, Erweka GmbH, Germany) using a 100 mL graduated cylinder.

The total tapped porosity (e%) was calculated from the particle tapped density values and the apparent density of particles according to the following formula (Rodriguez et al., 2001):

$$e\% = \left(1 - \frac{\text{tapped density}}{\text{apparent density}}\right) \times 100 \qquad (2)$$

The percentage deviation (PD) of the total tapped porosity from the ideal closest (rhombohedral) packing of monodispersed spheres (~26%) was calculated using the following equation (Rodriguez et al., 2001):

$$Percentage\_deviation = \left(\frac{e\%}{26} - 1\right) \times 100 \qquad (3)$$

Pellet flowability was expressed as repose angle values. Fifty grams of pellets were poured in a conical glass funnel (18.0 cm high, 9.7 cm top opening, and stem orifice with 0.8 cm diameter). Pellets flowed freely out from the stem that was positioned 10 cm above solid surface, and formed a cone. The repose angle (α) was calculated from the diameter base (d) and high (h) of the cone, using the following equation:

$$\alpha = \arctan\frac{2h}{d} \qquad (4)$$

The content of DHCl in pellets was determined. Firstly, pellets were pulverized using a mortar and a pestle. Forty milligrams of powdered pellets was accurately weighed, precisely transferred to a 1,000 mL volumetric flask, dissolved in purified water, and made up to the given volume. The absorbance of clear, previously filtered solution was measured at 237 nm using a UV spectrophotometer (spectrophotometer Lambda 25, Perkin Elmer Instruments, Shelton, USA). The actual drug content was subsequently calculated using an appropriate calibration curve.

The pycnometric, bulk, and tapped densities, repose angle, and drug content measurements were carried out in triplicate and the results were expressed as an arithmetic mean ± *SD*.

Statistical significance was tested using Student's *t* test for unpaired samples at a significance level of $p < .05$ and $p < .01$.

RESULTS AND DISCUSSION

Pellet Starters Characterization

The first step of our investigation was to compare the properties of raw nonpareils (for results see Table 2, *N* values). Cores of approximately comparable particle size 0.5 – 0.8 mm were chosen for the experiment.

It is known that ideal spheres of uniform size can assume either closest (rhombohedral) or loosest (cubic) packing which corresponds to the total tapped porosity of 26 or 48%, respectively. Real pellets and beads are neither spherical nor uniform and higher values of total tapped porosity e% are usual (Rodriguez et al., 2001). Almost ideal packing exhibited MCC cores Cellets® 500 as suggested by the total tapped porosity value of 31.7%. At the same time, these cores were found to have the most regular and spherical shape indicated by the highest sphericity value of 0.883. The LM cores had the highest value of the total tapped porosity (around 48.1%). This might be attributed to their biggest mean diameter, wider particle size distribution, and less spherical shape expressed as the smallest sphericity value of 0.855.

The packing ability of starters was evaluated from the changes in volume due to the rearrangement and packing occurring during tapping and was expressed as the HR. The HR could be considered as a measure of interparticle friction, and it is widely used to estimate the flow properties of powders, granules, or pellets. The HR value less than 1.20 indicates a good flowability of material under investigation (Kumar, Kohari, & Banker, 2001). Because the frictional forces depend on the particle size (i.e., the number of contact points), the particle shape, and surface roughness, it is no wonder the values of HR changed almost in parallel to that of PD from the ideal packing which increased in a row Cellets® 500 (PD = 21.8%) – sugar spheres (PD = 28.5%) – Celphere® CP 507 (PD = 48.50%) – LM cores (PD = 85.1%). Another common method to determine the flow property of pellets is the angle of repose measurements (Wan, 1994). The repose angle values changed very slightly (27.01– 27.50°); only in the case of LM cores, bigger difference was observed. However, their higher repose angle value of 28.20° was in a good agreement with their higher HR value determined (HR = 1.08).

When observed under an electron microscope (see Figures 1A, B), starters composed of MCC or its mixture with lactose displayed very dense fibrous structure given by the characteristic particle shape of raw MCC. Sucrose beads were rather granular and individual starch grains were distinguishable. On the sugar sphere cross-section (see Figure 1C), the lack of structural uniformity was clearly visible. It was possible to distinguish the single sucrose crystal, which was coated probably using sugar syrup and a starch dusting powder. Different nonpareil structure could be one possible explanation of significant differences observed in hardness and friability of selected inactive starters. Sucrose cores were the most fragile ones, exhibiting hardness of 0.86 N and friability value of 3.72%, which is

TABLE 2
The Properties of Nonpareils (N) and Prepared Pellets (P)

Nonpareil/ pellets containing nonpareil of	Size/mean diameter (mm)	Water solubility	Total yield/ agglomerates (%)	Hardness (N)	Friability (%)	Density (g/cm^3)			Total tapped porosity (%)	Percentage deviation (%)	Hausner ratio	Sphericity	Repose angle (°)	Drug content (%)
						Apparent	Bulk	Tapped						
Sucrose N	0.50 – 0.60	Freely soluble	–	0.86 ± 0.42	3.72 ± 0.06	1.4438 ± 0.0710	0.9151 ± 0.0258	0.9615 ± 0	33.4	28.5	1.05	0.864 ± 0.023	27.50 ± 1.03	–
Sucrose P	0.76	–	76.23 ± 2.05 21.40 ± 2.47	2.00** ± 0.12	1.563** ± 0.033	1.3437 ± 0.0017	0.7501** ± 0.0053	0.7803** ± 0.0102	41.9	61.3	1.04	0.830** ± 0.056	27.81 ± 0.29	45.84 ± 1.03
Celphere® CP507 N	0.50 – 0.71	Practically insoluble	–	1.29 ± 0.77	0.14 ± 0.02	1.5130 ± 0.0007	0.8722 ± 0.0087	0.9289 ± 0.0133	38.6	48.5	1.07	0.877± 0.021	27.01 ± 0.92	–
Celphere® CP507 P	0.83	–	85.66 ± 9.55 4.24 ± 1.14	2.58** ± 0.39	1.407** ± 0.065	1.3714** ± 0.0011	0.7438** ± 0.0196	0.7743** ± 0.0099	43.5	67.5	1.04	0.866** ± 0.023	25.68 ± 0.10	41.01 ± 0.77
Cellets® 500 N	0.50 – 0.70	Practically insoluble	–	1.49 ± 0.37	0.20 ± 0.02	1.3631 ± 0.0007	0.8877 ± 0.0088	0.9315 ± 0.0040	31.7	21.8	1.05	0.883 ± 0.015	27.33 ± 0.97	–
Cellets® 500 P	0.84	–	89.41 ± 4.70 4.69 ± 0.83	2.26** ± 0.10	1.301** ± 0.076	1.2935** ± 0.0040	0.7463** ± 0	0.7732** ± 0.0035	40.2	54.7	1.04	0.846** ± 0.030	24.28* ± 1.28	40.11 ± 0.37
LM cores N	0.50 – 0.80	Partially soluble	–	2.69 ± 0.80	0.35 ± 0.11	1.5391 ± 0.0001	0.7372 ± 0.0084	0.7982 ± 0.0196	48.1	85.2	1.08	0.855 ± 0.029	28.20 ± 0.89	–
LM cores P	0.85	–	90.36 ± 2.72 4.35 ± 0.78	4.28** ± 0.12	1.340** ± 0.020	1.3805** ± 0.0019	0.6913** ± 0.0073	0.7135** ± 0.0021	48.3	85.8	1.03	0.869** ± 0.009	24.80 * ± 1.24	39.96 ± 0.95

*Differences compared with the nonpareil were significant ($p < .05$).
**Differences compared with the nonpareil were very significant ($p < .01$).

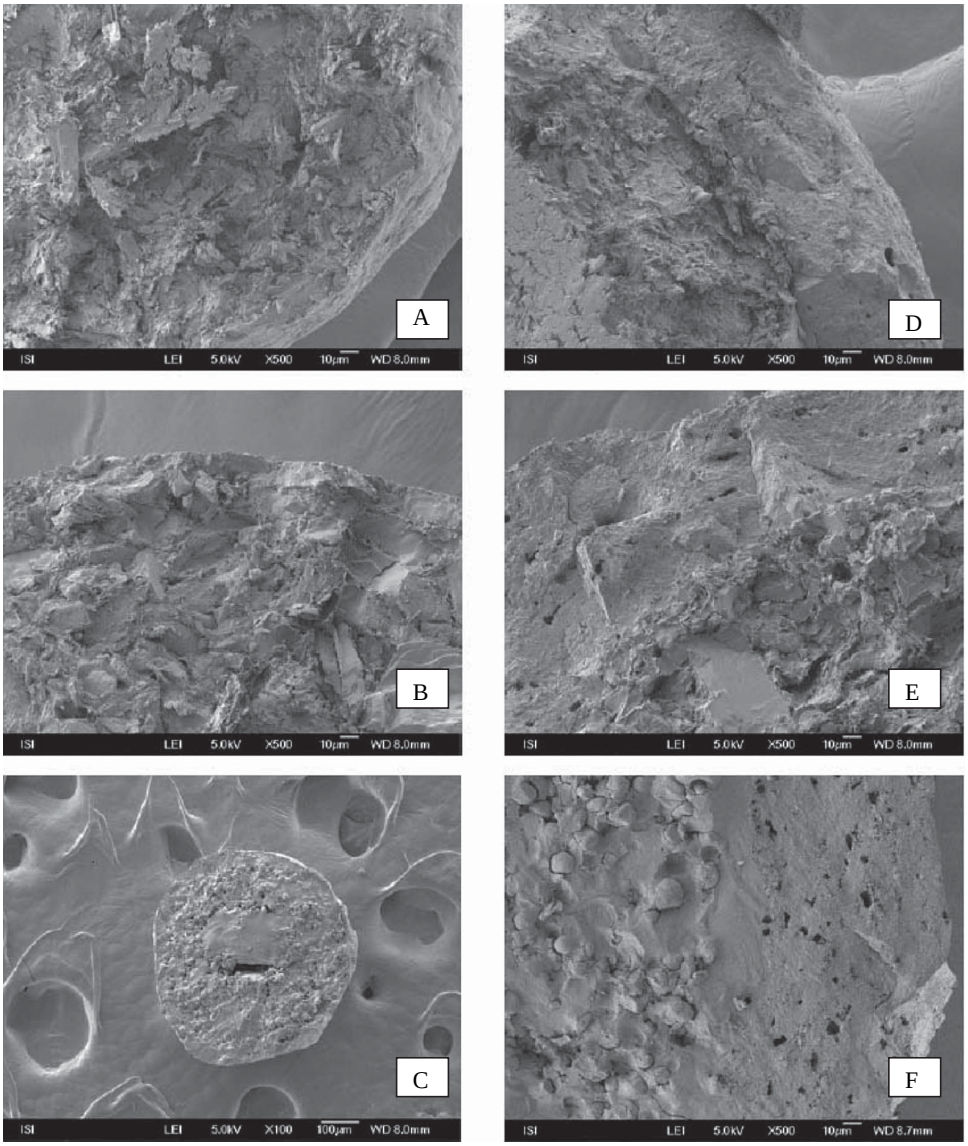

FIGURE 1. The appearance of the inactive starters (left) made from MCC (A), MCC and lactose (B), and sucrose (C). The cross-section of the layered pellet (right) containing the MCC (D), LM (E), or sucrose core (F) as observed under the scanning electron microscope (magnification × 500).

approximately twice higher than the recommended limit 1.7% (Vertommen & Kinget, 1997). As expected, cores made from MCC were harder and exhibited high resistance against friction (friability 0.14–0.20%). Excellent mechanical properties are probably given by the fact that MCC undergoes a plastic deformation during the cores formation and forms additional hydrogen bonds between individual adjacent chains which strengthen the resulted structure (Zhang, Law, & Chakrabarti, 2003). In the case of LM cores, this effect was probably accompanied by the recrystallization of lactose and solid bridges formation during rotoagglomeration; thus the hardest starters were obtained (hardness of 2.69 N).

The differences in apparent density observed among the four cores could be ascribed partly to the use of different starting materials, partly to different manufacturing processes leading to the nonpareil formation. For example, LM cores were produced by the rotoagglomeration, the pelletization technique carried out in rotogranulators. During the pellet formation, primary powder particles are forced toward each other and agglomerate. Thanks to the unique combination of three different forces, i.e., gravitational, fluidized and centrifugal, the most compact and hard indifferent beads are obtained although the density of raw powder blend (1.539 ± 0.001 g/cm^3) is lower than that of raw MCC (1.547 ± 0.001 g/cm^3) or sucrose (1.600 g/cm^3) (Rowe, Sheskey, & Owen, 2006).

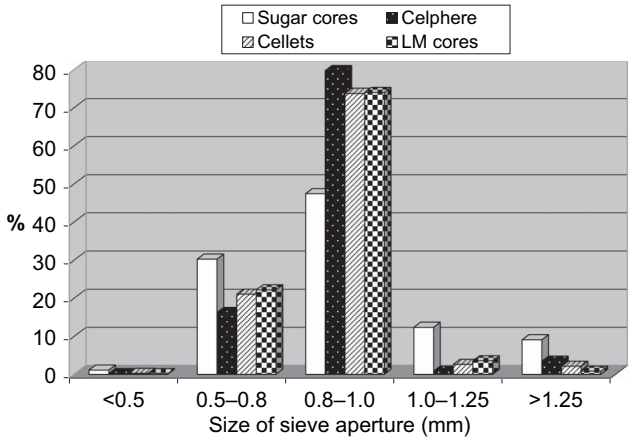

FIGURE 2. Size distribution of prepared pellets.

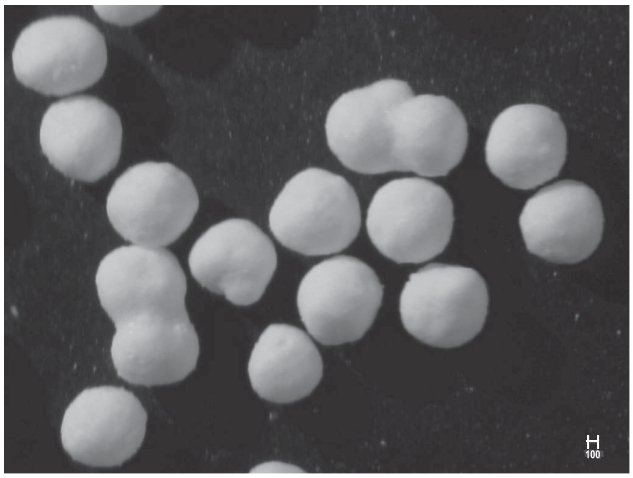

FIGURE 3. Pellets containing the sucrose starters as observed under the optical microscope. The measure bar corresponds to 100 μm.

Pellet Size and Size Distribution

When sugar spheres were used as a starting material for the drug layering process, then more than 20% of resulting pellets was bigger than 1.0 mm (see Figure 2, Table 2—*P* values). This was probably due to the fact sucrose nonpareils are freely soluble in water. When water drug solution was sprayed onto the sugar spheres, it could partially dissolve sucrose on their surface making it sticky. Pellets were "glued" together and after solvent removal during drying, larger agglomerates, irregular in shape and size, were formed (see Figure 3). As a result, the particle size distribution was wider and larger pellets were more frequent. On the contrary, layering on the sucrose seeds yielded the highest amount (around 1.1%) of the dust (i.e., pellets and irregular particles smaller than 0.5 mm). The most fragile sucrose nonpareils could crumble when exposed to the mechanical stress generated in fluid bed equipment during the layering process and thus produce higher amount of undesired powder.

The size distribution of the other pellet samples was almost the same. In general, the major pellet fraction was found between 0.8 mm and 1.0 mm and less than 4.7% pellets exceeded 1.0 mm. Also, the total pellet yields obtained by the drug layering using MCC and LM nonpareils as starters were comparable, i.e., from 85.66 to 90.36%. As already suggested, the total yield of the pelletization process employing sugar spheres was lower, around 76.23% (see Table 2). This observation could be explained in terms of lower mechanical resistance of sucrose nonpareils (i.e., lower values of hardness and friability) and larger agglomerates formation.

The mean particle diameter of prepared pellets exhibited slightly different values (see Table 2). Pellets with sucrose nonpareils were found to be the smallest (d = 0.76 mm) whereas pellets created from LM cores were the biggest ones (d = 0.85 mm). These results correspond to the original size of appropriate starters.

Mechanical Properties of Pellet Samples

Because pellets should withstand subsequent handling, coating, shipping, storage, and other processes following their formation, it is necessary to attain acceptable pellet hardness and friability.

Table 2 summarizes the results of friability measurements expressed as the percentage loss in weight during the friability testing. Pellets with the friability values <1.7% are judged as mechanically acceptable (Vertommen & Kinget, 1997). From this point of view, all the pellet samples exhibited good mechanical properties—the friability values varied between 1.301 and 1.563%. Despite the differences in friability observed in case of raw nonpareils, the friability of final pellets was in a relatively narrow range. These results suggest that the drug layer created on the surface of solid starters had always approximately the same properties regardless the starter type used.

As expected, the pellet hardness changed inversely to the pellet friability. Pellets produced by layering the drug on the sucrose spheres could be regarded as the most brittle ones. This corresponds to the fact the sucrose spheres themselves had the lowest hardness at all. When compared with the hardness of raw starters, all the pellet samples exhibited improved hardness (statistically very significant $p < .01$). This could be ascribed to the bigger particle diameter of resulting pellets and to the compact drug layer containing a strong binder (Kollidon® 25).

Pellet Density and Flow Properties

The density of pellets should be taken into consideration for several reasons. It can influence the pellet gastrointestinal transit time or the uniformity of their filling (usually volumetric) into hard gelatine capsules (Clarke, Newton, & Short, 1995).

The results of apparent density measurements are listed in Table 2. It is obvious that the apparent densities as well as the bulk and the tapped densities of pellets changed proportionally to density values of corresponding nonpareils.

The packing of pellet samples was expressed as total tapped porosity values (e) and PD from the ideal packing. The worst packing (e = 48.3%, PD 85.8%) had pellets with LM cores, the value was similar as for LM cores (e = 48.1%, PD 85.1%). The packing stayed almost untouched by layering. The total tapped porosity and PD of other samples increased when compared with cores, probably due to the wider particle size distribution of pellets.

In free flowing materials, the initial bulk and tapped densities would be more similar than in the case of poorly flowing materials which yield greater differences between the two values (Heng & Chan, 1997). Small differences between densities and HR values close to 1.0 indicate good flow properties of tested material. The ratio of tapped and bulk densities—the HR—of all pellet samples reached values from 1.03 to 1.04 suggesting low interparticle friction and excellent flow properties. Similarly, all pellet samples exhibited low values of repose angle. However, the repose angle of pellets with sucrose nonpareils was higher than in case of the others (27.81° in comparison to 25.68, 24.28, and 24.80°). The difference only reflects the fact that pellets containing sucrose cores had the lowest sphericity value at all, i.e., S = 0.830.

Drug Content

Pellets with a relatively high drug loading were produced via the layering of concentrated aqueous drug solution on all previously selected starters (i.e., sugar spheres, Celphere®, Cellets®, and LM cores). The theoretical content of DHCl should comprise 48.5% of the total pellet weight. The actual drug content in final pellets varied between 82.4 and 94.5% of the theoretical amount (39.96–45.84% of the total pellet weight). Surprisingly, the highest amount of DHCl contained pellets with sucrose cores (45.84%). If the drug solution layering process should be successful, it is necessary to wet properly the solid surface of the starter. Only at these conditions, droplets of the drug solution could spread all over the solid surface and create a continuous drug layer. As sucrose cores are freely soluble in water, one might presume their surface is evenly wetted by the drug solution making the layering process more effective. This theory could be supported by SEM images of layered pellets (see Figure 1D–F). In case of pellets with sucrose cores, DHCl layers adhere very tightly to the nonpareil surface and the boundary between them can be only hardly distinguished.

CONCLUSION

The results of this experimental study indicate that active pellets containing more than 40% of the soluble drug (DHCl) can be prepared by the layering of concentrated aqueous drug solution using the Wurster column process and different nonpareil kinds as a starting material (sucrose, MCC, and LM cores). It was found that the yield and some characteristics of resulted pellets are influenced by the original nonpareil properties, e.g., their solubility, hardness, and friability. Sucrose nonpareils were less suitable for high amount of drug solution in water due to their solubility and undesirable agglomerates formation resulting in lower yield and thus economical lost.

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