

Active Layering and Direct Compression of Sugar Spheres: Content Homogeneity in Low-Dosage Tablets

In the pharmaceutical industry, drug homogeneity has become more important in recent years as the efficiency of actives has increased and their concentrations in solid unit forms have decreased. Here, the layering of sugar spheres (250–355 μm) was studied as a process allowing the uniform distribution of a low-dose drug onto a carrier excipient. Textural analysis results indicated that the controlled spraying of a drug solution onto the spherical and monodispersed carrier led to a homogeneous population of layered sugar spheres. Furthermore, as a consequence of free-flowing properties and low stress heterogeneity inside the granular bed, compression parameters showed great reproducibility in tablet weight and hardness. Tensile strength measurements indicated that the layering process did not affect the spheres' cohesion within the tablets, and content uniformity could be observed as a result of the a priori drug stabilization onto the spheres.

Leticia Martinez is a PhD student, **Pierre Tchoreloff*** is a professor, **Bernard Leclerc** is a senior lecturer, **Madelaine Besnard** is a CNRS engineer and **Guy Couarraze** is a professor.

Laboratoire de Physique
Pharmaceutique UMR CNRS
8612, Faculté de Pharmacie
Paris-Sud, 5, rue Jean-Baptiste
Clément, F-92296 Châtenay-
Malabry Cedex, France.
Tel. +33 1 4683 5611
Fax +33 1 4683 5882

*To whom all correspondence
should be addressed.

The content uniformity of solid low-dosage forms is a major challenge in the pharmaceutical industry.^{1–3} This uniformity depends on the quality of the initial mixture and of the intermediate grain. The goal is thus to obtain the best dispersion of active within the excipients at every process level. Hitherto, powder blend homogeneity has been evaluated by sampling the intermediate products. Such a method is limited, though, because of its invasive nature and disruption of the powder bed structure.^{4,5} That is why, according to quality assurance, every production step should lead towards homogeneity. Stabilization of a granular blend can be achieved by fixing one of the components, in this case the drug, onto a carrier diluent.^{6,7} The pharmaceutical industry has already shown a large interest in spheroids, in terms of their free-flowing properties and available surface area for layering and coating. Here, we propose a method to guarantee the homogeneous drug

distribution within a final solid unit form.⁸ Our aim was to obtain homogeneity and reproducibility, combined with direct compression. The process comprises two steps. A layering process, spraying an aqueous drug solution (homogeneous molecular dispersion by definition) onto a carrier consisting of sugar spheres (homogeneous particle size and texture), is followed by direct compression of the layered sugar spheres. The mechanical resistance of the resulting tablets is related to both textural and compactibility properties of sugar spheres.

Materials and methods

Materials. Sugar spheres (250–355 μm) were kindly provided by NP Pharm (Bazainville, France; batch 903w). Polyethylene glycol 6000 (PEG 6000) was purchased from Hoechst AG (Frankfurt, Germany; batch GW 970047). Acetaminophen, used as a marker in the content uniformity assay, was obtained

Table I Process parameter values for layering in the fluidized bed apparatus.

Parameter	Value
Solid content	500 g
Mode	Top-spraying
Spraying rate	3 mL/min
Nozzle diameter	1.1 mm
Atomization pressure	0.4 bar
Air volume	0.5 m ³ /min
Inlet temperature	55 °C
Outlet temperature	39–41 °C

Table II Composition of the layering solutions.

Ingredients (for 500 g sugar spheres)	Placebo layering	Drug layering
PEG 6000	25 g	25 g
Acetaminophen	—	2 g
Purified water	125 g	200 g

from Rhodia (Decines, France; batch 9836439). All other chemicals were of analytical reagent grade. **Layering.** The layering of sugar spheres was done in a fluidized bed apparatus (Aeromatic-Fieldler AG, Bubendorf, Switzerland) using a stainless steel chamber (capacity 0.2–4 kg) loaded with 500 g of product. Formulation and process conditions are given in Tables I and II. To avoid the use of toxic components, all the solutions to be sprayed were prepared with water, a condition that may apply to all drugs. PEG 6000, chosen as the binder polymer, was dissolved in purified water to obtain a concentration of 5% (w/w, total weight of sugar spheres). Acetaminophen was added to a concentration of 0.4% (w/w, total weight of sugar spheres). Solutions were sprayed in top-spray conditions, followed by a final drying (up to 45 min at 40 °C). Layered sugar spheres were monitored in terms of residual moisture with an infrared balance (Breda Scientific Osi, Breda, The Netherlands). Results showed a residual moisture of 2%, compared with 3% in the original spheres.

Particle size distribution and textural properties. Textural studies were conducted before and after the lay-

ering process to emphasize its influence on the original carrier properties. Particle size distribution was determined by laser diffraction on a Coulter LS 230 apparatus (Beckman Coulter, Inc., Fullerton, California, USA). The Brunauer-Emmett-Teller method (Coulter SA 3100) allowed the measurement of the sugar spheres' specific surface area using nitrogen as the adsorbing gas, at the temperature of liquid nitrogen. Carrier surface morphology was also assessed by direct observation using scanning electron microscopy (SEM) (LEO 1530 Gemini; LEO Electron Microscopy Ltd, Cambridge, UK) without any metal coating.

Mechanical properties: compressibility and compactibility. Layered sugar spheres were lubricated with 0.125% w/w of magnesium stearate and then direct compressed on an instrumented alternative press (Frogerais OA, Vitry-sur-Seine, France; 1 cm² flat punches, 1 cm die height). PECAMEC software was used to record the compression cycles (3.1.1 version, 1996, J2P instrumentation). To cover a wide range of hardness and porosity, eight levels of pressure were applied: 50, 80, 110, 150, 170, 200, 240 and 270 MPa (that is, 5–27 kN according to the punch and die dimensions). Compaction force transmission (%), ejection forces and residual forces were obtained from the analysis of the compression cycles (mean of 10 determinations per compression pressure).

In addition, Heckel modelling^{9,10} — the plotting of the natural logarithm of the reciprocal of the porosity against compression pressure — was applied to the sugar spheres by exerting a continuous stress (up to 200 MPa), using a

hydraulic press (Perrier Labotest, Montrouge, France), and simultaneously registering the course of the upper flat punch (area: 0.79 cm², speed: 0.1 mm/s). Yield stress P_y (MPa) could thus be interpreted.

To determine the tensile strength of the resulting tablets, a diametral compression test was done at a constant speed using a texture analyser (TA-XT2, Stable Microsystems, Godalming, UK) (speed: 0.1 mm/s, maximal displacement: 1.0 mm).

The disintegration time of 500 mg tablets (1 MPa tensile strength) was measured according to the *European Pharmacopoeia* method¹¹ in a Sotax (Basel, Switzerland) DT3 Osi apparatus (mean of 3 determinations).

Acetaminophen dosage. For content uniformity studies, acetaminophen tablets were prepared on the Frogerais press at 150 MPa. Acetaminophen layered onto sugar spheres was compared with a physical mixture of acetaminophen and sugar spheres prepared in a Turbula (W.A. Bachofen, Basel, Switzerland) (speed: 48 rpm, time: 2 min). Acetaminophen tablet content was determined by ultraviolet spectrophotometry at 234 nm in a solution of 0.1 N hydrochloric acid.

Results and discussion

Particle size distribution and textural properties. Mean and median diameter values were used to calculate mean:median ratios (Table III). The ratios were close to unity in all cases, that is, for both non-layered and layered sugar spheres. This shows the symmetrical character of the distribution. The single modal profiles, associated with low standard deviations, revealed a very homogeneous population of layered sugar spheres (Figure 1).

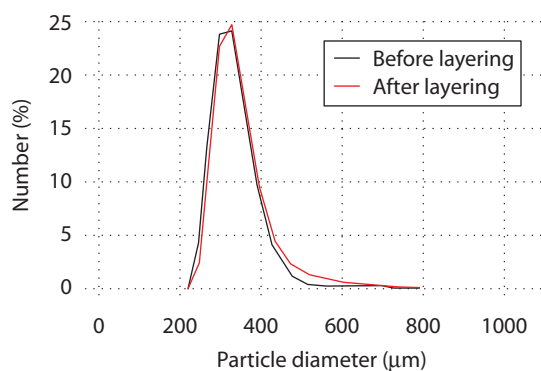
Table III Diameter and specific surface area of sugar spheres before and after layering (n = 3).

	Mean diameter (µm)	Median diameter (µm)	Mean:median ratio	Specific surface area (m ² /g)
Sugar spheres	326 ± 57	318 ± 2	1.03	0.199 ± 0.001
Sugar spheres with placebo layering ¹	338 ± 65	326.1 ± 0.1	1.04	0.180 ± 0.005
Sugar spheres with acetaminophen ²	339 ± 71	325.4 ± 0.6	1.04	0.180 ± 0.005

¹ 5% (w/w) PEG 6000.

² 5% (w/w) PEG 6000 + 0.4% (w/w) acetaminophen.

Figure 1 Particle size distribution of sugar spheres before and after layering.



In comparison with non-layered sugar spheres, the specific surface area decreased when sugar spheres were layered with PEG 6000, whether drug was present or not (Table III). This is the result of surface roughness reduction by the complete engulfment of carrier asperities by the binder.

All these results were confirmed by observation using SEM. Figure 2 shows the roughness of non-layered

sugar spheres. By contrast, layered sugar spheres show a much smoother surface. This smoothness contributes to greater sphericity (Figure 3). The narrow distribution range of sugar sphere size, as well as the regular fluidization and solution spraying, contributed to uniformity of layering. This layering uniformity guaranteed a homogeneous distribution of drug. **Mechanical properties: compressibility and compactibility.** The Heckel plot gives a linear relationship between pressures of approximately 30 and 175 MPa (Figure 4). The reciprocal of the slope of this rectilinear section (yield stress, P_y), is indicative of the consolidation mechanism of the solid.¹² P_y represents the ductility of the material. For layered and non-layered sugar spheres, P_y values correspond to a plastic rather than brittle behaviour during compression (Table IV). Besides, this property is more pronounced in the presence of PEG, which is known for its ductility. This factor aids the formation of contact surfaces necessary for cohesion. According to Figure 4, it is worth emphasizing that the large exploitable linear range of plastic

deformation leaves a considerable degree of freedom in the factor of applied pressure — reaching neither critical stress levels nor the mechanical resistance limits of the punches.

Considering non-layered as well as layered sugar spheres, and examining the range of applied pressure (50–270 MPa), compaction force transmission (%), ejection forces and residual forces, the results attest to satisfactory lubrication with a magnesium stearate concentration as low as 0.125% (Table V). This low level of required lubricant is a favourable point to the extent that magnesium stearate is known for its hydrophobic character and for increasing disintegration times. Compression parameters are also evidence of low stress heterogeneity inside the compact — most probably a result of carrier regularity and sphericity. This homogeneity of stress distribution resulted in reduced sensitivity to lamination incidents. By contrast, the tablets' appearance was perfectly smooth with glossy surfaces. So, layering with PEG 6000 did not disturb the excellent compression characteristics of sugar spheres. Moreover, disintegra-

Figure 2 Surface morphology of sugar spheres. (a) Before layering; (b) after layering.

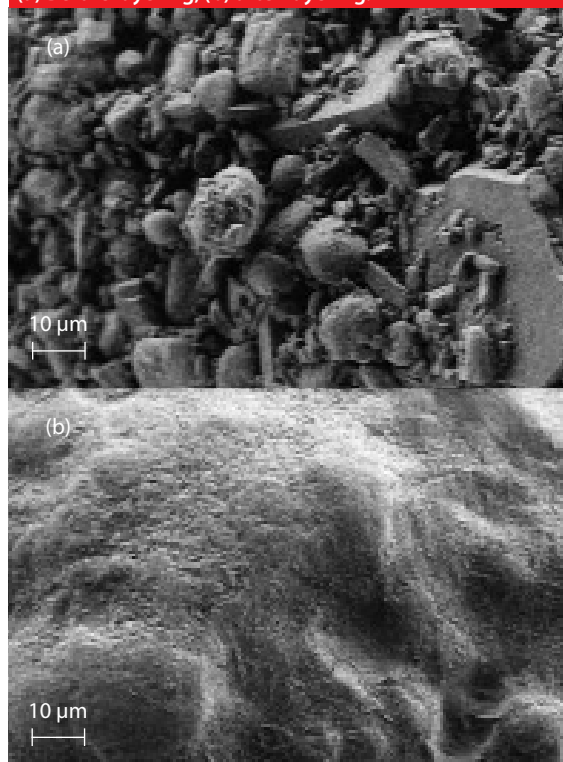


Figure 3 Morphology of sugar spheres. (a) Before layering; (b) after layering.

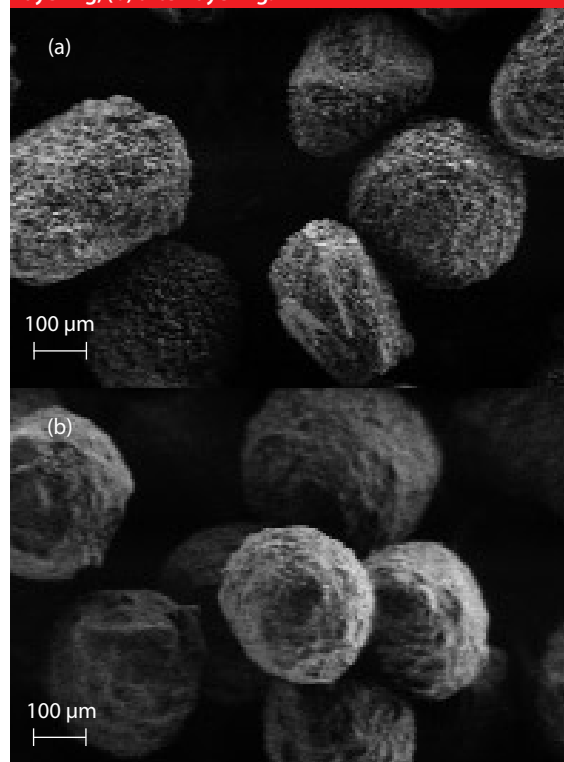


Figure 4 Heckel plot of layered sugar spheres.

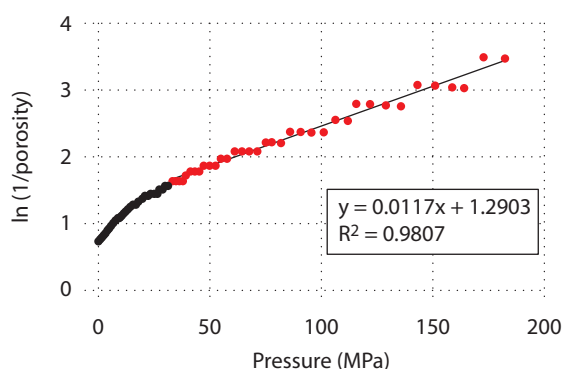


Table IV Calculated yield stress values (n = 3).

	P_y (MPa)
Sugar spheres	99 ± 4
Sugar spheres with placebo layering	84 ± 2

tion times did not exceed 400 s, even in the presence of the binder layer, and despite the absence of a disintegrant. This result was not surprising, as sugar spheres are very soluble in water and tablets simply erode from the outside.

Mean weight values with low standard deviations reflected weight uniformity, resulting from free flowability and regular filling of the die (Table VI). Percentage standard deviations in mean weight vary between 0.7% and 1.2%, which is well within the *European Pharmacopoeia* limit of 5% for tablets of 250 mg or more.¹¹ At the stage of machine feeding, homogeneity is thus ensured by the appropriate textural properties of the sugar spheres.

Tablet cohesion was determined from the force value F (N), at which the tablet fractured under diametral compression. This value permitted the calculation of tensile strength, σ_R (MPa), according to the following equation:¹³

$$\sigma_R = 2 \cdot F / \pi \cdot d \cdot e$$

where d is the tablet diameter (mm) and e is the tablet thickness (mm). For example, for a tablet of 9 mm diameter and 3 mm thickness,

a tensile strength of 1 MPa corresponds to a crushing strength of 42 N or 4.2 kg. σ_R has been expressed as a function of the compaction pressure (Figure 5). The linear relationship shows the predictive and reproducible character of tablet hardness. As shown in the graph, cohesion was already demonstrated at low stress levels (approximately 20 MPa) which means that energy supplied during compression was specifically used to create effective cohesive bonds. Hardness levels, consistent with industrial production requirements (approximately 1 MPa), were obtained with intermediate pressures (150 MPa).

To study the fluctuation of weight, hardness and friability as a function of production time, tableting was done on a rotary press (Manesty, Liverpool, UK) with the following formulation: sugar spheres lubricated with 0.125% magnesium stearate. All the batches exhibited very low mass fluctuations around the mean value and complied well with *European Pharmacopoeia* standards¹¹ (data not shown).

Acetaminophen dosage.

Acetaminophen content was determined for 25 tablets (Table VII). In this study, layered acetaminophen was compared with a physical mixture of acetaminophen and sugar spheres. Standard deviation for the latter batch was two-fold greater than that of the former. Two tablets departed from the average by more than two standard deviations, whereas for layered acetaminophen, none of the content values departed by more than two standard deviations. Many factors favoured segregation in the case of physical mixing: differences in particle sizes, densities

and proportions.¹⁴⁻¹⁶ By means of the layering process, stabilization between drug and carrier occurred, and the tendency to segregate was definitely avoided. We can, thus, conclude an excellent reproducibility of drug content in final solid unit forms.

Conclusion

Particle size distribution and textural analysis revealed a narrow size distribution of sugar spheres, before and after layering, as well as good sphericity — particularly when layered. Compression studies showed excellent reproducibility of compaction pressure and tablet weight, because of the free-flowing properties of sugar spheres. Sugar spheres also presented good compactibility properties, independently of the layering operation. As demonstrated by acetaminophen dosage, fixing drug onto the carrier by including it in an aqueous solution of PEG 6000 resulted in uniformity of the dosage unit.

Possible applications of this concept could be low-dosage tablets, low therapeutic margin drugs, as well as divisible tablets, using a simplified process but with a high level of confidence in terms of reproducibility and homogeneity.

Acknowledgements

The authors wish to thank Mr P. Sanial, general director of the NP Pharm Laboratories (F-78550 Bazainville, France) for his donation of sugar spheres, as well as Mrs I. Defer, microgranule technical manager. They also thank Ethypharm Laboratories (Bureaux de la Colline, F-92213 Saint-Cloud, France) for their research grant to support this work. They are grateful to Mr J-P.

Table V Extensometric studies (50–270 MPa) and disintegration times.

	Compaction force transmission (%)	Ejection force (daN)	Residual force (daN)	Disintegration time (s)
Sugar spheres	91 ^a < T < 94 ^b	12 ^a < F _e < 35 ^b	0 ^a < F _r < 13 ^b	300
Sugar spheres with placebo layering ¹	93 ^a < T < 97 ^b	24 ^a < F _e < 65 ^b	5 ^a < F _r < 20 ^b	380
Sugar spheres layered with acetaminophen ²	93 ^a < T < 96 ^b	22 ^a < F _e < 54 ^b	5 ^a < F _r < 14 ^b	370

^a Minimal pressure of 50 MPa. ^b Maximum pressure of 270 MPa.

Table VI Weight uniformity.

	Mean weight value* (mg)
Sugar spheres	844 ± 10 (± 1.2%)
Sugar spheres with placebo layering	719 ± 8 (± 1.1%)
Sugar spheres layered with acetaminophen	677 ± 5 (± 0.7%)

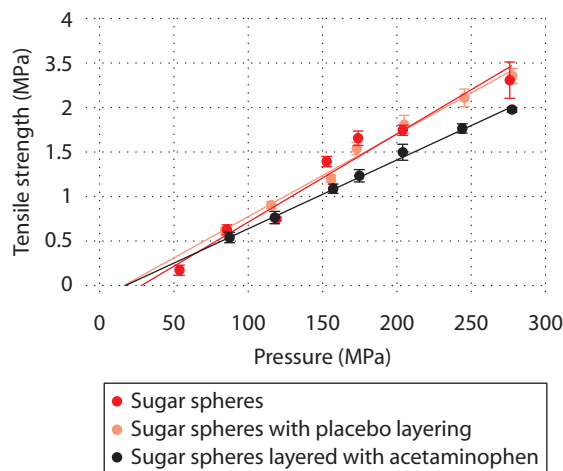
*n = 80 tablets.

Table VII Content uniformity.

	Mean content value* (mg)	Standard deviation (mg)
Sugar spheres mixed with acetaminophen	1.8	0.1
Sugar spheres layered with acetaminophen	2.04	0.05

*n = 25 tablets

Figure 5 Tensile strength as a function of pressure (n = 10).



Pastol of the Metallurgy Center of the CNRS (Vitry-sur-Seine, France) for his help with the SEM studies.

References

1. D. Train, "Pharmaceutical Aspects of Mixing Solids." *Pharm. J.* **185**, 129–134 (1960).
2. A.G. Lord, "Content Uniformity in Tablets: A Literature Review," *Pharm. Technol.* **11**(9), 64–70 (1987).
3. H.H. El-Shattawy, "Micromixing of Oral Contraceptives," *Drug Dev. Ind. Pharm.* **7**(4), 439–451 (1981).
4. F.J. Muzzio *et al.*, "Sampling Practices in Powder Blending," *Int. J. Pharm.* **155**, 153–178 (1997).
5. F.J. Muzzio *et al.*, "An Improved Powder-Sampling Tool," *Pharm. Technol.* **23**(4), 92–110 (1999).
6. A. Michoel *et al.*, "Carrier Granulation: A New Procedure for the Production of Low-Dosage Forms," *Pharm. Technol.* **12**(6), 66–84 (1988).
7. J.A. Napper *et al.*, "Process for Preparing Solid Dosage Forms of Very Low-Dose

Drugs," World patent number WO 97/04750 (SmithKline Beecham plc, UK, 13 February 1997).

8. G. Couarraze *et al.*, "Comprimés Faiblement Dosés et Procédé de Préparation," French patent number FR 2 796 840–A1 (Laboratoires des Produits Ethiques Ethypharm, France, 2 February 2001).
9. R.W. Heckel, "Density–Pressure Relationship in Powder Compaction," *Trans. Metall. Soc. A.I.M.E.* **221**, 671–675 (1961).
10. R.W. Heckel, "An Analysis of Powder Compaction Phenomena," *Trans. Metall. Soc. A.I.M.E.* **221**, 1001–1008 (1961).
11. *European Pharmacopoeia 3rd Edition* (European Pharmacopoeia Commission, Council of Europe, Strasbourg, France, 1997) pp 126–153.
12. R.C. Rowe and R.J. Roberts, "Mechanical Properties," in G. Alderborn and C. Nystrom, Eds., *Pharmaceutical Powder Compaction Technology* (Marcel Dekker, New York, New York, USA, 1995) pp 283–322.
13. J.T. Fell and J.M. Newton, "Effect of Particle Size and Speed of Compaction on Density Changes in Tablets of Crystalline and Spray-Dried Lactose," *J. Pharm. Sci.* **60**, 1866–1869 (1971).
14. J.C. Williams, "The Mixing of Dry Powders," *Powder Technol.* **2**, 13–20 (1969).
15. C.W. Yip and J.A. Hersey, "Segregation in Ordered Powder Mixtures," *Powder Technol.* **16**, 149–150 (1977).
16. N. Sommier *et al.*, "Magnetic Resonance Imaging Investigation of the Mixing–Segregation Process in a Pharmaceutical Blender," *Int. J. Pharm.* **222**, 243–258 (2001). ■