Mini-tablets solution coating vs powder layering process comparison in fluid bed dryer

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Purpose

Manufacturing of coated solid dosage forms entails the deposition of different materials onto substrate cores, such as powder particles, granules, pellets, tablets and capsules, with the aim of improving organoleptic and aesthetic characteristics, providing physical and chemical protection or modifying the drug release profile [1]. Traditional coating techniques involve the use of polymeric formulations dissolved or dispersed in aqueous or organic solvents. In recent years, layering of powder has emerged as a useful alternative for depositing polymeric layers onto coating cores avoiding organic solvents and/or reducing drying process. This technique becomes particularly interesting in the manufacturing of high-level coated products as it allows to shorten the processing time and avoids problems typical of the processes of liquid-based stratification [2]. This is the specific case relating to the preparation of pulsatile release systems consisting of a drug-containing core coated with a relatively thick layer of high viscosity polymers (>50% weight gain). The reference apparatus to realize coating on small cores is represented by the bottom-spray fluid bed, also known as Wurster insert. Aim of this study was to evaluate and compare the performances of two different coating techniques in fluid bed dryer for the preparation of pulsatile drug release minitablets coated with hypromellose. Solution coating in bottom-spray insert and powder layering in tangential-spray insert were studied.

Materials

MATERIALS

Core Tablets formulation: DC Paracetamol (Rhodapap™ Novacyl powder, RPC) 80%, MCC (Avicel PH102, FMC, Italy) 12.5%, Sodium Starch Glycolate (Explotab, JRS Germany) 4.5%, Copovidone (Kollidon VA64, BASF, Germany) 2%, Silica (Aerosil 200, Evonik, Germany) 0.5%, Mg Stearate (Sigma Aldrich, Germany) 0.5%

Tabletting: Ronchi AS8 tablet press

Fluid bed Granulator: Freund-Vector VFC-Lab3 in Wurster configuration, equipped with AcceleratorTM System and in Rotor configuration equipped with Granurex™ insert.

Process Parameters		
Parameter	*Solution coating*	*Powder layering*
Batch size	5 kg	2 kg
Atomization pressure	1.5-1.6 bar	1.5 bar
Accelerator pressure	2.0-2.1 bar	-
Partition height	1.0-2.0 inch	-
Solution spray rate	10-25 g/min	10-20 g/min
Total solution sprayed	55.5 kg	1.5 kg
Rotor speed	-	250 rpm
Product temperature	41-43 °C	17-18 °C
Powder feeding rate	-	10-12 g/min
Total powder dosed	-	900 g
Slit airflow	-	10/12 m³/h
Drying air temperature	75 °C	75 °C
Drying air flow	100 m³/h	100 m³/h
Process time	2550 min	135 min
Process time /kg batch	504 min	67.5 min

Methods

Tablets production: Minitablets were manufactured using a rotary tablet press (FA8, Ronchi, Italy) equipped with 8 punches tooling each equipped with 8 concave punches 2.5 mm, radius curvature 3 mm. Powders (8 kg batch size) were mixed in bin tumbler (20 L bin, VIMA, Italy) for 20 min. Composition of tablets was DC Paracetamol 80%, MCC 12.5%, Sodium Starch Glycolate 4.5%, Copovidone 2%, Silica 0.5%, Mg Stearate 0.5%. The compression force used per punch was 15kN. Minitablets had weight 12±1 mg, crushing strength 13.18±0.96 N, thickness 2,50±0.2 mm, friability mass loss 0,49%, no broken tablets.

Solution coating: The minitablets were filmed by solution coating using a bottom-spray fluid bed system (VFC-Lab3, Freund-Vector corp., USA) equipped with a 2-way nozzle and Accelerator™ System. A 4,5% w/w solution of HPMC E50, added with 0,45% w/w PEG 400 in DI water was used. The solution was sprayed on the tablets aiming to a weight gain of 50%. Process parameters are reported in Table 1.

Powder Layering coating: Tablets were coated by powder layering using a tangential-spray rotary fluid bed system (VFC-Lab3, Freund-Vector corp., USA) equipped with a 2-way spray nozzle and Granurex™ rotor insert. As the liquid binder, an aqueous solution of HPMC E50 at 4,5% w/w added with 7% w/w PEG 400, as the plasticizer, was used. HPMC E50 powder was sieved to remove the fraction above 75 µm, and the fine fraction (≤75µm) was distributed into the rotor at a constant rate using a gravimetric twin-screw powder feeder (K-Tron Coperion, USA). Process parameters are reported in Table 1.

Characterization: 100 tablets from each batch were characterized for their sizes, coating thickness, and mass uniformity . Three minitablets per sample were tested individually for drug release profile in dissolution apparatus type I basket dissolution equipment (Distek 2100b, Germany), using 800 mL DI water at 37 °C as the release medium. The amount of paracetamol released was quantified by UV spectrophotometry at 248 nm wavelength (Lambda 35, Perkin Elmer, USA). Release performance was evaluated by calculating time to release 10% of paracetamol ($t_{10\%}$).

Solution Coating

Pros

- Easy, controllable and feasible process
- Homogeneous product
- Smooth and even surface
- High Yield
- Narrow core weight span
- High industrial scale batch size
- Very good release control

Cons

- Long process time (42 hours)
- High use of water/solvent
- High energy use for air heating

	SPRAY TIME	DRYING TIME	COATING YIELD	BATCH SIZE (TEST)	SPRAY TIME / Kg BATCH (TEST)	BATCH SIZE (INDUSTRIAL)	BULK DENSITY	DISSOLUTION TIME
BOTTOM-SPRAY SOLUTION COATING	42 HOURS	30 MINUTES	94,23%	5Kg	8 HOURS 24 MINUTES	970L (717,8 Kg)	0,74	22+/-2 MINUTES

Powder Layering

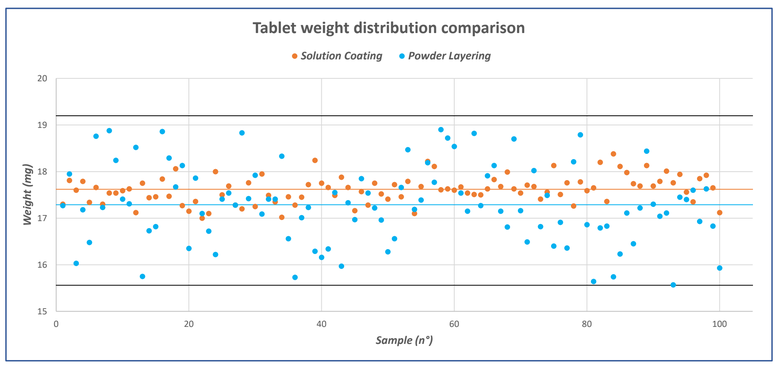
Pros

- Easy, controllable and feasible process
- Reasonably homogeneous product
- High Yield
- Acceptable core weight span
- Very fast process (1,5 hours)
- Low use of water/solvents
- Low energy use for air heating
- Very good release control

Cons

- Low industrial batch size
- Slightly rough and uneven surface

	SPRAY TIME	DRYING TIME	COATING YIELD	BATCH SIZE (TEST)	SPRAY TIME / Kg BATCH (TEST)	BATCH SIZE (INDUSTRIAL)	BULK DENSITY	DISSOLUTION TIME
TANGENTIAL-SPRAY POWDER LAYERING	75 MINUTES	1 HOUR	91,58%	2Kg	37,5 MINUTES	370L (273,8 Kg)	0,65	24+/-4 MINUTES



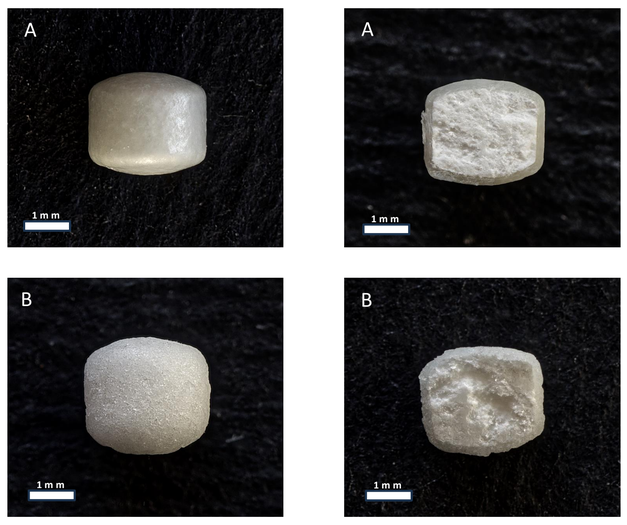
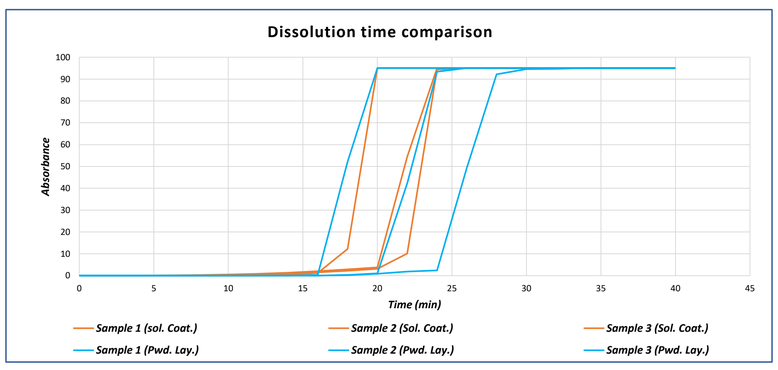


Figure 1 – Pictures of minitablets coated by solution coating (A) and powder layering (B) up to 50% weight gain.



Results

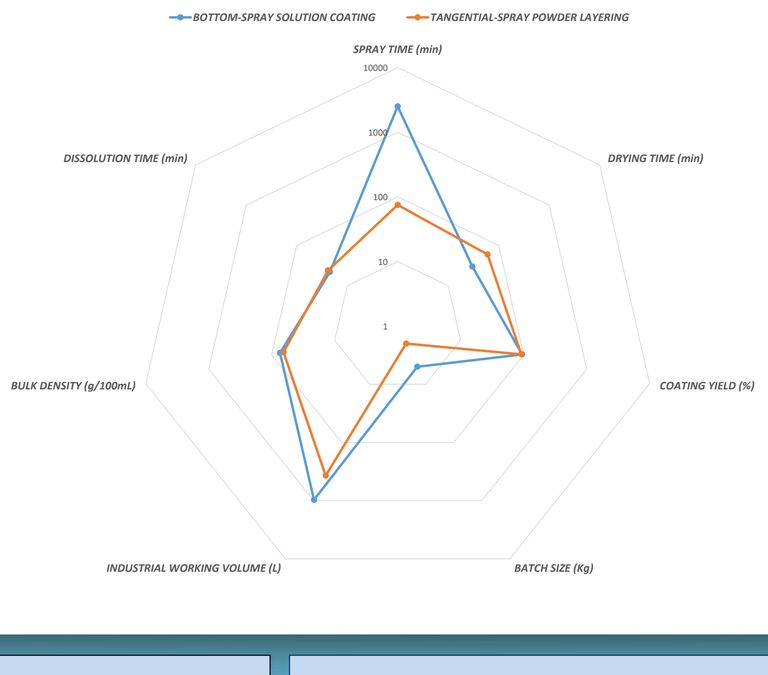
Due to the high molecular weight of the hypromellose selected for the preparation of pulsatile delivery system, the aqueous solution was characterized by high viscosity. For ensuring a good sprayability of the coating system, necessary to guarantee the reproducibility of the process and the consistency of the batches, a preliminary spraying study was performed to determine the best concentration for the coating solution, by testing the spray rate of hypromellose solution at increasing concentration and evaluating the spray pattern generated. For this study concentrations from 2 to 10% w/w with step 0.5% were considered.

The best solution able to create a viscosity feasible of being sprayed was obtained with 4.5% w/w. The process conditions of the powder layering process were set on the basis of preliminary studies aimed at finding the correct relationship between the quantity of stratified powder and the nebulization rate of the binder solution. The same solution already selected for spray coating (4.5% w/w) was used as the binding solution. The same ratio between the plasticizer PEG400 was used for both the processes. Both in the solution coating and in powder layering, the process turned out to be feasible involving fairly high process yields, 94,5% and 91,5% for solution coating and powder layering, respectively, to attain coating levels up to 50% w.g. In Figure 1, it is possible to observe a different superficial morphology of the different coated tablets. Those obtained by solution coating resulted in smoother surface compared to powder layered systems.

The two coating processes were also evaluated by comparing technological characteristics and delaying performance of coated tablets. The tablet weight distribution was evaluated to determine the homogeneity of the product, all the tablets analyzed were included in a ±10% mass range both for solution coating and for powder layering. During the powder layering process in rotor, a slightly higher mass distribution span was observed: a possible explanation could regard the effect of the centrifugal force that tends to emphasize the mass differences between the cores. Since the powder distribution gun is placed tangentially, horizontal and immersed in the cores bed, the particles rotating towards the periphery probably tend to collect slightly more material. This phenomenon was not observed using lighter cores (e.g. pellets). This aspect will be investigated in future studies. The final mean weight for coating solution was 17.62 mg ± 0.29 sd and for the powder layering 17.29 mg ± 0.83 sd. Thickness of coated film applied resulted slightly higher for powder layered tablets: solution coated layers were 219 µm ± 25 sd and powder layered tablets were 249 µm ± 45 sd. Nevertheless, in both cases, the layers applied resulted homogeneous even on the edges.

The release test was performed in order to evaluate the retarding ability of coating layers applied ($t_{10\%}$). It was possible to notice that both coating techniques are capable of ensuring a control of the drug release, creating a lag time included between 15 and 25 min, that is comparable between the two batches realized with the two techniques (Figure 2). However, it is also possible to observe a higher variability in the times, which is in agreement with the variability of coating weights. T10% resulted 19 min ± 2 sd for coated systems obtained by solution coating and 20 ± 5 sd for those obtained by powder layering.

Conclusions



The two techniques proved to be comparable regarding the yield of the process and both the characteristics of the coating itself: the release profile, and the mass distribution of the tablets. The solution coating process points out a higher homogeneity of mass distribution of the tablets compared to the powder layering technique.
From an industrial point of view, a big advantage of time is highlighted by the powder layering process, that allows to considerably shorten process duration. At the opposite, a big advantage in terms of batch size is represented by the solution coating process that allows maximum batch sizes almost 3 times larger than the rotor process, and avoids the issue related to the temperature increase due to the friction generated between the tablets in the rotor product movement.

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