

PREPARATION OF MULTI-PARTICULATE DRUG DELIVERY SYSTEMS BY FLUID BED PELLET COATING

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ABSTRACT

In comparison to tablets drug loaded pellets exhibit the advantageous properties of multi-particulate drug delivery systems. After administration homogeneous distribution in the gastrointestinal tract takes place, drug is released over a large area avoiding concentration peaks, and bioavailability is improved. Up to this time the number of market products with drug coated inert pellets manufactured with fluid bed technology is limited, and systematic investigations of the process and possible coating amounts fail.

Inert microcrystalline cellulose pellets were coated with different amounts of water soluble sodium benzoate (model drug substance) and the excipients polyvinylpyrrolidone (binder) and talcum (anti-sticking agent). The formulation of the coating suspension was kept constant, by prolongation of the spray process time the coating amount was increased from a coating to core ratio of 0.5:1 to 5:1. All trials were carried out twice. A batch laboratory fluid bed apparatus GPCG 1.1 (Glatt GmbH, D-Binzen) with Wurster technique was used.

The coating processes were stable and reproducible. Yields were in the range 87-95% without any tendency due to process time. With increasing coating amount particle size rises continuously. The products have a narrow particle size distribution. Sphericity is improved due to homogeneous film formation. The recovery rate of sodium benzoate diminishes with increasing process times due to abrasion at the chamber wall and dust formation. Sodium benzoate is released with very high rate without any influence of polyvinylpyrrolidone and talcum. The weight ratio of coating to core of 3:1 represents the best compromise of high drug loading, sufficient yield and high drug recovery.

Key Words: Pellets, Multiparticulate systems, Fluid bed coating, Wurster technique

INTRODUCTION

Pellets as a part of multiparticulate drug delivery systems become more and more important due to advantageous properties in comparison to tablets and single unit dosages, first of all the uniform spreading throughout the gastrointestinal tract, the regular drug release during the gastrointestinal passage and therefore improved bioavailability. High local drug concentration with undesirable side effects is avoided [1, 2]. Retarded release is achieved by coating of the pellets with special film forming substances or by manufacturing of the pellets with release influencing excipients. So far inert carriers were predominantly coated with comparatively small amounts of active pharmaceutical ingredients (APIs). The development of drug coated pellet formulations was limited to strong potent APIs. Therefore, the question arises whether inert pellets may also be coated with large API amounts in a wide range without addition of significant excipient amounts to minimize the weight of the final dosage form.

Pellet coating is preferably performed by fluid bed technology due to homogeneous coating leading to an efficient and predictable drug release. In a fluidized bed coater, the particles are fluidized by air, while a liquid suspension is sprayed onto the particles. Four key processes are important for the coating process quality control (Figure 1): particle-droplet impact and adherence, liquid spreading, drying and accidental particle agglomeration [3].

Regarding the spray mode in coating processes, three elementary configurations are used: top spray, bottom-spray (Wurster apparatus) and side spray [4]. The Wurster apparatus is most commonly used for the coating of small particles [5, 6]. A controlled fluidization of the primary particles is provided by process air forcing them to follow a circulation flow trajectory (Figure 2) producing homogeneous and very dense films [7]. Furthermore, there is only low risk of spray drying of the atomized droplets so that the process may run in a wide range of coating liquid viscosity, spray rate, process air volume and process air temperature [8]. An insert bottom spray granulator/coater with Wurster partition can be divided into four parts [7], the spouting zone (1) where particles are sucked by the process air to the entry of the Wurster partition. Particles are wetted in this area by the sprayed coating liquid. In the upper part (2) of the Wurster partition the particles are transported by pneumatic conveying opposite to the

gravitation force, and solvent evaporation and drying takes place. In the annular zone (3) the particles fall downward to the bottom of the process chamber and in the tampon zone (4) the particles are accelerated and sucked into the spouting zone. The filter housing with textile filters on the top of the apparatus prevents the particles from leaving the process chamber providing low material loss.

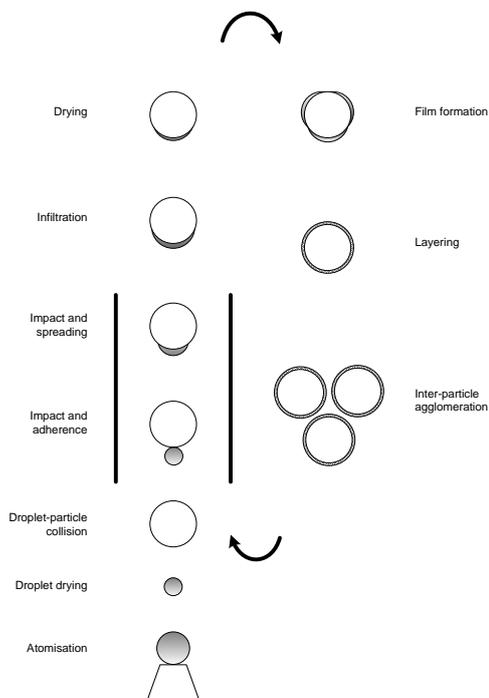


Figure 1. Schematic drawing of the coating process

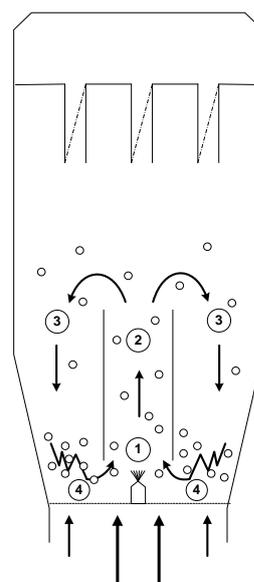


Figure 2. Schematic drawing of the fluid bed with Wurster technique

To achieve an homogeneous coating, the wetted particles must be dried during the transit in the upper zone of the Wurster partition. Otherwise, if too wet particles reach the annular zone, they will stick and agglomerate because of the low velocity compared to that in the Wurster partition [9].

The coating process with Wurster technique in laboratory scale was performed to find out possibilities and limits of the coating process for pellets with low, middle and large amounts of solid coating material. Therefore, inert microcrystalline cellulose pellets were coated with different amounts of water soluble sodium benzoate (model API) and polyvinylpyrrolidone as binder and talcum as anti-sticking agent. The formulation of the coating suspension was kept constant. By spray process time prolongation the coating amount was increased from a coating to core weight ratio of 0.5:1 to 5:1. All trials were carried out twice. The process stability and the yield were regarded. The product quality was investigated by sodium benzoate recovery and release, homogeneity of the layer, particle size, sphericity, compressibility index calculated from bulk and tap density and friability.

MATERIAL AND METHODS

Materials

Inert pellets (Cellets[®] 200, IPC GmbH, D-Dresden) were used as carrier material possessing a narrow particle size distribution in the range 200-400 µm, Sauter diameter 310 µm, sphericity 0.937 and true density 1380 kg·m⁻³. Freely water soluble sodium benzoate (570 g·l⁻¹ at 20°C [10]) was used as model drug substance, polyvinylpyrrolidone (Kollidon 25[®], BASF AG, D-Ludwigshafen) and talcum (Chemie Vertrieb GmbH, D-Magdeburg). The coating liquid consisted of sodium benzoate 28% (w/w), polyvinylpyrrolidone (PVP) 1.5% (w/w) and talcum 0.5% (w/w) in purified water. Pellet lots were prepared in a weight ratio of coating to core of 0.5:1, 1:1, 2:1, 3:1, 4:1 and 5:1 (Table 1).

Table 1: Formulation of coated pellet lots, amount in [%]

Ratio coating to core	0.5:1	1:1	2:1	3:1	4:1	5:1
Sodium benzoate	32.6	46.7	62.2	70.0	74.7	77.8
Microcrystalline cellulose	65.2	50.0	33.3	25.0	20.0	16.7
Polyvinylpyrrolidone	1.7	2.5	3.4	3.8	4.0	4.1
Talcum	0.5	0.8	1.1	1.2	1.3	1.4

Preparation of the coating liquid

Sodium benzoate and PVP were dissolved in purified water at 80°C under stirring (stirrer IKA Labortechnik, D-Staufen, speed 250 r.p.m.). Talcum was dispersed in the solution, the suspension was homogenized with an Ultra-Turrax (T50, IKA, D-Staufen, 2 min, speed 4500 r.p.m.) and finally cooled to ambient temperature. During the coating process the suspension was stirred to prevent talcum sedimentation in the supply beaker, in the tube or at the spray nozzle.

Fluid bed coating

The coating process was performed in a laboratory fluid bed granulator and coater (GPCG 1.1., Glatt, D-Binzen) equipped with a Wurster partition. Process parameters were constant (Table 2), process air flow rate was adjusted at process start to 50 m³·h⁻¹ and adapted in the course of the process. The apparatus was preheated without material just before the coating process over 10 minutes. Starting Cellet amount was 150 g and the spray liquid amount was varied in a range 250-2500 g to achieve different coating amounts.

Table 2. Fluid bed coating process parameters

Process air volume	50 m ³ ·h ⁻¹
Process air temperature	90°C
Product temperature	50°C
Nozzle diameter	1.0 mm
Spray rate	20 g·min ⁻¹
Atomization air pressure	2.0 bar
Perforated plate	Type C
Partition diameter / length	74 / 250 mm
Distance partition-plate	20 mm

Investigation of the coated pellets

The particle size of the coated pellets was measured offline by digital image processing (Camsizer[®], Retsch GmbH, D-Haan), the results were recorded in tables and graphics (Sauter diameter, d₁₀, d₅₀, d₉₀, density distribution and cumulative distribution). Sauter diameter is described by the ratio of particle volume to surface area (Eq.1) indicating the pellet growth and therefore considered as a quantitative criterion of the coating result. The standard deviation of the measuring method of Sauter diameter was below 0.15% for Cellets[®] 200 (n=6).

$$d = \frac{\mu_3}{\mu_2} = \frac{6V_p}{A_p} \quad \text{Eq.1}$$

The sphericity of the pellets was calculated from the chord length of the particles by Camsizer software program. The particle shape of the coated pellets was investigated by stereo light microscopy (Stemi 2000-C, Carl Zeiss GmbH, D-Oberkochen) and the surface structure by scanning electron microscopy (Philips SEM). Sodium benzoate content was measured by UV spectroscopy (Spekol 1300, Analytik Jena, D-Jena, wave length 220 nm, quartz cell 10 mm). Therefore, a defined amount of coated pellets was dispersed in purified water under agitation, filtered and transferred to a 1 L-volumetric flask. Sodium benzoate release was investigated by a dissolution tester (Pharmatest), 1 L-vessels, 37°C, purified water and paddle speed 50 r.p.m. [10]. Bulk and tap volume were investigated with a tap volumeter (Erweka SVM, D-Heusenstamm) [10], and compressibility index (CI) was calculated (Eq. 2).

$$CI = (\rho_t - \rho_b) * 100 / \rho_t \quad \text{Eq.2}$$

Friability of the coated pellets was investigated with a modified method according to Ph.Eur. [10, 11].

RESULTS AND DISCUSSION

The mechanical stiff Cellets were successful coated with high sodium benzoate amounts. The fluid bed process was stable, neither pellet agglomeration nor material precipitation were detected. The yield was in the range 87-95% without tendency due to increasing process times (Figure 3). Material loss was feared to occur by mutual friction and abrasion of the particles at the process chamber wall, followed by exhaust air transport of the dust across the textile filter and by material precipitation at the inner wall of the process chamber, at the air dispersion plate and in the space between the dispersion plate and the wall, but the observed precipitated amounts at the end of the process were negligible.

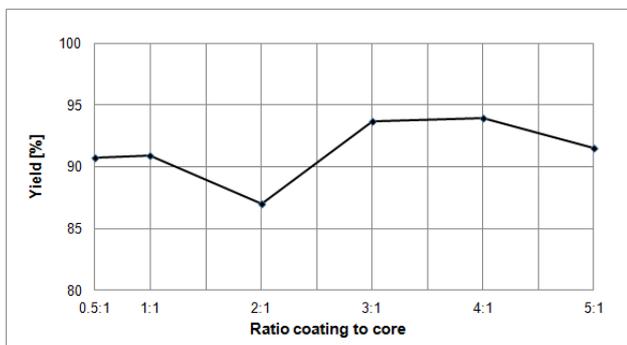


Figure 3. Yield of coated pellet lots versus ratio coating to core

Sodium benzoate coated pellets were received as white, homogeneous particular product. By the naked eye as well as by stereo microscope agglomerates or particle fragments were not observed. The particles are spherical with an uneven surface (Figure 4).

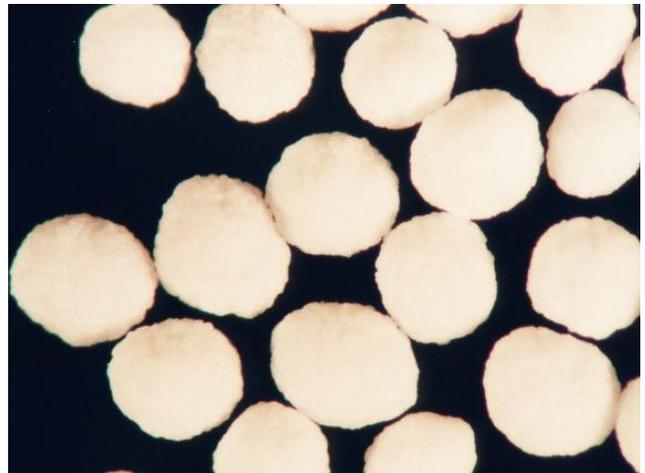


Figure 4. Stereo microphotograph of sodium benzoate loaded pellets, ratio coating to core 3:1

With increasing coating amount the particle size rises continuously from 310 μm (uncoated Cellets) up to 573 μm (coating to core ratio 5:1). Sauter diameter increase in correlation to the coating amount is almost linear indicated by a coefficient of determination of $R^2=0.9888$ referring to a homogeneous film formation during the entire process (Figure 5).

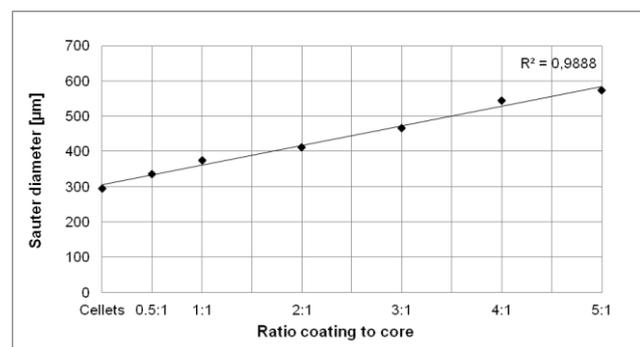


Figure 5. Sauter diameter versus ratio coating to core

The coefficient of variation (CoV) of the Sauter diameter of uncoated Cellets amounts 15.1% and that of the coated pellet lots 12.5-15.0% (Figure 6). With increasing film thickness no significant change of CoV of Sauter diameter is observed indicating regular and homogeneous film formation of small as well as large particles without particle sticking or agglomeration. The relatively narrow particle size distribution of the uncoated Cellets is not changed by the coating process and the film formation.

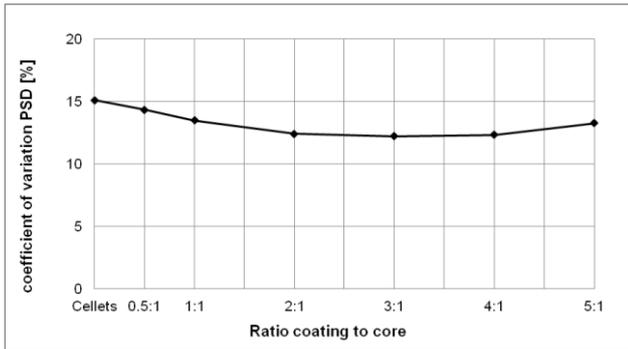


Figure 6. Coefficient of variation of Sauter diameter versus ratio coating to core

Sphericity values in the range of 0.937-0.961 of Cellets as well as coated pellet lots (Figure 7) refer to satisfactory spherical shape confirming the microscopic observation (Figure 4). The sphericity values are improved showing a tendency with increasing coating amount due to homogeneous film formation in the fluid bed process and smoothing of the surface.

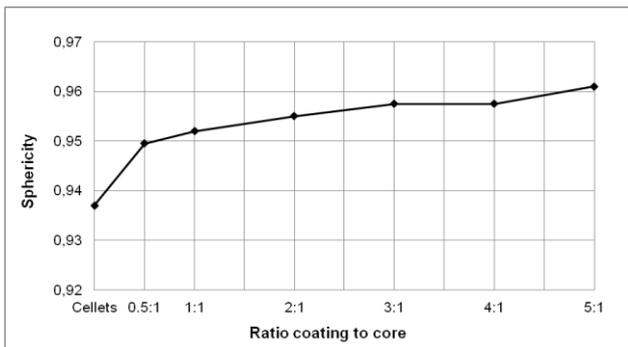


Figure 7. Sphericity versus ratio coating to core

Bulk and tap density were investigated to get information about densification of the pellet lots, mechanical hardness of the pellets and eventual tendencies to brittle. The bulk density values of the coated pellets are decreased compared to Cellets due to increased particle size (Figure 8). A bulk density increase at high coating amount (ratio coating to core 4:1 and 5:1) may derive from more even and smooth surfaces and therefore improved particle packaging. Densification of the pellet lots in the tapping process was low indicated by insignificant increase of the tap density values with increasing coating amount and therefore low compressibility index values of 5-8% (Figure 9). During the accomplishment of the tapping procedure the pellets are exposed to shear and abrasion forces. Nevertheless, pellet rupture or abrasion of material was not observed what gives an additional hint to sufficient hardness of the coated pellets.

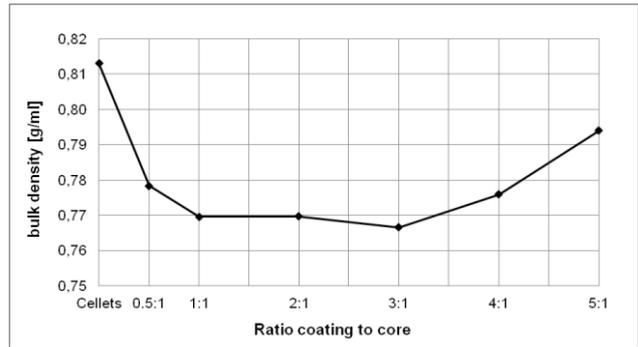


Figure 8. Bulk density versus ratio coating to core

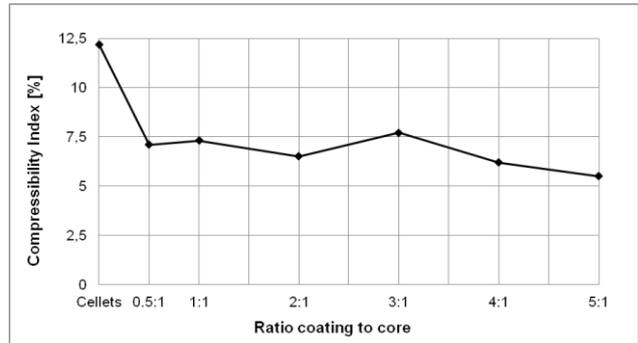


Figure 9. Compressibility index versus ratio coating to core

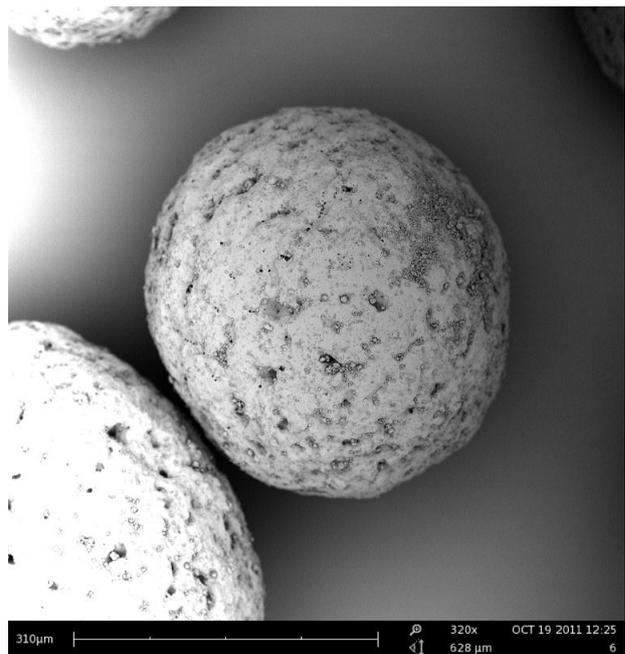


Figure 10. SEM of coated pellet lot, ratio coating to core 0.5:1, sphericity 0.949

Scanning electron microscopy investigation shows a surface structure similar to orange peel. The surface of a pellet lot with a comparable thin sodium benzoate layer (ratio coating to core 0.5:1, Figure 10) is uneven and coarse with many pores of different size. With increasing film thickness (ratio coating to core 4:1, Figure 11) the pellet surface becomes smoother and pores disappear.

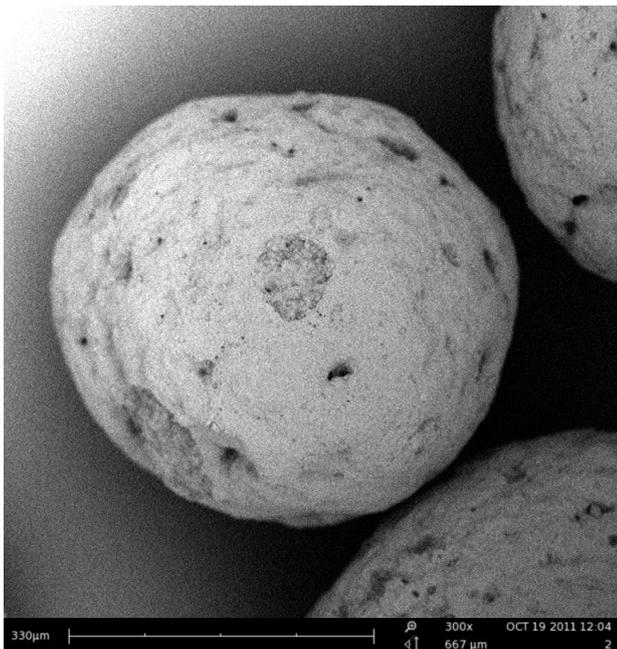


Figure 11. SEM of coated pellet lot, ratio coating to core 4:1, sphericity 0.958

The spherical shape of the coated pellets is once more illustrated by the scanning electron microphotographs.

A complete recovery rate of sodium benzoate was expected because significant material losses, precipitation or particle rupture was visually not observed, but recovery rate diminishes with increasing coating amount from 96% (ratio 0.5:1) to 86% (ratio 5:1, Figure 12). Presumably, first of all sodium benzoate from the outer coating layer is exposed to abrasion in the course of the fluid bed process with prolonged process time and the dust may be removed from the process chamber by exhaust air.

Nevertheless, the friability values of the coated pellet lots are below 0.5% indicating a sufficient mechanical hardness and stability of the sodium benzoate layer, but it should be taken into consideration that the shear and friction forces in the friability investigation procedure are lower than those in the fluid bed in the expansion chamber, where the particles are dry and favored to abrasion.

Sodium benzoate is released with very high rate ($t_{90\%} < 2$ min) due to high solubility and fast dissolution rate independent of coating amount and layer thickness. It is water soluble and low concentrated in the coating film. There is no influence of polyvinylpyrrolidone or talcum on the release behavior of sodium benzoate.

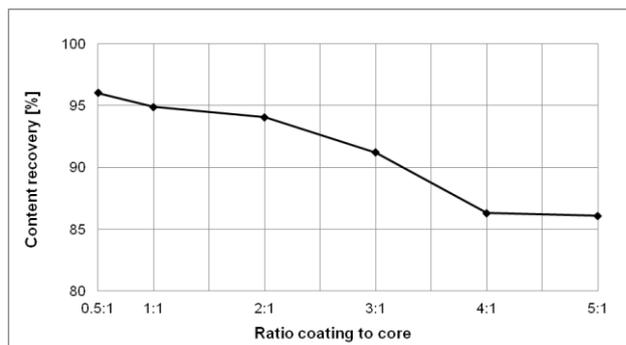


Figure 12. Sodium benzoate recovery rate versus ratio coating to core

CONCLUSION

Inert pellets of microcrystalline cellulose were successfully coated with different amounts of the model API sodium benzoate in a weight ratio of coating to core of 0.5:1 to 5:1. Polyvinylpyrrolidone and talcum were added to the coating solution to increase layer stability and to prevent pellet agglomeration, respectively. The fluid bed coating processes were stable and reproducible. The yield was in the range 87-95% without any tendency due to increasing process time with lots of higher ratio coating to core.

The coated pellets were received as white, homogeneous granular product consisting of hard particles without tendency of agglomeration and absence of particle fragments and acceptable friability below 1%.

Particle size rises continuously with increasing coating amount. The coated pellets have a narrow particle size distribution. Sphericity is improved due to homogeneous film formation. The recovery rate of sodium benzoate diminishes with increasing process time due to particle abrasion at the chamber wall and dust removal by the exhaust air. Sodium benzoate is released from the pellets with very high rate without any influence of the excipients polyvinylpyrrolidone and talcum. The weight ratio of coating to core of 3:1 represents the best compromise of high drug loading, satisfactory yield and high drug recovery rate. With the restriction of incomplete recovery rate but high drug loading in combination with high yield, a coating to core ratio 5:1 is suitable.

Acknowledgment

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NOMENCLATURE

A_p particle Area [m^2]
 D_S Sauter diameter
 V_p particle volume [m^3]
 $t_{90\%}$ time of 90% drug release [min]

Greek Letters

ρ_b bulk density [g/ml]
 ρ_t tap density [g/ml]
 μ_2 Mean diameter of area distribution
 μ_3 Mean diameter of volume distribution

Subscripts

API Active pharmaceutical ingredient
CI Compressibility index
CoV Coefficient of variation of the Sauter diameter
SEM Scanning electron microscopy

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