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Suspension pellet layering using PVA–PEG graft copolymer as a new binder

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ABSTRACT

Flow characteristics and binding properties of Kollicoat® IR solutions are promising for an application in suspension layering processes to obtain drug loaded pellets. This study is based on the results of three experimental designs. Within the first one, a suitable binder concentration in suspensions with 35–45% solids was determined. The required binder level was high with 20% in the layer, but led to good and robust process performance with a yield between 92.6% and 97.6%. Since the polymer succeeded to immobilize particles on the starter surface, the second set of experiments observed whether Kollicoat® IR was able to layer coarser drug particles with only 8% or 30% of the drug mass below ten microns. Large particle size is a generally known limitation for effective suspension layering. It was shown, that Kollicoat® IR was suited to bind 98.5% of the coarsest drug quality on the surface. Additionally these coarse particles acted like a separating agent and kept the pellets from sticking to each other. The third experimental design observed the influence of particle size and viscosity changes. All suspensions had a suitable viscosity with maximum of 120 mPa s. A viscosity change, due to solids in the suspension, did not influence the process performance. The product properties were investigated. The pellets were spherical and size distribution of the pellets was excellent. However the structure was porous, due to the sterical arrangement of the drug particles, although the polymer concentration in the layer was high with a polymer to drug ratio of 1:4.

1. Introduction

Layering of drug solution/suspension or drug powder onto non-active, spherical starter cores is a widely used drug-loading technique and numbers among the most important pelletization processes in the pharmaceutical industry (Ghebre-Sellassie, 1989a).

Non-soluble drug particles in suspension layering formulations are unable to form a solid, coherent drug layer unless a hardening binder is added. In general, binding additives play an important role in drug layering, since it is a particular type of wet agglomeration. They give the new layer the needed strength for subsequent processing (Ghebre-Sellassie, 1989b; Jones, 1989).

The literature on binders for layering is limited and does not specify the correct type or required concentration, in respect of the rheological properties of the spraying liquid, process performance and the quality characteristics of the final product. Besides a balanced bonding power, a general requirement for binders in solution or suspension layering is that the binder solution has a low viscosity. In low viscous liquids, drug concentration can be maximized, meaning that the production of high potency pellets is time-saving and economically feasible (Jones, 1989).

Binder levels are calculated as the binder percentage in the layer. For example, 10–15% low viscous maltodextrins and PVP were compared in a powder layering study. Both binders were effective at the higher binder level, but PVP showed a greater tendency to produce oversized agglomerates. On the other hand, the lowest level of maltodextrins was not effective, with the result that more drug was lost during the process (Rashid et al., 2000).

Iyer et al. investigated product characteristics in solution layering processes. They used 5% and 11% PVP, gelatine and HPMC. PVP was perceived to be tacky and led to uneven surfaces. In the case of gelatine and HPMC, rough pellet surfaces were determined for the upper binder level (Iyer et al., 1993). Sinchaipanid et al. tested a more viscous HPMC type at comparable levels of between 6% and 12% in suspension and powder layering processes. As the binder level increased, the pellet surface became smoother and pellet porosity decreased (Sinchaipanid et al., 2004).

Based on these studies, neither the result for well-known binders nor the efficiency and optimum binder level for new binding substances could be predicted.

In this study, the new excipient Kollicoat® IR (PVA–PEG graft copolymer) is applied. It showed bonding power in wet granulation, but was primarily developed as an instant-release coating material. Kollicoat® IR solutions fulfill the requirement of low viscosity.

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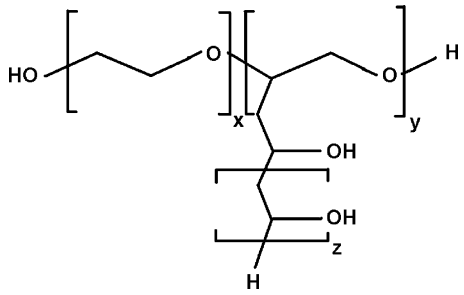

Fig. 1. Chemical structure of Kollicoat® IR.

Compared to low viscous HPMC types, Kollicoat® IR showed a high pigment-binding capacity with a low increase in the viscosity of the solutions or suspensions and flexibility of the pigment-containing films (Kolter, 2004; Bühler, 2007). Kollicoat® IR binding properties were observed in a wet granulation process and binding strength ranged between PVP K25 and PVP K90 (Agnese et al., 2010). With its low viscosity and high capacity to incorporate pigments or, probably, drug particles, Kollicoat® IR is a promising binder for drug layering. However, to the best of our knowledge, it has not been used in layering before.

With the exception of binder properties, the particle size of a drug in a suspension is the most critical factor for effective drug binding to starter cores. A large quantity of binder is required to immobilize drug particles greater than 10 μm. It must be considered that the use of bigger particles results in a decreasing core-to-drug-size ratio. Drug losses are unavoidable if this ratio drops to below 10:1 (Jones, 1989).

Experiments with different particle sizes of indomethacin substantiated that a micronization step ensures maximum yield for a suspension layering process and leads to a smoother pellet surface (Li et al., 1989).

Objectives of the present study were:

- To find out whether the new, low viscous polymer Kollicoat® IR is effective as a binder in a suspension layering process.
- To propose a suitable binder level and solid content with respect to the low viscosity and high pigment-binding capacity of a Kollicoat® IR solution.
- To evaluate process quality and process robustness, and give a better understanding of process-influencing factors through use of design of experiments (DoE).
- To re-investigate the influence of different drug particle sizes for the new binder in view of the general interest in overcoming the difficulty of layering coarse and unmicronized drug.

2. Materials and methods

2.1. Materials

In this study, hydrochlorothiazide (HCT; Teva Group, Israel) was used as the model drug. It was obtained in three particle size distribution grades. Kollicoat® IR (BASF, Ludwigshafen, Germany) was used as the binder. Microcrystalline cellulose spheres (Cellets® 500; IPC, Dresden, Germany) with a diameter of 500–710 μm were used as starter cores.

2.2. Kollicoat® IR

The chemical structure of the poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer, Kollicoat® IR; BASF, Ludwigshafen, Germany) is shown in Fig. 1. Polyvinyl alcohol (PVA) side chains are grafted onto a polyethylene glycol (PEG) base chain in a ratio of 1:3. The mean molecular weight is approximately 45,000. The high level of solubility in water and fast release of Kollicoat® IR when used as a coating, embedding or binding material is due to the frequency of polar groups. Covalently bound polyethylene glycol functions as an internal plasticizer and results in a great tensile strength and high flexibility of Kollicoat® IR films (Bühler, 2007).

2.3. Drug layering on pellets

The experiments were carried out in the laboratory scale. Kollicoat® IR was dissolved in water, with moderate stirring. The insoluble drug was subsequently added and finally dispersed with an Ultra – Turrax® dispersing tool once a homogenous suspension was achieved (10 ± 5 min). Binder level and solid content changed in the tested formulations. The solid content was calculated as the sum of binder and drug mass divided by the suspension mass. The values for binder level were calculated as the binder percentage referred to the solids in the suspension and thus the given value is equal to the percentage of binder in the layer. The used binder level and solid content for each experiment are given in Table 2. A fluid-bed apparatus (GPCG 1; Glatt GmbH, Binzen, Germany) was fitted with a Wurster partition (distance to the bottom plate: 25 mm) and a S 970 bottom-spray two-substance nozzle with a 1.2 mm orifice (Düsen Schlick GmbH, Untersiemau, Germany). 1000 g of starter cores were fluidized with a constant air flow rate of 60–70 m^3/h. The suspension was applied with an initial spray rate of 5 g/min, which was increased in increments of +10 g/min after 5 min until the maximum desired spray rate was achieved. The process was stopped once the theoretical HCT content of the final pellets was 30%, and each batch was then dried for 10 min at a temperature of 34 °C and an air flow rate of 60 m^3/h.

2.4. Experiments

Design of experiments (DoE) was used to analyse formulation and process parameter impacts on process efficiency. DoE 1 and DoE 2 observed n parameters on 2 settings, a lower and an upper level (−1/+1). As a result 2^n experiments were necessary to calculate the impact of each parameter and the impact of interacting parameters. However, a rough estimation of acceptable formulation and process parameters can also be achieved with a confounded 2^{n-1} screening design (DoE 1). This way, all the probably considerable parameters as binder level, solid content, product temperature and a combined factor of spray rate/atomizing air pressure (−1/+1; $n = 4$) were investigated with a reduced number of experiments in DoE 1. 2^n full factorial design (DoE 2) had to be added for an intensified look at selected parameters with respect to their interacting effects. The parameters in the DoE 2 were drug particle size, atomizing air pressure and product temperature (−1/+1; $n = 3$). For a closer view on suspension viscosity and drug particle size effects a multifactorial 2×3 design (DoE 3) was added using 2 suspension viscosity levels (−1/+1) and 3 available qualities of drug particle size (−1/0/+1). Changes in solid content were made in order to prepare suspensions with a given viscosity level. For each DoE three replications of a centre-point experiment with a medium setting of n parameters (level 0) were carried out. The statistical analysis was based on a linear regression model which was calculated with MODDE version 8.0.1 (Umetrics, Umeå, Sweden). MODDE effect plots show the increase/decrease of a response (e.g. yield), when the observed parameter changed from the lower to the upper setting (−1 to +1 level). The parameters and settings for DoE 1–3 are given in Table 1.

Table 1
Test parameters and settings for DoE 1–3. Fixed settings are printed in italics.

DoE [no]	Level	Binder level [%]	Solid content [%]	Spray rate [g/min]	Atomizing air pressure [bar]	Product temperature [°C]	Drug particle size $d(90)$ [μm]	Viscosity of suspension [mPa s]
1	−1	15	35	15	2.5	32		
	0	20	40	20	2.8	36	*26*	
	+1	25	45	25	3.1	40		
2	−1				1.6	30	26	
	0	*20*	*40*	*25*	2.2	34	45	
	+1				3.4	38	68	
3	−1						26	45
	0	*20*		*25*	*1.6*	*30*	45	80
	+1						68	120

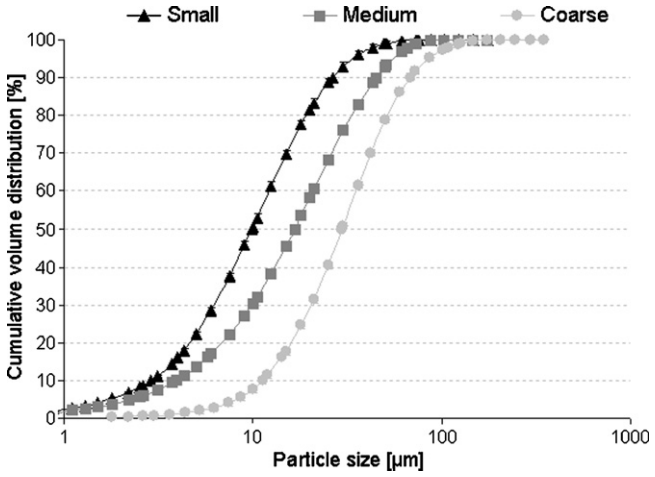

Fig. 2. Particle size distribution of the three HCT grades ($n = 3$; $\bar{x} \pm s$).

2.5. Determination of particle size distribution

The three drug qualities were examined with a HELOS laser diffractometer, using the RODOS dry dispersion device (HELOS/RHODOS Sympatec GmbH, Clausthal-Zellerfeld, Germany). A sample volume of 150 mg was dispersed at an air pressure of 3 bar. The lens focal distance was 100 mm (working range 0.9–175 μm) for micronized HCT and 200 mm (working range: 1.8–350 μm) for the coarsest quality. Each drug quality was measured three times (Fig. 2).

2.6. Viscosity of spraying suspension

Viscosity measurements were carried out using a rotational coaxial cylindrical system (Haake VT550, Thermo Electron GmbH, Karlsruhe, Germany). Flow profiles were determined with increasing and decreasing shear rates of between 13 s^{-1} and 300 s^{-1} at a temperature of 23 °C. The viscosity data, provided in the present study, are average values measured with shear rates of between 50 s^{-1} and 200 s^{-1}. In this range, the fluids behave like a Newtonian fluid.

2.7. Quantification of yield, layering efficiency and amount of agglomerates

The product was separated into three fractions by sieve analysis with a 500 μm and 1000 μm mesh. The minimum starter size was 500 μm. Single and agglomerated drug and binder particles below 500 μm were not bound onto a core surface and so only the mass of fractions above 500 μm $m_{(\text{fraction}>500)}$ was considered in the calculation of layering efficiency (LE), as shown in Eq. (1):

$$\text{LE}\,(\%) = \frac{m_{(\text{fraction}>500)} - m_1}{m_2 + m_3} \times 100 \tag{1}$$

The weight of each fraction as well as the weight of the applied mass of starters m_1, drug m_2 and binder m_3, which were required to calculate LE, were rectified by the different residual moisture contents. The fraction between 500 μm and 1000 μm was defined as the "yield" and further investigations of product quality were carried out with this fraction. Particles larger than 1000 μm were twins and multiples and are called "agglomerates" in this study.

2.8. Residual moisture content

The moisture of raw materials and yield fraction were determined using a halogen moisture analyser (HR83, Mettler Toledo, Giessen, Germany). For all samples, a temperature of 105 °C was applied, and the mass of water removed within 30 min was determined. The resultant value was used to calculate the real net weight of solids. The suitable sample volume was different for raw materials and product: 5 ± 0.25 g HCT; 2 ± 0.1 g Kollicoat® IR; 7 ± 0.35 g Cellets® 500 and layered pellets.

2.9. Density and porosity of the pellets

All density measurements were carried out twice and the average was taken for the evaluation.

Bulk density ρ_{bulk} of the layered pellets was analysed with a bulk density measuring device according to EN ISO 60 (SMG 53 466, Powtec Machinen und Engineering GmbH, Remscheidt, Germany).

The densities of the starters (ρ_1:1.45 g/cm^3), drug (ρ_2: 1.70 g/cm^3) and binder (ρ_3: 1.15 g/m^3) were determined by the helium displacement method (Pycnomatic ATC, Porotec GmbH, Hofheim, Germany).

Eq. (2) was used to calculate a theoretical density value ρ for the layered pellets, using the measured densities of the starters, drug and binder (ρ_1; ρ_2; ρ_3) and their per cent by weight in the layered pellet (m_1; m_2; m_3).

$$\rho = \frac{\sum_{i=1}^{3} m_i}{\sum_{i=1}^{3} (m_i/\rho_i)} \tag{2}$$

Additionally, a mercury pycnometer was used to define the mercury density ρ_{Hg} of starters and layered pellets (PASCAL 140, Porotec GmbH, Hofheim, Germany). Mercury intrusion in porous material is dependent on the ambient air pressure, and the given density values ρ_{Hg} were determined at an air pressure of 1 bar.

The porosity ε of the layered pellets was calculated from the relationship shown in Eq. (3):

$$\varepsilon = 1 - \frac{\rho_{Hg}}{\rho} \tag{3}$$

Table 2
Settings (left) and results (right) of preliminary experiments and DoE 1–3.

DoE [no]	Batch [no]	Binder level [%]	Solid content [%]	Spray rate [g/min]	Product temp. [°C]	Atom. air pressure [bar]	Inlet air quantity [m^3/h]	Drug particle size $d(90)$ [μm]	Viscosity of suspension [mPa s]	Agglomerates [%]	LE [%]	Yield [%]
	1	5	20.0	30	30	2.0	70	26	n.d.	0.0	71.4	90.5
	2	30	40.0	30	36	2.5	70	26	n.d.	52.0	99.1	47.8
	3	20	40.0	28	36	3.5	60	26	120	0.0	89.3	96.0
	4	30	30.0	17	40	3.8	60	26	n.d.	1.5	91.9	95.1
	5	20	40.0	20	36	2.8	60	26	120	0.1	90.7	96.5
	6	20	40.0	25	32	3.1	60	26	120	0.1	97.2	98.8
1	7	15	35.0	15	32	2.5	60	26	n.d.	0.1	87.1	95.4
	8	15	45.0	25	32	3.1	60	26	n.d.	0.0	87.7	95.6
	9	25	35.0	25	32	3.1	60	26	n.d.	4.9	99.1	94.7
	10	25	45.0	15	32	2.5	60	26	n.d.	3.0	97.2	95.9
	11	15	35.0	25	40	3.1	60	26	n.d.	0.0	82.8	93.9
	12	15	45.0	15	40	2.5	60	26	n.d.	0.1	79.3	92.6
	13	25	35.0	15	40	2.5	60	26	n.d.	0.1	90.2	96.0
	14	25	45.0	25	40	3.1	60	26	n.d.	2.7	96.2	95.8
	15	20	40.0	20	36	2.8	60	26	120	1.6	95.9	96.8
	16	20	40.0	20	36	2.8	60	26	120	1.1	96.7	97.6
	17	20	40.0	20	36	2.8	60	26	120	1.0	95.5	97.3
2	18	20	40.0	25	30	1.6	60	26	120	36.3	98.8	63.3
	19	20	40.0	25	30	1.6	60	68	45	3.7	98.6	95.8
	20	20	40.0	25	30	3.4	60	26	120	1.5	98.1	97.9
	21	20	40.0	25	30	3.4	60	68	45	0.1	96.2	98.5
	22	20	40.0	25	38	1.6	60	26	120	17.7	98.5	81.7
	23	20	40.0	25	38	1.6	60	68	45	0.9	94.7	97.0
	24	20	40.0	25	38	3.4	60	26	120	1.4	93.8	96.2
	25	20	40.0	25	38	3.4	60	68	45	0.0	89.8	96.1
	26	20	40.0	25	34	2.2	60	45	45	1.6	96.8	97.2
	27	20	40.0	25	34	2.2	60	45	45	1.4	97.1	97.5
	28	20	40.0	25	34	2.2	60	45	45	2.1	97.3	96.9
3	29	20	35.0	25	30	1.6	60	26	45	54.5	99.2	45.2
	30	20	40.0	25	30	1.6	60	45	45	15.7	97.6	83.4
	31	20	40.0	25	30	1.6	60	68	45	3.9	97.2	95.0
	32	20	40.0	25	30	1.6	60	26	120	69.5	99.2	30.3
	33	20	46.0	25	30	1.6	60	45	120	19.0	98.6	80.5
	34	20	44.2	25	30	1.6	60	68	120	2.6	96.4	96.0
	35	20	43.5	25	30	1.6	60	45	80	24.8	98.4	74.6
	36	20	43.5	25	30	1.6	60	45	80	24.2	99.1	75.4
	37	20	43.5	25	30	1.6	60	45	80	26.2	98.9	73.4
	38	20	40.0	25	34	3.4	60	26	120	0.1	93.7	97.5

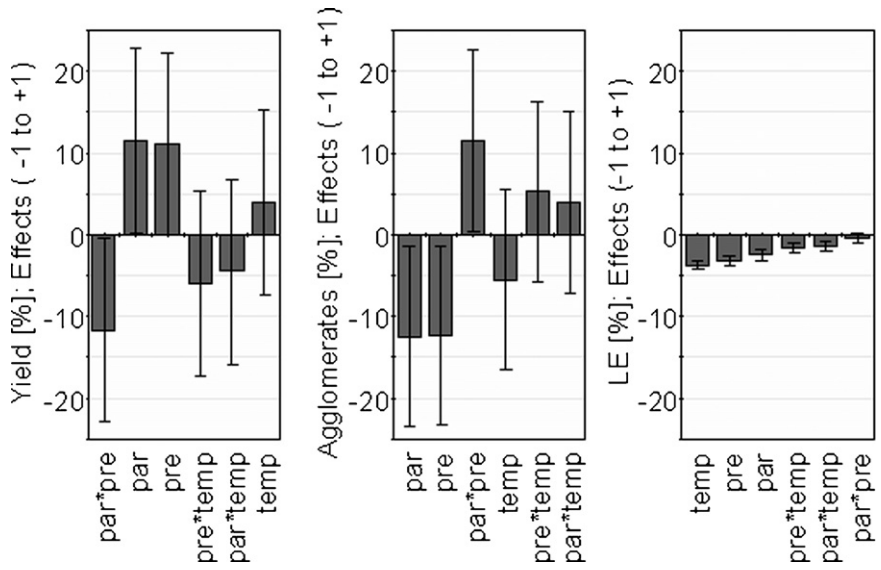

Fig. 3. Effect plot for DoE 2 ($p < 0.1$). Parameters investigated: drug particle size (par), atomizing air pressure (pre), temperature (temp) and interactions.

2.10. Scanning electron microscopy (SEM)

The pellet surface topography of the starters or layered pellets and cross-sectional layer structure were evaluated by scanning electron microscopy (Gemini Supra 55VP, LEO Elektronenmikroskopie GmbH, Oberkochen, Germany). The energy of the electron beam used for the detection of secondary electrons was 1–3 kV.

Backscattered electron (BSE) imaging was used to differentiate the starter core from the drug layer. In this case, the reflection of electrons depends on heavy or light elements in the compartments. The model drug, HCT, contains nitrogen and sulphur with a high atomic number. The heavier the element is, the stronger the reflection, thus it appears brighter in the image. A high energy electron beam of 10 kV was required for BSE images.

The pellet images were taken with a magnification of 200/300, whereas images of the layer were magnified 2000 times. Cross-sectional samples were prepared, using a razor blade.

2.11. Pellet shape and size

Pellet shape and size were determined via automatic image analysis (QICPIC & RHODOS/L, Sympatec GmbH, Clausthal-Zellerfeld, Germany). Compressed air of 0.5 bar was used to disperse the sample and to forward single pellets through a light beam from the high-speed camera with a frequency of 500 images s^{-1}. The image analysis sensor enables two-dimensional detection of particle area A and perimeter P, and allows calculation of pellet size distribution (PSD). For the size calculation, the diameter d of a circle with equivalent projection area A was calculated in Eq. (4):

$$d = 2\sqrt{\frac{A}{\pi}} \tag{4}$$

The median $d(50)$ was used to compare the pellet size of different batches. To characterize the range of size distribution, the diameter d of each pellet image was standardized onto this median to get a dimensionless diameter d_d by Eq. (5). This allows for the distribution range to be compared independently of size. The fraction of pellets with a d_d within the 10% – interval (d_d values between 0.9 and 1.1) was determined.

$$d_d = \frac{d}{d(50)} \tag{5}$$

The shape was classified by sphericity S and aspect ratio as. Sphericity means the ratio between the particle perimeter P and the perimeter of a circle with an equivalent projection area A (Eq. (6)), whereas the aspect ratio is calculated as the ratio of maximum and minimum Ferret diameter.

$$S = 2\frac{\sqrt{\pi A}}{P} \tag{6}$$

A sample mass of 3 ± 0.3 g was used for the measurements and it produced about 2500–3500 single pellet images. The results given are average values of the data generated from three single measurements.

2.12. Drug content

HCT was extracted from a sample of 420 mg pellets, using 0.005 M sodium hydroxide in methanol. An acetonitrile/methanol mixture and phosphate buffer pH 3.0 were used as the mobile phase for a validated gradient HPLC method with an Inertsil C8 column as a retention phase (Inertsil C8; 125 mm × 4.0 mm; 5 μm; MZ-Analysentechnik GmbH, Mainz, Germany). Attached to the HPLC device was an photodiode array detector to measure the concentration of HCT at a wavelength of 270 nm (Agilent 1100 Series, Agilent technologies, Waldbronn, Germany; Photodiode array detector 2996, Waters GmbH, Eschborn, Germany).

Measurements were replicated twice, and the average taken for calculation of the recovery rate rr. The concentration c_m in Eq. (7) is the HPLC result and c_f is the HCT percentage of the formulation:

$$rr = \frac{c_m(1 - c_f)}{c_f(1 - c_m)} \tag{7}$$

3. Results and discussion

3.1. Binder level and solid content – preliminary experiments and DoE 1

Preliminary experiments were necessary to find suitable process conditions and a suitable formulation. See Table 2, batches

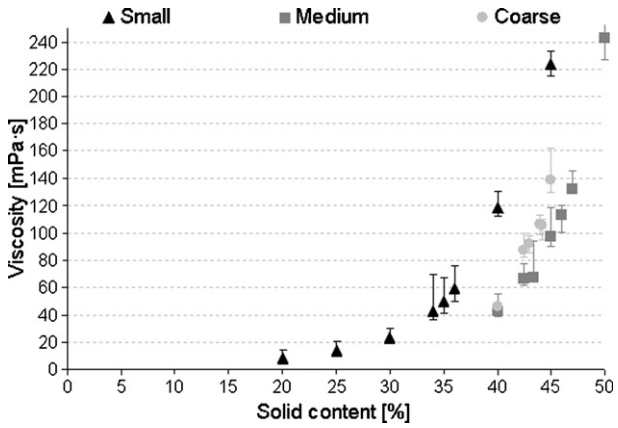

Fig. 4. Viscosity measurements: average and range of drug suspensions with 20% binder level (Kollicoat® IR).

1–6, for the relevant settings and results. With the exception of the spray rate, the formulation and process parameters in batch 1 were based on the settings commonly used in laboratory scale fluid-bed equipment. The spray rate (30 g/min) was rather fast for an aqueous spraying suspension, considering that a rate of 3–10 g/min is described in most literature. Nevertheless, moisture-induced agglomerates could not be found, but the process was dusty, and only a low LE of 71% was achieved. The binder concentration of 5% was probably not enough to produce the layering strength needed. In the following trials, involving batches 2–6, the LE was improved (89–99%). These experiments were carried out with high binder levels of 20% and 30%.

For layering purposes, a binder level of 2–10% is specified for gelatine, sucrose, starch and natural or synthetic polymers, e.g. HPMC or PVP (Harris and Ghebre-Sellassie, 1989). In wet agglomeration processes, Kollicoat® IR could be used analogously to HPMC with 3% (Kolter, 2003), and different types of PVP with 1.5%, 3% and 5% in the finished granules (Agnese et al., 2010). However, based on the preliminary experiments it can be expected that 20% Kollicoat® IR is required to prevent drug loss in a layering process. Only batches 2 and 4, with a binder level of 30% formed agglomerates.

DoE 1 showed good LE for binder levels of 20% and 25% (Table 2). Low level experiments with 15% binder achieved less than 88% LE and the high binder level of 25% led to greater fractions of agglomerates. The yield was high for each factor combination and varied only within a narrow range of between 92.6% and 97.6%. Except for the formulation parameter binder level, the confounded DoE 1 showed no significant effects on yield, agglomerates or LE. With respect to the process parameters: spray rate, atomizing air pressure and product temperature, the process was robust within the tested limits.

The robustness of processes with high solid contents of between 35% and 45% was investigated. The proposed limit for proper atomization is 250 mPa s (Kolter, 2002). For example, with a 20% binder level and a small drug particle size, this is not achieved until a solids level of 45% (210–240 mPa s).

Generally speaking, high-load solutions or suspensions are preferable to achieve economical and fast processes. This advantage is already described in respect of Kollicoat® IR, but only for coating processes that focus on a high polymer content. Suspensions with a 2:1 Kollicoat® IR:talc ratio and a 30% solid content were low in viscosity (Kolter, 2004), and the addition of pigments did not influence spread (Dashevsky et al., 2002). However, the drug load in the layering suspensions in this study was much higher than the pigment load in the references. In layering processes the focus is on drug load, and the ratio between the binding polymer and the drug (comparable to pigment) must be as small as possible. As the concentration of a polymer in the suspension increases, the potency of the final product decreases with the same mass gain. Additionally, the release profile of the layer can be influenced by an increasing polymer concentration, except in the case of highly water-soluble polymers like Kollicoat® IR.

Although the solid content was high at 40%, the polymer-to-drug ratio was only 1:4 because a binder level of 20% was required. Fast drug loading was achieved due to the high solid content, but the maximum potency of the layer was 80%.

3.2. Influence of drug particle size – DoE 2

The laser diffraction measurements of three HCT particle grades are illustrated in Fig. 2. Kollicoat® IR as the binding agent succeeded in layering all HCT particle size grades with a LE of at least 89.8% in DoE 2. The settings and results are given in Table 2. The impacts of the parameters observed on yield, agglomerates and LE ($p < 0.1$) are shown in Fig. 3.

LE was worst in batch 25 with 89.8%. The decrease of LE was mainly caused by the high temperature and high atomizing air pressure. Both parameters were shown to impact on LE, as is shown in the effect plot. The coarse particles used in batch 25 made a minor contribution to LE, and it was possible to achieve 98.6% LE in batch 19 with the same coarse particles.

Agglomerates formed at a low atomizing air pressure or in the case of small drug particle size. For this reason, yield could be optimized by using coarse drug particles or high atomizing air pressure.

As a result of good binder properties, a target specification above 95% for yield and LE was possible with formulations of all three drug particle sizes (see batches 19–21, 26–28). Particle size was known as the most critical factor in process efficiency (Jones, 1989). Despite this, the process and formulation in general produced particularly good results.

Li et al. established a process efficiency of only 88% (assay of drug content compared to theoretical drug content) when they applied drug with a particle size distribution of nearly 70% below 10 μm. In the case of coarser particles, the efficiency decreased and only particles with a median diameter of 3.3 μm and a narrow distribution of 1–13 μm were layered with satisfactory results of 97% process efficiency (Li et al., 1989).

According to Jones, effective layering requires a drug particle size smaller than 10 μm and a maximum core-to-drug-size ratio of 10:1 (Jones, 1989). The results of the HCT particle size distribution are summarized and compared with the requirements in Table 3. To calculate the core-to-drug-size ratio, the minimum specification limit for starter size (500 μm) and the $d(99)$ value of each HCT size distribution were taken. So only the smallest HCT quality was partly acceptable for layering purposes. Half its volume was of an acceptable particle size below 10 μm, and the minimum core-to-drug-size ratio meets the requirement of 10:1. However, the new binder Kollicoat® IR succeeded in overcoming the difficulties in layering the medium and coarse particles, although the size was outside the required specification.

3.3. Influence of viscosity – DoE 3

The increase in viscosity observed with the increase in solid content on the spraying suspension is illustrated in Fig. 4 and can be explained by Einstein's Eq. (8):

$$\eta_S = \eta_0[1 + 2.5\phi] \quad (8)$$

η_S: viscosity of the suspension; η_0: Viscosity of the continuous phase; ϕ: internal phase content (ratio of internal phase volume to total dispersion volume).

Table 3
Particle size classification of three HCT qualities and their conformance to the requirements.

Size distribution	Requirements	Coarse	Medium	Small
$d(10)$ [μm]	<10	11	4	3
$d(50)$ [μm]	<10	30	17	10
$d(90)$ [μm]	<10	69	45	26
$d(99)$ [μm]	<10	125	72	49
Fraction within requirements	–	0.08	0.3	0.5
Minimum core-to-drug size ratio	>10:1	4:1	7:1	10:1

The hydrodynamic flow of a continuous phase is disrupted by the presence of particles. However, a linear dependence on the content ϕ is only applicable for diluted suspensions, when particles are too far apart from each other to interact. More complex equations can be found at high solid contents. In these cases, the effective internal phase content ϕ in the equation differs from the solid content of the suspension because parts of the continuous phase become trapped between interacting particles. As a result, the total volume of continuous phase available to reduce particle interactions decreases (Briceno, 2000).

With the same solid content in Fig. 4, small-sized drug led to the highest viscosity. Interactions (e.g. between particles) increase with a higher total particle surface in the case of a smaller particle size. As a result, the effective internal phase content ϕ increases. However, a more spherical shape and a small fraction of fines in a polydisperse size distribution can be due to a decreasingly effective internal phase content ϕ (Briceno, 2000).

Shape modification and a small increase of fines during the first micronization step might be the explanation for the lowest viscosity in the case of medium HCT particle size (Fig. 4).

With a solid content of 40% in DoE 2, the suspensions applied in these experiments had different viscosities of about 45 mPa s in the case of coarse or medium HCT quality and of about 120 mPa s in the case of small drug particles. The relevant amounts of solids applied to modify the viscosity in DoE 3 are given in Table 2, in relation to the applied particle size, the viscosity level yielded and the results observed. Atomizing air pressure and product temperature were low, with the result that the formation of agglomerates was facilitated. The effects for yield, agglomerates and LE ($p < 0.05$) are shown in Fig. 5. The increase in viscosity did not affect the results, but a significant impact was detected for the drug particle size. The small particle size resulted in the formation of agglomerates and an increase in LE. However, the influence on LE was low, compared to the disadvantageous effect on agglomerates. The results substantiated the particle size effects previously observed, and also meant that the viscosity influences in DoE 2 were negligible.

The response for yield can be considered an indicator of process performance because it is influenced by both LE and agglomerates. Under the process conditions of DoE 3, only the coarse particles resulted in a high yield of 95%.

3.4. Qualitative analysis of pellets

SEM pictures of starter cores and pellets, layered with the small HCT particle size, are presented in Fig. 6A–E. Some product properties can be seen in Table 4, with the measurements for the batches in the DoE 2 taken as an example.

The drug, which appears brighter in the BSE image (Fig. 6A), forms a closed and uniform layer around the core. The surface structure of a layered pellet (Fig. 6C) was rough and porous compared with the starter core surface (Fig. 6B). The layered pellets of DoE 2 showed a porosity of between 7.0% and 10.4%. Core porosity was only 1.1%.

A rough surface, determined by Iyer et al. was explained as the result of incomplete coalescence caused by the tackiness of the binder or by viscous, immobile liquid bridges at high binder levels (Iyer et al., 1993). Cross-sectional images of the layer (Fig. 6D and E) showed that, in this study, roughness was caused by the sterical arrangement of drug particles, but it was not possible to detect the polymer lumps described by Iyer.

In a range of between 22% and 28% pellet porosity, Sinchaipanid et al. observed the lowest porosity value at the highest binder level of 12% (Sinchaipanid et al., 2004). Starter porosity is not specified in this study, and the absolute porosity values are difficult to compare

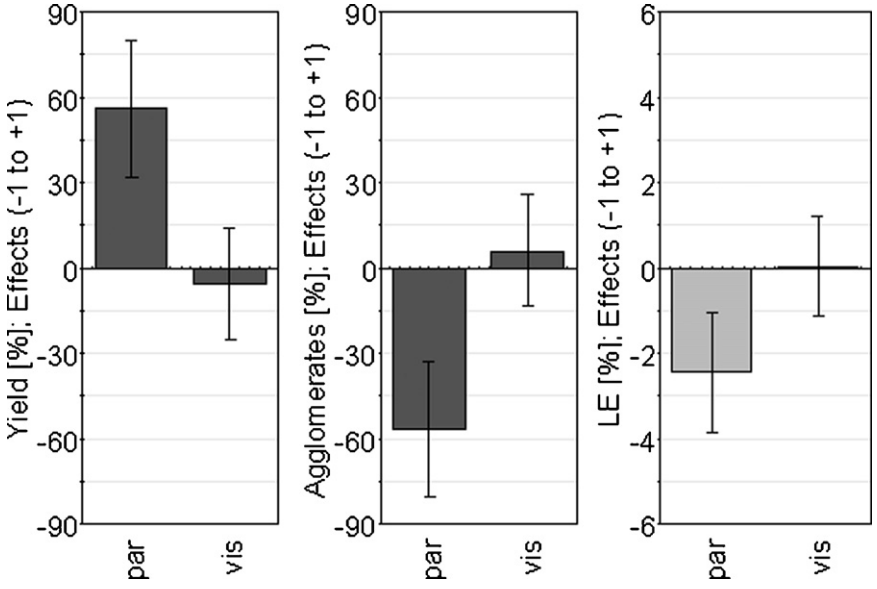

Fig. 5. Effect plot for DoE 3 ($p < 0.05$). Parameters investigated: drug particle size (par) and viscosity (vis). Magnified plot scale in Chart 3.

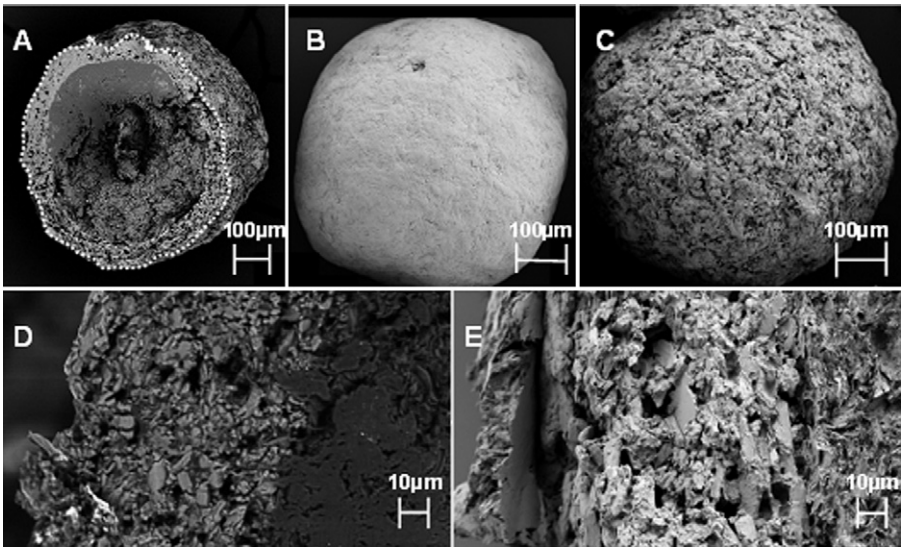

Fig. 6. BSE imaging and SEM pictures of starter cores (B) and layered pellets (A, C and E: batch 38; D: batch 14; HCT particle size: small). (A) BSE imaging, layered pellet, cross-section. (B and C) SEM, starter core (B) and layered pellet (C), surface. (D and E) BSE imaging (D) and SEM (E), layer, cross-section.

Table 4
Pellet properties for starters and layered pellets of DoE 2: bulk density ρ_{bulk}, calculated density ρ, mercury density ρ_{Hg}, porosity ε, medium pellet size $d(50)$, fraction within the 10% interval of dimensionless diameter d_d: 0.9–1.1, sphericity S, aspect ratio as and drug recovery rate rr.

Batch no.	ρ_{bulk} [g/cm^3]	ρ [g/cm^3]	ρ_{Hg} [g/cm^3]	ε [%]	$d(50)$ [µm]	d_d: 0.9–1.1 [%]	S	as	rr [%]
Starter cores	0.82	1.45	1.43	1.1%	651	74	0.94	1.12	
18	0.69	1.49	1.34	10.4%	802	72	0.93	1.14	
19	0.65	1.49	1.39	7.0%	802	79	0.93	1.12	93.7
20	0.75	1.49	1.37	8.1%	773	80	0.94	1.11	
21	0.71	1.49	1.37	8.1%	777	78	0.93	1.11	95.8
22	0.68	1.49	1.30	13.1%	795	75	0.93	1.12	
23	0.65	1.49	1.35	9.4%	793	78	0.92	1.11	
24	0.74	1.49	1.35	9.4%	774	79	0.94	1.11	
25	0.71	1.49	1.36	8.7%	773	76	0.94	1.10	
26	0.70	1.49	1.36	8.7%	789	77	0.93	1.11	
27	0.70	1.49	1.35	9.7%	784	78	0.93	1.11	93.9
28	0.70	1.49	1.37	8.4%	783	76	0.93	1.11	

since the main mass fraction of a layered pellet is still the starter core. In this study, the porosity for layered pellets was much higher than for starter cores, though layer porosity was high, contrary to the expectations for a high binder level. Even at a concentration of 20% in the layer, pores did not close and drug was not embedded in a pore-free polymer matrix.

The pellet size distribution after processing was narrow and, for single batches, even better than the size range for starter cores. For nearly all the batches, a fraction of more than 75% was in the 10% interval, thus the size distribution could be regarded as excellent.

Perfect spheres have a sphericity and aspect ratio close to 1. If the aspect ratio is defined as the ratio of the maximum Feret diameter to its orthogonal Feret diameter, a value of less than 1.1 is desirable. In this study, the values given for aspect ratio represent the worst case since the minimum Feret diameter was used instead of the orthogonal diameter. In this case, an aspect ratio of 1.10–1.14 is still good.

The drug content measured for three batches with a layering efficiency of more than 95% was compared with the drug percentage calculated for the solids applied. The lowest HCT mass recovered, bound on the pellet surface, was 93.7% which is a little less than the value for layering efficiency, determined by mass gain calculation.

4. Conclusion

In this study, Kollicoat® IR was successfully applied as a binder for suspension layering purposes. The LE and recovery rate of drug indicated that the binder applied was strong enough to immobilize the drug particles on the surface.

Kollicoat® IR showed the advantage of economical and fast processing because a high solid content of at least 40% was possible. However, the 20% binder level required was much higher than expected and reduced the maximum potency of the layer to 80%.

A change of viscosity had no significant effect on process performance and was negligible in the range investigated. A high binder level, small particle size or low atomizing air pressure resulted in the formation of agglomerates. The impact on LE was small for all parameters, except for a low binder level. Different settings were suitable for obtaining a high-quality process and adequate robustness even with small variations in the settings.

It was possible to exceed the general limit of suitable drug particle size. Coarse drug particles could be used to avoid agglomerates in processes with a low product temperature and low atomizing air pressure. For the first time ever, by using Kollicoat® IR as a binder, advantage has been taken of coarse particles which until now, have presented insuperable drawbacks for layering.

The new binding excipient led to a rough and porous, but nevertheless uniform drug layer. The high binder level did not reduce porosity and indicates that Kollicoat® IR behaves differently than other polymers.

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