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Short communication

Fluid bed thin film coating of ultrafine Acetaminophen particles

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Introduction

Fine/ultrafine powder coating offer many advantages in pharmaceutical industry including improved surface quality, very high surface area, better compressibility, adequate flow characteristics etc. Thin film coated fine powders with modified physical properties showing good flowability, compressibility and blending potential may be directly compressed in tablets showing optimal dissolution, with addition of low number/amount of excipients. However, optimal handling of cohesive small particles powders during the process of fluid bed coating is a problem existing throughout several decades due to severe agglomeration, solid-bridging, poor flowability and luck of fluidization. Fluid bed coating processes without severe agglomeration are typically limited to particle sizes greater than 100 μm.

Acetaminophen (N-acetyl-p-aminophenol, APAP (or AP, paracetamol) particles with d(50) of 9.56 μm, Hausner index 1.96 (often categorized as Geldart C group) are very difficult to fluidize in a fluid bed due to their high cohesivity resulting in formation of channels and ratholes during fluid bed processing. The aim of this investigation was to develop fluid bed technique for thin film coating of APAP powder with a mean diameter less than 10 μm, which is extremely difficult to fluidize due to high relative cohesion. In order to overcome fluidization issues of APAP particles and create favorable processing conditions to avoid agglomeration, in the present study, co-fluidization of two categories of particles (APAP powder mixed with glass beads, d(50) 1 mm and density of 2.5 g/cm3) with diameters several orders of magnitude apart was used. Further, measurement of flow properties, particle size & particle size distribution, and the analysis of the FTIR, NIR and Raman spectra of APAP coated powders were performed.

Materials and methods

Fluid bed - Wurster coater VFC-LAB MICRO FLO-COATER, (Freund-Vector Corporation, USA) with a classical air-distributor plate and a top-spray arrangement was used in a coating process. Ratio of 1:1 mixtures of the glass beads and the APAP (Ph Eur grade) powder was used during the coating in order to maintain the powder bed fluidization. 0.5% HPMC, Methocel E5, Dow Chemicals, was used as a coating solution. Airflow was set at 75 LPM, inlet air temperature at 65 °C, nozzle atomization pressure was 0.255 bars, pump speed 10 rpm (0.7g/min). Outlet air temperature was 25-27 degrees.

Raman spectra were recorded using ATR 3000DH (Optosky, China) instrument. Scans were performed using a fiberoptic probe under the following conditions: laser power 400mW, integration time 60s, resolution 8 cm^{-1}, range 190-2000 cm^{-1}. NIR spectra were recorded using MicroNIR 1700 ES (Viavi, USA) instrument under the following conditions: scan resolution 40 cm^{-1}, spectral range 11000-6000 cm^{-1}, integration time 10s. FTIR spectroscopy was performed using Diamond ATR-FTIR, Carry 600 (Agilent, Germany) under the following conditions: resolution 4 cm^{-1}, 32 scans per spectrum, and a

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range of 4000 to 650 cm^{-1}. Particle size analysis was performed on Mastersizer 2000 particle size analyzer (Malvern, UK), using Scirocco 2000 automated dry powder dispersion unit at dispersion pressure of 3 bars.]

Results and discussion

Mixtures of particles with dissimilar densities and with order of magnitude difference between mean diameters of a factor of 100 for improvement of fluidization of ultrafine powders is uncommon. However, in this example the raw particles stayed constantly in motion circulating at the bottom of the fluid bed, promoting formation of winding channels inside the bed, improving the fluidization and preventing agglomeration of the fine particles. Theoretically estimated, 0.06%, 0.12%, 0.18% and 0.24% HPMC coating was applied during the coating process for sample A, B, C and D, respectively (50 g). Hausner ratio (HR, Table 1) values point to transition of the bulk properties during thin film coating from cohesive (1,4 < HR), to intermediate flow behavior (1,25 < HR < 1,4) and non-cohesive free flowing powder characteristics (HR < 1,25) (Sutton et al., 2016). Further, in accordance with HR, the angle of repose (AoR) values which were in a range of 29 º to 36 º pointed to powders with some cohesiveness (30 º < AoR < 45 º). In addition, thin film modification of the particles' surfaces improved the flow properties (Table 1) without changes in the particle size or the particle size distribution of the APAP powder. As a comparison different commercially available spray-dried lactose monohydrate products show HR in a range of 1.18 to 1.25 and AoR of 27 – 32^0, respectively.

Table 1. Powder properties

S	HR	d(0.1) μm	d(0.5) μm	d(0.9) μm
AP	1.95	2.08±0.02	9.56±0.02	102.21±0.31
A	1.43	2.09±0.07	10.41±0.10	100.66±0.21
B	1.27	2.07±0.12	10.87±0.05	103.76±0.42
C	1.23	2.03±0.22	10.75±0.11	106.09±0.35
D	1.20	2.10±0.02	11.24±0.20	103.76±0.28

Detailed inspection of FT-IR, NIR and Raman spectra of the coated acetaminophen powders pointed that all characteristic bands of the active substance were present in all the spectra. No shifting of the characteristic absorption bands or appearance of new bands were noticed in the FTIR spectra suggesting that there is no physical or chemical interaction among the drug substance and the coating agent. Minor changes in the intensity appearing with increased coating percentage in the 3000 – 3400 cm^{-1} region bands associated with N–H stretching and O–H stretching signify a change in the molecular environment of these functional groups during the coating process (Fig. 1). Also, inspection of the Raman spectra confirmed that there is no interaction among the drug substance and the coating agent, and the slight difference in the band intensity among the spectra may be attributed to the effect of the particle size and size distribution among the samples (Fig. 2). NIR spectra of the coated powders were identical to the spectrum of APAP. Slight variance in the NIR spectra slope can be attributed to the granulometry and other physical properties of the powder samples.

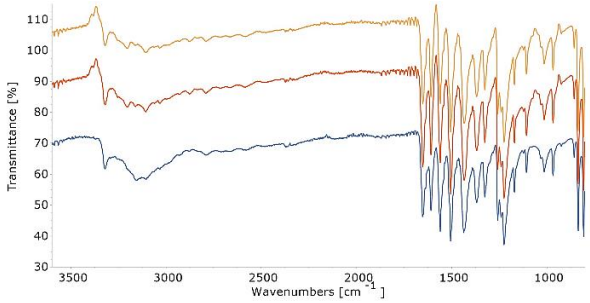

Fig. 1. FT-ATR spectra of APAP [yellow], sample A[red] and sample D [blue]

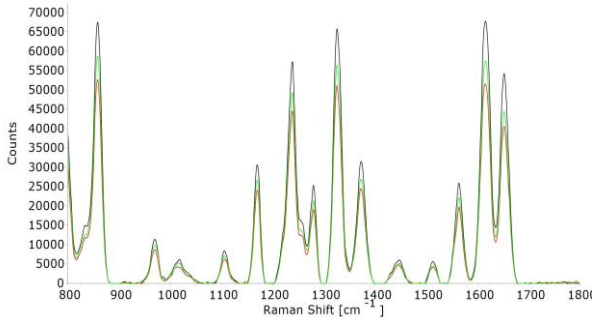

Fig 2. Raman spectra of the APAP (blue), sample A (green) and sample D (red)

Conclusion

Our preliminary experiments point that Acetaminophen ultrafine powder with a median diameter 9.56 micrometers can be coated with a thin film in a top spray fluidized bed granulator without agglomeration. Thin film coated powders showed Hausner ratio values below 1.25 and may be considered as free flowing.

References

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