Micron-sized Spherical Agglomerates of Pure Drug Nanoparticles for Improved Pulmonary Delivery

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ABSTRACT SUMMARY
Micron-sized spherical agglomerates of pure drug nanoparticles were produced through liquid antisolvent precipitation followed by immediate (on-line) spray drying. In-vitro aerosol deposition studies showed that as-achieved highly porous drug particles presented significantly improved aerosol delivery performance in comparison with the conventionally spray-dried nonporous spherical drug microparticles with similar geometric size distribution.

INTRODUCTION
With rapid advances in nanotechnology, the use of drug nanoparticles has become a subject of very active research in pulmonary drug delivery for both systemic and local treatment. Unfortunately, drug nanoparticle suspensions used in nebulizers and metered dose inhalers (MDIs) often suffer from physical instability (Ostwald ripening) and uncontrolled agglomeration. Besides, the application of drug nanoparticles for pulmonary delivery in dry powder inhalers (DPIs) is also not straightforward due to the persisting uncontrolled aggregation problem arising from their extreme small size. In order to circumvent the problems of application of drug nanoparticles in DPIs, large porous or hollow carrier particles composed of nanoparticles aggregates have been reported to be an effective approach.¹ Such carrier particles are with small aerodynamic diameter leading to enhanced aerosol performance, but relatively large geometric diameter and spherical shape preventing further uncontrolled aggregation of dry nanoparticles. However, unlike other delivery systems, the current excipients approved by the Food and Drug Administration for respiratory drug delivery are very limited in number. Therefore, carrier-free and excipient-free formulation approaches, especially the use of pure drug nanoparticles agglomerates for enhanced pulmonary drug delivery in DPIs, have recently gained a lot of attentions, since the absence of excipients in the formulation may reduce the occurrence of unseen side effects, avoid the problem of long-term and costly safety studies and the risk of rejection by regulatory authorities.²³ In this study, sodium cromoglicate (SC) was used as a model drug. Pure SC nanoparticles were formed by liquid antisolvent precipitation, and then rapidly agglomerated into porous spherical microparticles by immediate (on-line) spray drying. Nonporous spherical SC microparticles were produced by conventional spray drying of drug solution for comparison.

EXPERIMENTAL METHODS
Liquid antisolvent precipitation was employed to produce SC nanoparticles suspension, which was then spray dried immediately to obtain micron-sized spherical agglomerates of pure SC nanoparticles. Briefly, 3g of SC was dissolved in 30ml of water to form SC solution. Ethanol was chosen to be the antisolvent for precipitation of SC nanoparticles from solution. In order to conduct immediate (on-line) spray drying, the experiment was conducted this way: 1ml of drug solution was added into 19 ml of antisolvent at magnetic stirring rate of 1000 rpm. The formed milky precipitates suspension was then immediately spray dried at the condition of inlet temperature of 130 °C and feeding rate of 5 ml/min using Büchi mini spray dryer B-290. The freshly precipitated drug nanoparticles suspension could thus be turned into powders within minutes and the Ostwald ripening was minimized. When the spray drying process was almost completed, the second batch precipitation was carried out in the same way as described above and the spray drying was conducted immediately after depletion of the first batch particle suspension. Totally, 3g of dry powder was produced by the repeated precipitation followed by immediate spray drying process. By this way, all the drug nanoparticles formed by antisolvent precipitation could be spray dried within minutes.

The nonporous spherical SC microparticles with similar geometric size distribution were produced by conventional spray drying of the diluted SC solution. These two samples were then characterized by scanning electron microscopy (SEM), laser diffraction, Brunauer–Emmett–Teller (BET) analysis, density measurement, X-ray diffraction (XRD), and in vitro aerosol deposition measurement with a multistage liquid impinger (MSLI).

RESULTS AND DISCUSSION
SEM image (Fig.1 B) shows ~100nm SC nanoparticles were agglomerated into spherical microparticles with rough surfaces and porous structures. Both types of particles showed similar geometric size distribution (Fig.2) and same XRD pattern of amorphous form. BET analysis and density measurement results (Table 1) confirmed the high porosity of the spherical agglomerates of
nanoparticles. In vitro aerosol deposition profiles (Fig.3) showed the fine particle fraction (FPF) of such spherical agglomerates of SC nanoparticles was increased by more than 50% in comparison to the conventionally spray-dried nonporous spherical SC microparticles, demonstrating significant improvements in aerosol performance were achieved.

![Image 1](https://via.placeholder.com/150)

**Fig.1.** Scanning electron micrographs of (A) conventionally spray-dried nonporous spherical SC microparticles and (B) micron-sized spherical agglomerates of SC nanoparticles.

![Image 2](https://via.placeholder.com/150)

**Fig.2.** Size distribution of (A) conventionally spray-dried nonporous spherical SC microparticles and (B) micron-sized spherical agglomerates of SC nanoparticles.

Table 1

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>BET Surface Area (m²/g)*</th>
<th>Bulk Density (g/cm³)</th>
<th>Tapped Density (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.24</td>
<td>0.1825</td>
<td>0.2441</td>
</tr>
<tr>
<td>B</td>
<td>158.63</td>
<td>0.0671</td>
<td>0.0868</td>
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</tbody>
</table>

*mean, n=2

![Image 3](https://via.placeholder.com/150)

**Fig.3.** Drug deposition profiles in the multistage liquid impinge as mass percentage of (A) conventionally spray-dried nonporous spherical SC microparticles and (B) micron-sized spherical agglomerates of SC nanoparticles (mean ± sd, n=3).

**CONCLUSION**

Micron-sized spherical agglomerates of pure drug nanoparticles with improved aerosol performance were successfully produced through the process of liquid antisolvent precipitation followed by immediate (on-line) spray drying, indicating the potential application of this particle engineering process in the development of carrier-free or excipient-free formulation products for improved pulmonary delivery of drugs.

**REFERENCES**


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