CHEMISTRY AND AERODYNAMIC PERFORMANCE OF IPRATROPIUM MICROCRYSTALS – AN EXPERIMENTAL APPROACH

Dr. Piyush Pradeep Mehta [1, 2] and Debjit Ghoshal [1, 3]

[1] Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune, Maharashtra 411038, India

[2] Cipla R & D, Vikhroli (W), Mumbai, Maharashtra 400083, India and [3] Systematic Review Team, Lumanity, India.

piyu053@gmail.com and debjitghoshalkol@gmail.com

cwcp2022.07000d4

✓ Study motivation

✓ **Dry powder inhalers (DPIs) –** The most commonly prescribed pulmonary dosage form. DPI is composed of 3 elements – Micronized drug (> 5 µm) + Coarse carrier (160 µm) + Inhaler device (single or multi-dose)

✓ Ipratropium is a synthetic anticholinergic agent that is used in the treatment of acute bronchospasm due to chronic bronchitis and emphysema

✓ Ipratropium is available in form of lactose based DPIs. It consist of high energy jet-milled ipratropium particles. Jet-milling process has a considerable impact on particle physical properties and induce high surface charge on micronized drug particles. Which ultimately raised several handling, processing issues and poor lung deposition

✓ Thus, key objective of present study is to developed simple, one-step and green crystal engineering method to synthesized ipratropium microcrystals (IPMCs) to improve physical properties and lung deposition performance

✓ Study design

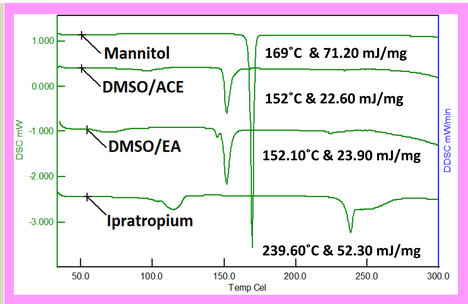
✓ IPMCs were synthesized using mannitol (carrier and crystallization inducing agent) by anti-solvent crystallization method. Initially, ipratropium bromide (1 mole) and mannitol (1 mole) in a relative molar ratio (1:1) was dissolved carefully in a DMSO (10 mL) under heating (55-55 °C) with continues stirring (100 rpm)

✓ After achieving a clear solution, the mixture was crystallized by the addition of 50 mL (5 mL/min) of ethyl acetate (EA) and acetone (ACE), respectively

✓ After anti-solvent addition, the obtained suspension was permitted to stay under the same stirring conditions for 2 h. Then, the crystalline mass was filtered using Type A/E-1 glass fiber filter and allowed to dry at 60-65 °C in the oven for 24 h

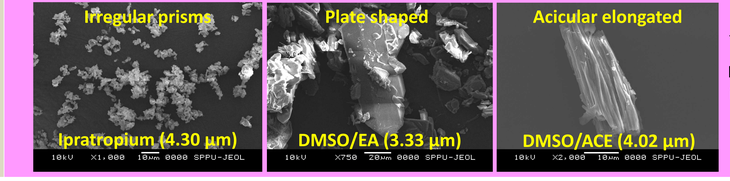
✓ The dried crystals were poured into a glass vial, sealed and stored in a desiccated environment until further use

✓ IPMCs were subjected to physical and aerodynamic properties analysis



✓ Change in melting onset and marked difference in enthalpy values (ΔH) for the synthesized IPMCs compared to the ipratropium bromide and mannitol indicate the formation of new chemical entity

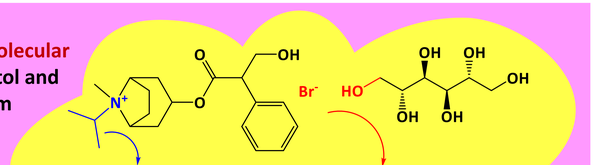
✓ The difference in the melting-onset may reveal a change in the molecular arrangement, crystal habit, crystal lattice, intermolecular properties



Marked change in crystal shape and size

Chemistry

The possibility of an intermolecular interaction between mannitol and ipratropium bromide to form IPMCs



IPMCs powder ready for pulmonary application

Aerodynamics

In-vitro aerodynamic properties of IPMCs were determined using 8-stage Andersen cascade impactor (ACI) equipped with low resistance capsule-based inhaler device i.e. Breezhaler® at flow rate of 60 L/min (± 5 %) for 4 s (n=3). Size 3 HPMC Capsules were used.

In aerosolization study - EA/IPMCs, ACE/IPMCs and untreated ipratropium showed a marked difference in drug retention within the inhaler device and capsules.

EA/IPMCs and ACE/IPMCs showed a marked 1.12 and 1.20-fold superior emitted dose compared to untreated ipratropium.

Moreover, ACE/IPMCs presented a significant 1.66-fold higher impactor size mass (ISM) compared to untreated ipratropium.

- Needle-like or elongated ACE IPMCs showed superior aerodynamic properties due to narrow aerodynamic size and low geometric standard deviation.
- Additionally, elongated crystals reached alveoli region via interception mechanism while compact crystals of the similar aerodynamic attributes were easily exhaled unless extended breath holding is applied. Moreover, elongated crystals hold a larger drug mass compared to compact crystals.

BALANCED JUDGMENT ON IPRATROPIUM MICROCRYSTALS SUSTAINABLE DEVELOPMENT

Opportunities	Obstacles
• Simple and one-step crystal engineering	• Need on-line reaction monitoring
• GRAS Listed excipients and solvents	• Need PAT tools to ensure environmentally correct synthesis
• Minimum innocuous degradation products	• Need to plan for scale-up issues
• Minimum handling and processing issues	

Conclusion

- The investigation exposed the value of simple, one-step green crystallization method to enhance the chemical, physical and aerodynamic properties of ipratropium and could be explored for clinically important lipophilic substances to enhance their pharmaceutical and aerodynamic properties
- The proposed method practically showed the application of green and efficient crystallization method for sustainable pharmaceutical development

References

1. Soares et al., Crystal growth & design. 2013;13(4):1510-7.
2. Engel and Scott, Green Chemistry. 2020;22(12):3693-715.