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Development and Evaluation of Terbutaline Sulphate and Itraconazole Nanoparticles Dry Powder Inhalers for Asthma Management

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ABSTRACT:
The present study aimed to develop and evaluate nanoparticle-based dry powder inhalers (DPIs) containing terbutaline sulphate and itraconazole for pulmonary delivery in asthma management. Terbutaline sulphate acts as a bronchodilator, while itraconazole serves as an antifungal agent against Aspergillus-associated allergic conditions in asthma. Nanoparticles were prepared by physical milling and spray-drying techniques using D-mannitol and trehalose as carriers. The prepared formulations were characterized for flow properties, particle size distribution, zeta potential, moisture content, drug content, and aerosolization performance. The spray-dried formulations demonstrated particle sizes ranging from 216.7 to 423.7 nm with improved zeta potential and lower polydispersity indices compared with milled formulations. Fine particle fraction values ranged from 66.35% to 71.86%, while emitted doses exceeded 93%. The formulations exhibited acceptable flow properties, low moisture content, and excellent drug content uniformity. The findings suggest that spray-dried terbutaline sulphate and itraconazole nanoparticle DPIs possess suitable physicochemical and aerodynamic characteristics for pulmonary drug delivery and may offer improved therapeutic efficacy in asthma management.
Keywords: Terbutaline sulphate, Itraconazole, Aspergillus, polydispersity, aerodynamic, polydispersity

Introduction

Asthma is a chronic inflammatory airway disorder characterized by bronchoconstriction, airway hyperresponsiveness, and recurrent respiratory symptoms. Pulmonary drug delivery offers several advantages including rapid onset of action, reduced systemic adverse effects, and improved bioavailability. Nanoparticle-based dry powder inhalers have emerged as promising systems for targeted lung delivery because of their small particle size, large surface area, enhanced dissolution, and improved deposition in the lower respiratory tract. Terbutaline sulphate is a selective β2-adrenergic agonist used as a bronchodilator, whereas itraconazole is an antifungal agent effective against Aspergillus-related allergic conditions. The present investigation aimed to formulate and evaluate nanoparticle-based dry powder inhalers containing terbutaline sulphate and itraconazole using D-mannitol and trehalose carriers.

Methodology

Materials

Terbutaline sulphate and itraconazole were used as active pharmaceutical ingredients. D Mannitol and trehalose served as carrier materials.

Preparation of Formulations

Nanoparticle formulations were prepared by

- Physical milling
- Spray drying

Physical milling:

Terbutaline sulphate, Itraconazole and the sugar used as carriers (D-Mannitol, Trehalose) were dried at 37^0 c for 12 Hrs in a vaccum oven. The size of drug and carriers were reduced using grinding mill for 3Hrs for nanosized particles and for 2 hours for fine particles. The 50mg: 2.5g terbutaline: carrier, 5gm:5 gm itraconazole: carrier, 50/5000mg: 7.5gm terbutaline/ itraconazole : carrier were prepared at room temperature. Each of these mixtures is 100 inhalation doses (Terbutaline 0.5mg/ dose, Itraconazole 50mg/dose). The formulations were blended over a V- Cone blender and rotated at 50 rpm for 2 hours. All the formulations was kept in a desiccator over silica gel at room temperature. An accurately weighed amount of Terbutaline sulphate and Itraconazole was mixed separately in each case with milled D-mannitol and milled trehalose in geometric progress and passed through 60# mesh and blended in polybag and filled in to size "3" hard gelatin capsules with manual capsule filling machine with fill weight of 25.5 mg per capsule of Terbutaline sulphate, 100 mg per capsule of Itraconazole, 125.5 mg per capsule containing Terbutaline sulphate and Itraconazole in combination.

Spray Drying

Spray drying process using dilute solutions was performed in a mini spray dryer using high performance cyclone separator.

Solution-1:

The feed solution was prepared by dissolving each component, consisting of terbutaline with D-Mannitol and terbutaline with trehalose with rationally selected molar ratios in methanol to make total powder concentrations of 0.3%W/v.

Solution-2: The feed solution was prepared by dissolving each component, consisting of itraconazole with D-Mannitol and

itraconazole with trehalose with rationally selected molar ratios in methanol to make total powder concentrations of 0.3%W/v.
Solution-3: The feed solution was prepared by dissolving each component, consisting of terbutaline and itraconazole with D-Mannitol, terbutaline and itraconazole with trehalose with rationally selected molar ratios in methanol to make total powder concentrations of 0.6%W/v.

Frequency (cm^{-1})	Bond/Funtional Group
1745	C=O
1543	C=C ring stretching
1543 and 1422	C-H bending of CH3 and CH2 group
1254	O-H bending
874	Substituted Phenyl ring
3300-3521	Broad Peak of OH and NH hydrogen bond
3233	Aromatic C-H stretching

Results and Discussion

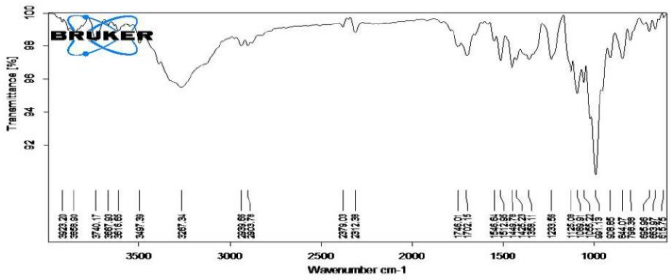

Fig 1: IR Spectrum - Terbutaline Sulphate

Frequency (cm^{-1})	Bond/Funtional Group
2939-2903	C-H Stretching of CH3 and CH2 group
1548	C=C ring stretching
1548 and 1449	C-H bending of CH3 and CH2 group
1233	O-H bending
991	Substituted Phenyl ring
3300-3497	Broad Peak of OH and NH hydrogen bond
3267	Aromatic C-H stretching

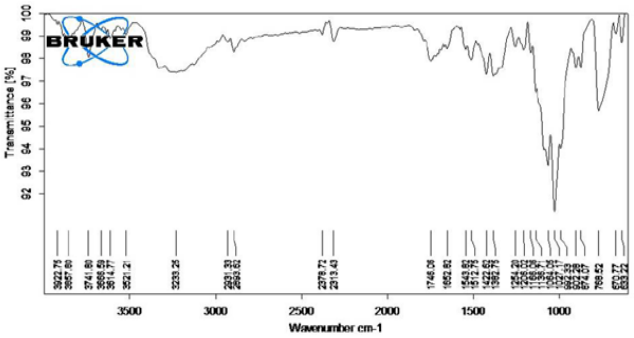

Fig 2: IR Spectrum - Terbutaline + D-Mannitol

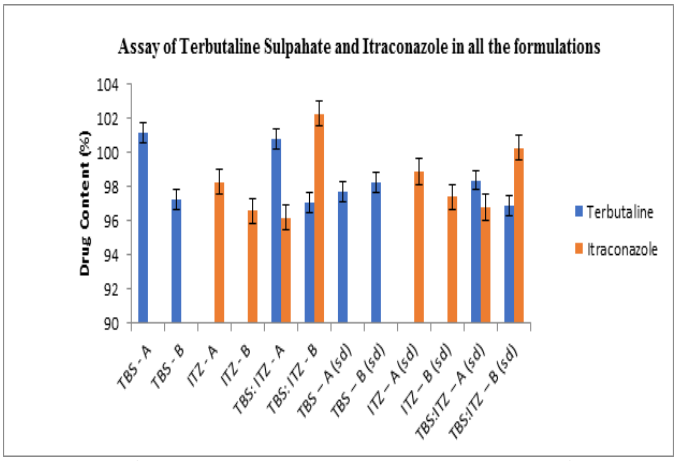

Fig.3: Assay of Terbutaline Sulpahate and Itraconazole in all the formulations

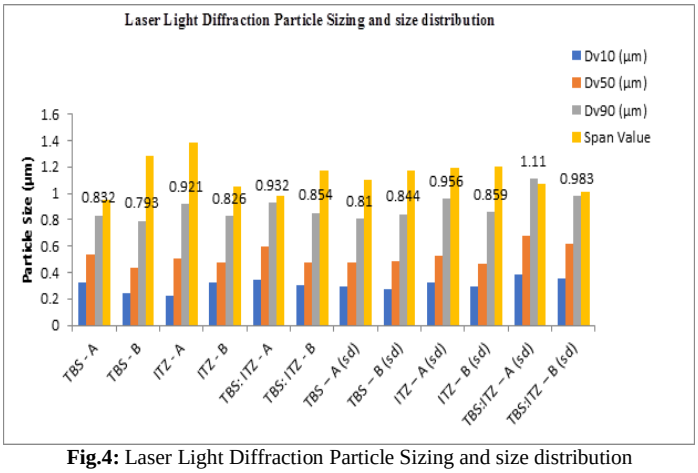

Fig.4: Laser Light Diffraction Particle Sizing and size distribution

Table 1: Formulation table – Physical mixing

Method	Formulation Code	Milled Drug (For 100 Doses)	Carrier (For 100 Doses)
Milling	TBS - A	Terbutaline (50 mg)	Milled D-Mannitol (2.5 g)
	TBS - B	Terbutaline (50 mg)	Milled Trehalose (2.5 g)
	ITZ - A	Itraconazole (5 g)	Milled D-Mannitol (5 g)
	ITZ - B	Itraconazole (5 g)	Milled Trehalose (5 g)
	TBS: ITZ - A	Terbutaline and Itraconazole (50mg:5000 mg)	Milled D-Mannitol (7.50 g)
	TBS: ITZ - B	Terbutaline and Itraconazole (50mg:5000 mg)	Milled Trehalose (7.50 g)

Table 2: Formulation table – Spray drying

Method	Formulation No	Formulation Code	Drug: Carrier (Milled)	TPC (% W/V)	Solvent Used
Spray Drying	1	TBS – A (sd)	Terbutaline:D-Mannitol	0.3	Methanol
	2	TBS – B (sd)	Terbutaline:Trehalose	0.3	Methanol
	3	ITZ – A (sd)	Itraconazole:D-Mannitol	0.3	Methanol

	4	ITZ – B (sd)	Itraconazole: Trehalose	0.3	Methanol
	5	TBS:ITZ – A (sd)	Terbutaline:Itraconazole:D-Mannitol	0.6	Methanol
	6	TBS:ITZ – B (sd)	Terbutaline:Itraconazole:Trehalose	0.6	Methanol

**TPC – Total Powder Concentration

Table 3: Organoleptic Properties

Property	Terbutaline Sulphate	Itraconazole
Colour	White to grey white	White
Odour	Odourless/ faint odour of acetic acid	Odourless
Taste	Tasteless	Bitter
Texture	Crystalline	Amorphous

Table 4: Solubility & Melting Point

Property	Terbutaline Sulphate	Itraconazole
Solubility	Soluble in water (>20 mg/ml). Slightly soluble in methanol (2.7 mg/ml) and ethanol (1.2 mg/ml) and insoluble in chloroform	Soluble in acetonitrile, chloroform (50 mg/ml), slightly soluble in alcohol and insoluble in water.
Melting Point	248-251^{O}c	166-170^{O}c

Table.5: Evaluation of various physical properties –Formulations

Drug/Excipient	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose (^{0})	Hausner's Ratio	Carr's Index (%)
TBS - A	0.61±0.001	0.69±0.006	29.44±0.12	1.13±0.003	11.59±0.02
TBS - B	0.78±0.003	0.84±0.012	21.72±0.15	1.08±0.007	7.14±0.15
ITZ - A	0.66±0.014	0.78±0.012	28.62±0.02	1.18±0.015	15.38±0.01
ITZ - B	0.62±0.012	0.68±0.003	23.17±0.16	1.10±0.016	8.82±0.11
TBS: ITZ - A	0.57±0.011	0.64±0.012	30.72±0.04	1.12±0.006	10.94±0.13
TBS: ITZ - B	0.67±0.003	0.72±0.014	29.79±0.05	1.07±0.002	6.94±0.16
TBS – A (sd)	0.73±0.005	0.84±0.015	26.23±0.03	1.15±0.001	13.10±0.13
TBS – B (sd)	0.77±0.012	0.82±0.016	22.63±0.15	1.06±0.012	6.10±0.15
ITZ – A (sd)	0.54±0.003	0.63±0.014	25.37±0.15	1.17±0.015	14.29±0.13
ITZ – B (sd)	0.62±0.011	0.69±0.015	23.66±0.14	1.11±0.016	10.14±0.14
TBS:ITZ – A (sd)	0.66±0.015	0.75±0.015	26.14±0.11	1.14±0.011	12.00±0.15
TBS:ITZ – B (sd)	0.73±0.017	0.79±0.014	21.48±0.16	1.08±0.014	7.59±0.03

Table.6: Average fill weight per capsule

Formulation Code	Actual fill wt per capsule (mg)	Average fill wt per capsule (mg)
TBS - A	25.5	25.17±0.14
TBS - B	25.5	25.30±0.23
ITZ - A	100	99.80±0.18
ITZ - B	100	100.01±0.32
TBS: ITZ - A	125.5	124.32±0.09
TBS: ITZ - B	125.5	124.61±0.05
TBS – A (sd)	25.5	25.54±0.04
TBS – B (sd)	25.5	25.43±0.14
ITZ – A (sd)	100	99.8±0.16
ITZ – B (sd)	100	100.2±0.14
TBS:ITZ – A (sd)	125.5	124.8±0.06
TBS:ITZ – B (sd)	125.5	123.9±0.08

Table .7: Percentage Yield & Drug Content

Formulation Code	Theoritical Yield	Practical Yield	% Yield	Drug Content (%)	
Physical Mixing	(gm) for 100 Doses	(gm) for 100 Doses		Terbutaline sulphate	Itraconazole
TBS - A	2.55	2.50	98.04	101.2±0.31	-
TBS - B	2.55	2.51	98.43	97.3±0.24	-

ITZ - A	10	9.94	99.40	-	98.3±0.36
ITZ - B	10	9.87	98.70	-	96.6±0.34
TBS: ITZ - A	12.55	12.42	98.96	100.8±0.15	96.2±0.14
TBS: ITZ - B	12.55	12.32	98.17	97.1±0.18	102.3±0.25
Spray Drying	**% w/v (TPC)**	**TPC**	**-**	**%**	**%**
TBS – A (sd)	0.3	0.29	77.50	97.7±0.36	-
TBS – B (sd)	0.3	0.28	82.50	98.3±0.12	-
ITZ – A (sd)	0.3	0.23	87.50	-	98.9±0.24
ITZ – B (sd)	0.3	0.26	80.00	-	97.4±0.18
TBS:ITZ – A (sd)	0.6	0.52	86.25	98.4±0.16	96.8±0.21
TBS:ITZ – B (sd)	0.6	0.51	88.75	96.9±0.14	100.3±0.26

Table.8: Laser light diffraction particle sizing and size distribution

Method	Formulation Code	D_{v10} (µm)	D_{v50} (µm)	D_{v90} (µm)	Span Value
Milling	TBS - A	0.321±0.024	0.536±0.021	0.832±0.002	0.95±0.005
	TBS - B	0.241±0.031	0.432±0.025	0.793±0.014	1.28±0.014
	ITZ - A	0.219±0.024	0.510±0.004	0.921±0.016	1.38±0.032
	ITZ - B	0.322±0.033	0.478±0.005	0.826±0.025	1.05±0.021
	TBS: ITZ - A	0.344±0.014	0.597±0.032	0.932±0.021	0.98±0.024
	TBS: ITZ - B	0.299±0.012	0.475±0.004	0.854±0.024	1.17±0.031
Spray Drying	TBS – A (sd)	0.289±0.008	0.473±0.026	0.810±0.021	1.10±0.008
	TBS – B (sd)	0.274±0.013	0.489±0.032	0.844±0.033	1.17±0.004
	ITZ – A (sd)	0.324±0.014	0.531±0.013	0.956±0.004	1.19±0.012
	ITZ – B (sd)	0.298±0.016	0.467±0.008	0.859±0.007	1.20±0.015
	TBS:ITZ – A (sd)	0.389±0.018	0.675±0.003	1.11±0.013	1.07±0.002
	TBS:ITZ – B (sd)	0.354±0.013	0.622±0.015	0.983±0.016	1.01±0.016

Table.9: Particle Size and Zeta potential

Method	Formulations	Particle Size (nm)	Poly Dispersity Index (PDI)	Zeta Potential (mV)
Milling	TBS - A	563.0±0.13	0.283±0.11	+19±0.11
	TBS - B	488.7±0.12	0.243±0.08	+28±0.03
	ITZ - A	550.0±0.13	0.296±0.11	+17±0.13
	ITZ - B	542.0±0.11	0.233±0.14	+25±0.11
	TBS: ITZ - A	624.3±0.08	0.344±0.16	+18±0.02
	TBS: ITZ - B	542.7±0.17	0.314±0.12	+27±0.01
Spray Drying	TBS – A (sd)	245.0±0.19	0.132±0.14	+28±0.14
	TBS – B (sd)	216.7±0.16	0.101±0.11	+32±0.12
	ITZ – A (sd)	278.7±0.17	0.179±0.05	+26±0.04
	ITZ – B (sd)	232.3±0.19	0.142±0.16	+30±0.03
	TBS:ITZ – A (sd)	423.7±0.03	0.213±0.13	+28±0.12
	TBS:ITZ – B (sd)	412.0±0.16	0.198±0.08	+31±0.07

Conclusion

The present study successfully developed and evaluated nanoparticle-based dry powder inhaler (DPI) formulations containing terbutaline sulphate and itraconazole for pulmonary drug delivery in asthma management. Both physical milling and spray-drying techniques were employed using D-mannitol and trehalose as carrier materials. The formulated DPIs exhibited satisfactory physicochemical characteristics, including acceptable flow properties, uniform capsule fill weight, low moisture content, and high drug content. Spray-dried formulations demonstrated superior performance compared with milled formulations, producing smaller particle sizes (216.7–423.7 nm), lower polydispersity index, and higher zeta potential, indicating improved nanoparticle stability. In addition, the formulations showed excellent aerosolization properties, with high emitted dose and fine particle fraction suitable for efficient deep lung deposition. These findings indicate that spray-dried terbutaline sulphate–itraconazole nanoparticle DPIs are promising pulmonary drug delivery systems that may enhance therapeutic efficacy by combining rapid bronchodilation with antifungal activity for the management of asthma, particularly in patients with Aspergillus-associated allergic airway disease. Further in vivo, pharmacokinetic, and clinical studies are warranted to establish their long-term safety, efficacy, and therapeutic potential.

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AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Conflict of Interests

The authors declare no conflict of interest

Data Availability

Data will be available on request

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