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Formulation, characterization and evaluation of nanoparticles based dry powder insufflation containing terbutaline sulphate and itraconazole for the treatment of asthma

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ABSTRACT

Many factors affect the pulmonary drug delivery and stability of the nanoparticles an acupuncture consisting of bronchial asthma. Present research envisages on the development of dry powder nanoparticles as insufflation a acupuncture consisting of bronchial asthma (allergy due to *Aspergillus fumigatus*) using physical mixing and spray drying. Different founding are prepared and characterized with suitable excipients like lactose and trehalose. The particle size distribution of nano milled and spray-dried particles of Terbutaline Sulphate and Itraconazole showed unimodal size distribution. The formulations prepared with trehalose as the carrier showed less D_{v90}, D_{v50} and D_{v10} values due to the fineness in the particles of trehalose when compared to lactose. The D_{v50} and D_{v10} values were in the range of mountains of 0.43-0.89 μm and 0.21–0.49 μm for all formulations, which shows the primary particle size in the nanometer scale. Smooth and nearly spherical particles were produced for spray-dried formulations when compared to milled formulations. Zeta potential comes across until be between +17$\pm$0.13 to +32$\pm$0.12, which explains the particles as moderately stable. MMAD values ranges from 3.19 μm to 4.78 μm for milled nanoparticles and 3.45 μm to 4.21 μm for spray-dried particles. *In-vitro* drug release studies explains that spray-dried formulations of Terbutaline sulpahte and Itraconazole using lactose as excipients released the drug upto 98.9% and 99.1% in 180mts.

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INTRODUCTION

Nanoparticles gained therapeutic importance flourishing respiratory organ trental delivery due to its ability to enter into deeper parts of the lung, to elude powerful pulmonic dendrites along with mucociliary consent methods, sequent in prolonged residence time (Daniher and Zhu, 2008; Daraghmeh *et al.*, 2002). Statistical data on asthma showed that children missed 12.8 million school days, with 444,000 patients hospitalized, 1.7 million emergency visits, physician visits of about 10.6 million and 3,613 deaths (NIH Publication 10-7542., 2010).

Due to the unique features like surface to mass ratio, the ability to absorb creates an exterior region to carry various compounds, and nanoparticles gained much importance in acupuncture in reference to an asthma attack. Dry powder inhaler (DPIs) finds up to be effective to deliver a drug into the lung efficiently (Dolovich and Dhand, 2011; Edwards *et al.*, 1998). DPIs can be easily carried with less drug loss as well as provides spectacular drug effectively to the lung (Hickey and Garcia-Contreras, 2001; Roy and Vij, 2010). The particles with a mass median aerodynamic diameter (MMAD) under 5μ hit in order to be the best candidates for a pulmonic orphan drug. Particles in the above range will deposit in stroke and therefore increases systemic drug absorption (Zhang *et al.*, 2011; Li and Mansour, 2011).

Aspergillus fumigatus is a fungus which is likely one of the major cause for asthma. Hence in this comprehensive study, Terbutaline Sulphate (a bronchodilator) and Itraconazole (an antifungal) was used for spectacular acupressure going from asthama attack. This study was planned to design, optimize and develop a novel dry powder aerosol using physical mixing and spray drying.

MATERIALS AND METHODS

Terbutaline Sulphate and Itraconazole were obtained from KP Labs Hyderabad. Lactose was obtained from Drugs India Hyderabad. Trehalose from Hyashibara Co Ltd Japan. Methanol was obtained from Himalaya Scientific Nellore. Other chemicals used in the entire work owe allegiance analytic shortlist.

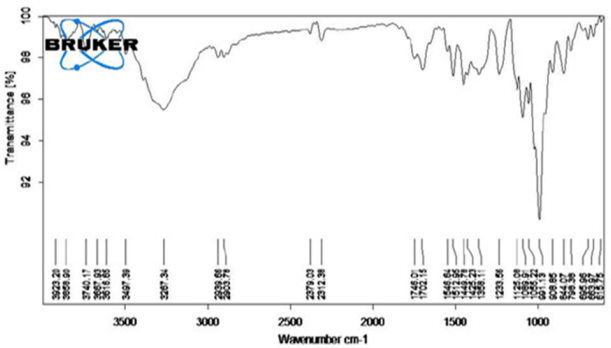

Figure 1: IR Spectrum - Terbutaline Sulphate

Pre-formulation

Preformulation parameters like organoleptic properties, Solubility, the Melting point was determined. Compatibility between drug and excipients and thermal properties of the drug was determined using FT-IR Spectroscopy and Differential Scanning Calorimetry. All the Drugs and Excipients have been

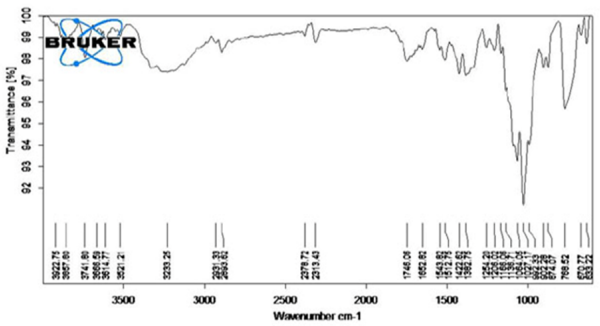

Figure 2: IR Spectrum – Terbutaline + Lactose

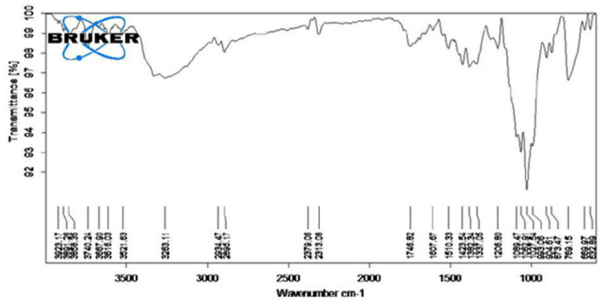

Figure 3: IR Spectrum - Terbutaline sulphate+Trehalose

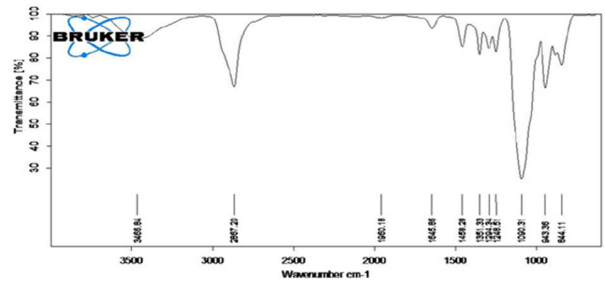

Figure 4: IR Spectrum – Itraconazole

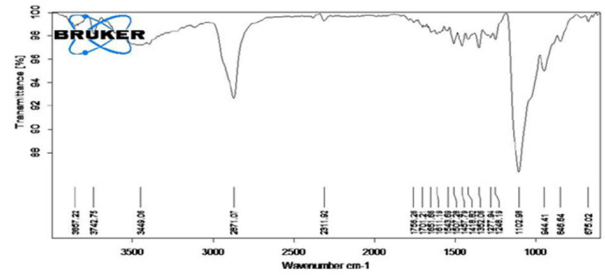

Figure 5: IR Spectrum – Lactose

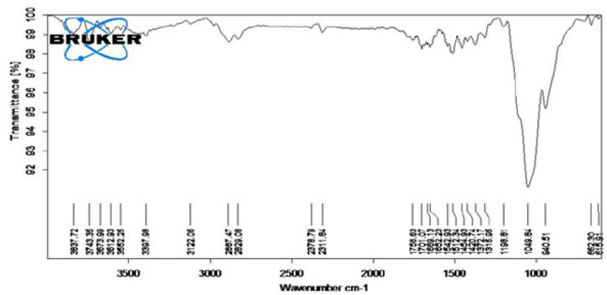

Figure 6: IR Spectrum - Itraconazole+Trehalose

Table 1: Evaluation of various physical properties – Drugs and Excipients

Drug/Excipient	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose (θ)	Hausner's Ratio	Carr's Index (%)
Terbutaline	0.48±0.015	0.62±0.011	26.51±0.12	1.29±0.003	22.5±0.01
Milled Terbutaline	0.65±0.011	0.74±0.013	23.52±0.04	1.13±0.001	12.16±0.12
Itraconazole	0.24±0.004	0.32±0.013	36.48±0.08	1.33±0.011	24.4±0.14
Milled Itraconazole	0.72±0.013	0.86±0.014	32.47±0.11	1.19±0.013	16.27±0.07
Lactose	0.52±0.011	0.59±0.011	24.34±0.04	1.13±0.011	11.86±0.03
Milled Lactose	0.57±0.014	0.62±0.004	22.22±0.03	1.08±0.012	8.06±0.05
Trehalose	0.65±0.005	0.77±0.002	36.74±0.11	1.18±0.013	15.58±0.05
Milled Trehalose	0.77±0.003	0.84±0.011	32.49±0.13	1.09±0.015	8.33±0.03

Table 2: Formulation Table – Physical mixing

Method	Formulation No	Formulation Code	Milled (Nano) Drug (For 100 Doses)	Carrier (For 100 Doses)
Physical Mixing	1	TER - A	Terbutaline Sulphate (50 mg)	Lactose (2.5 g)
	2	TER - B	Terbutaline Sulphate (50 mg)	Trehalose (2.5 g)
	3	TER - C	Terbutaline Sulphate (50 mg)	Milled Lactose (2.5 g)
	4	TER - D	Terbutaline Sulphate (50 mg)	Milled Trehalose (2.5 g)
	5	ITR - A	Itraconazole (5 g)	Lactose (5 g)
	6	ITR - B	Itraconazole (5 g)	Trehalose (5 g)
	7	ITR - C	Itraconazole (5 g)	Milled Lactose (5 g)
	8	ITR - D	Itraconazole (5 g)	Milled Trehalose (5 g)
	9	TER:ITR - A	Terbutaline Sulphate and Itraconazole (50mg:5000 mg)	Lactose (7.5.0 g)
	10	TER:ITR - B	Terbutaline Sulphate and Itraconazole (50mg:5000 mg)	Trehalose (7.5.0 g)
	11	TER:ITR - C	Terbutaline Sulphate and Itraconazole (50mg:5000 mg)	Milled Lactose (7.5.0 g)
	12	TER:ITR - D	Terbutaline Sulphate and Itraconazole (50mg:5000 mg)	Milled Trehalose (7.5.0 g)

Table 3: Formulation Table – Spray drying

Method	Formulation No	Formulation Code	Drug-Carrier (Milled)	TPC (% W/V)	Solvent Used
Spray Drying	1	TER – A (sd)	Terbutaline Sulphate: Lactose	0.4	Methanol
	2	TER – B (sd)	Terbutaline Sulphate: Trehalose	0.4	Methanol
	3	ITR – A (sd)	Itraconazole: Lactose	0.4	Methanol
	4	ITR – B (sd)	Itraconazole: Trehalose	0.4	Methanol
	5	TER:ITR – A (sd)	Terbutaline Sulphate:Itraconazole: Lactose	0.8	Methanol
	6	TER:ITR – B (sd)	Terbutaline Sulphate:Itraconazole: Trehalose	0.8	Methanol

TPC – Total Powder Concentration

Table 4: Outlet temperatures of spray-dried formulations

Spray Drying	Molar Ratios	Outlet Temperature ºC
Terbutaline Sulphate-Lactose	1:1	66
Terbutaline Sulphate-Trehalose	1:1	63
Itraconazole-Lactose	1:1	58
Itraconazole-Trehalose	1:1	52
Terbutaline Sulphate-Itraconazole-Lactose	1:1:1	61
Terbutaline Sulphate-Itraconazole-Trehalose	1:1:1	64

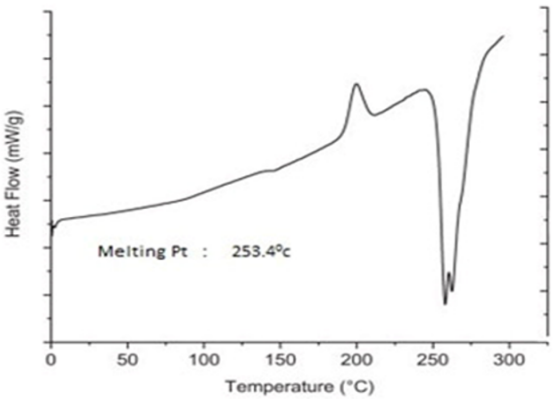

Figure 7: DSC of Terbutaline Sulphate

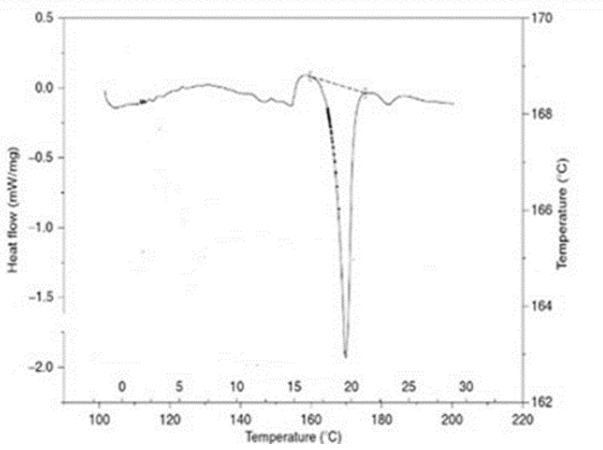

Figure 8: Thermogram of Itraconazole

verified as various physical properties like Bulk Density, Tapped Density, Angle of Repose, Hausner's Ratio, Compressibility Index and the results revealed the poor flow properties of drug and excipients. So, in order to improve the flow properties, drugs and excipients were milled to nano size and further evaluations were done (Meenach *et al.*, 2012; Ali and Lamprecht, 2014).

Formulation

Physical Mixing

Terbutaline Sulphate, Itraconazole and the sugar

Table 5: Average fill weight per capsule

Formulation Code	Actual fill wt per capsule (mg)	Average fill wt per capsule (mg)
TER - A	25.5	25.13±0.04
TER - B	25.5	24.96±0.11
TER - C	25.5	25.17±0.14
TER - D	25.5	25.30±0.23
ITR - A	100	100.05±0.11
ITR - B	100	99.94±0.16
ITR - C	100	99.80±0.18
ITR - D	100	100.01±0.32
TER:ITR - A	125.5	124.30±0.14
TER:ITR - B	125.5	125.52±0.16
TER:ITR - C	125.5	124.32±0.09
TER:ITR - D	125.5	124.61±0.05
TER – A (sd)	25.5	25.54±0.04
TER – B (sd)	25.5	25.43±0.14
ITR – A (sd)	100	99.8±0.16
ITR – B (sd)	100	100.2±0.14
TER:ITR – A (sd)	125.5	124.8±0.06
TER:ITR – B (sd)	125.5	123.9±0.08

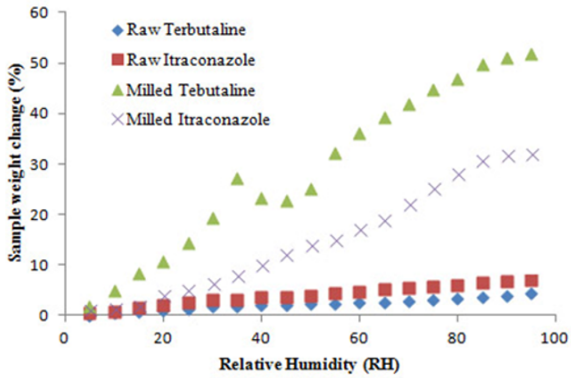

Figure 9: Water vapor natural process isotherms at 250C for raw API vs. milled API (weight change % vs. RH)

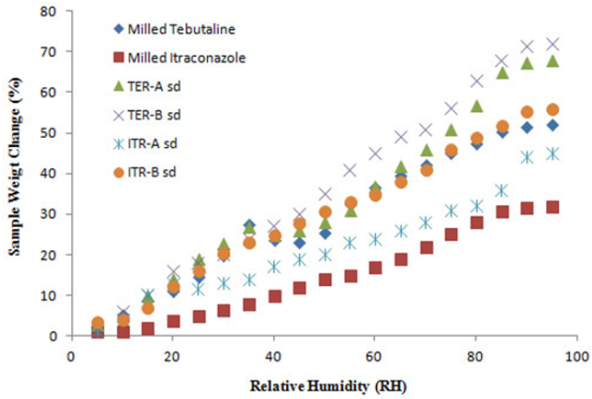

Figure 10: Water vapor sorption isotherms at 250C for Milled API vs. Spray Dried Formulations (Weight change % vs. RH)

used as carriers (Lactose, Trehalose) were taken in specified quantities shown in Table 2 and dried at 37^0 c using vacuum oven for 12 Hrs. The size of drug and carriers were reduced using grinding mill (Jet mill, air is supplied at 110 psig with air classifier speed of 4200 rpm) for 3 Hrs for nanosized particles and for 2 hours for fine particles (Jet mill, air is supplied at 90 psig with air classifier speed of 3800 rpm). Calculated amount of Terbutaline Sulphate and Itraconazole was mixed separately in every formulation with fine lactose and micronized lactose, fine trehalose and micronized trehalose in geometric dilutions and passed through 60# screen, blended and filled into size "3" hard gelatin capsules in addition to booklet silique weft roadster (SS handbook space capsule woof machine by Pharmafill Technologies) with a weight of 25.5 mg per capsule of Terbutaline Sulphate, 100 mg per capsule of Itraconazole, 125.5 mg per containing Terbutaline Sulphate and Itraconazole in combination (NIH Publication, 2010; Newman *et al.*, 2009).

Spray Drying

Mini spray dryer (SS Laboratory Spray Dryer (LSD 01)) using a high-performance cyclone separator

Table 6: Percentage Yield & Drug Content

Formulation Code	Theoretical Yield (gm) for 100 Doses	Practical Yield (gm) for 100 Doses	% Yield	Drug Content (%)	
				Terbutaline Sulphate	Itraconazole
Physical Mixing					
TER - A	2.55	2.48	97.25	96.3±0.12	-
TER - B	2.55	2.44	95.69	98.4±0.32	-
TER - C	2.55	2.50	98.04	101.2±0.31	-
TER - D	2.55	2.51	98.43	97.3±0.24	-
ITR - A	10	9.89	98.90	-	95.8±0.15
ITR - B	10	9.92	99.20	-	96.6±0.21
ITR - C	10	9.94	99.40	-	98.3±0.36
ITR - D	10	9.87	98.70	-	96.6±0.34
TER:ITR - A	12.55	11.98	95.46	97.7±0.24	98.8±0.19
TER:ITR - B	12.55	12.36	98.49	98.3±0.31	97.4±0.32
TER:ITR - C	12.55	12.42	98.96	100.8±0.15	96.2±0.14
TER:ITR - D	12.55	12.32	98.17	97.1±0.18	102.3±0.25
Spray Drying	% w/v (TPC)	TPC	-	%	%
TER – A (sd)	0.4	0.36	77.50	97.7±0.36	-
TER – B (sd)	0.4	0.38	82.50	98.3±0.12	-
ITR – A (sd)	0.4	0.33	87.50	-	98.9±0.24
ITR – B (sd)	0.4	0.36	80.00	-	97.4±0.18
TER:ITR – A (sd)	0.8	0.72	86.25	98.4±0.16	96.8±0.21
TER:ITR – B (sd)	0.8	0.71	88.75	96.9±0.14	100.3±0.26

was used for performing a spray drying process using dilute solutions. All the ingredients were taken in specified quantities shown in Table 3.

Solution-1

Dilute way out used to be mapped out by means of dissolving each ingredient in calculated quantities, consisting of Terbutaline Sulphate with lactose and Terbutaline Sulphate with trehalose using methanol to make total powder concentrations of 0.4%W/v.

Solution-2

Dilute way out turned into mapped out with the aid of dissolving each ingredient in calculated quantities, consisting of Itraconazole with lactose and Itraconazole with Trehalose using methanol to make total powder concentrations of 0.4%W/v (Olsson *et al.*, 2013).

Solution-3

Dilute solution way out used to be mapped out by means of dissolving each ingredient in calculated quantities, consisting of Terbutaline Sulphate and Itraconazole with lactose, Terbutaline Sulphate and Itraconazole with Trehalose using methanol to make total powder concentrations of 0.8%W/v (Pritchard, 2001).

Spray Drying- Conditions

1. Atomization Rate-600 L/Hr
2. Pump Rate-15 ml/min (Medium Pump Rate)
3. Inlet Temperature-150ºc
4. Nozzle Diameter-0.7mm

Sprayer dehydrated vectors have been separated by cyclone separator and sealed in the glass vials and stored in dessicator under ambient pressure. Outlet temperatures were given in Table 4.

Evaluation

Average fill weight per capsule

Table 7: Laser light diffraction

Method	Formulation Code	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)	Span Value
Physical Mixing	TER - A	0.478±0.021	0.785±0.002	1.43±0.021	1.21±0.028
	TER - B	0.491±0.002	0.695±0.032	1.24±0.005	1.08±0.024
	TER - C	0.321±0.024	0.536±0.021	0.832±0.002	0.95±0.005
	TER - D	0.241±0.031	0.432±0.025	0.793±0.014	1.28±0.014
	ITR - A	0.532±0.006	0.822±0.013	1.52±0.021	1.20±0.023
	ITR - B	0.439±0.003	0.754±0.016	1.33±0.013	1.18±0.013
	ITR - C	0.219±0.024	0.510±0.004	0.921±0.016	1.38±0.032
	ITR - D	0.322±0.033	0.478±0.005	0.826±0.025	1.05±0.021
	TER:ITR - A	0.544±0.012	0.893±0.031	1.76±0.023	1.36±0.032
	TER:ITR - B	0.611±0.023	0.899±0.012	1.59±0.032	1.09±0.021
	TER:ITR - C	0.344±0.014	0.597±0.032	0.932±0.021	0.98±0.024
	TER:ITR - D	0.299±0.012	0.475±0.004	0.854±0.024	1.17±0.031
Spray Drying	TER – A (sd)	0.289±0.008	0.473±0.026	0.810±0.021	1.10±0.008
	TER – B (sd)	0.274±0.013	0.489±0.032	0.844±0.033	1.17±0.004
	ITR – A (sd)	0.324±0.014	0.531±0.013	0.956±0.004	1.19±0.012
	ITR – B (sd)	0.298±0.016	0.467±0.008	0.859±0.007	1.20±0.015
	TER:ITR – A (sd)	0.389±0.018	0.675±0.003	1.11±0.013	1.07±0.002
	TER:ITR – B (sd)	0.354±0.013	0.622±0.015	0.983±0.016	1.01±0.016

Laser Light Diffraction Particle Sizing and size distribution: (mean±SD, n=3)

Table 8: Particle Size and Zeta potential

Method	Formulations	Particle Size (nm)	Poly Dispersity Index (PDI)	Zeta Potential (mV)
Physical Mixing	TER - A	897.7±0.02	0.301±0.14	+21±0.08
	TER - B	808.7±0.11	0.292±0.11	+26±0.16
	TER - C	563.0±0.13	0.283±0.11	+19±0.11
	TER - D	488.7±0.12	0.243±0.08	+28±0.03
	ITR - A	958.0±0.06	0.342±0.01	+14±0.06
	ITR - B	841.0±0.04	0.311±0.13	+24±0.08
	ITR - C	550.0±0.13	0.296±0.11	+17±0.13
	ITR - D	542.0±0.11	0.233±0.14	+25±0.11
	TER:ITR - A	1065.7±0.17	0.423±0.05	+16±0.13
	TER:ITR - B	1033.3±0.07	0.467±0.03	+26±0.05
	TER:ITR - C	624.3±0.08	0.344±0.16	+18±0.02
	TER:ITR - D	542.7±0.17	0.314±0.12	+27±0.01
Spray Drying	TER – A (sd)	245.0±0.19	0.132±0.14	+28±0.14
	TER – B (sd)	216.7±0.16	0.101±0.11	+32±0.12
	ITR – A (sd)	278.7±0.17	0.179±0.05	+26±0.04
	ITR – B (sd)	232.3±0.19	0.142±0.16	+30±0.03
	TER:ITR – A (sd)	423.7±0.03	0.213±0.13	+28±0.12
	TER:ITR – B (sd)	412.0±0.16	0.198±0.08	+31±0.07

Particle Sizing and Zeta potential (mean±SD, n=3)

Table 9: Determination of MMAD using cascade impactor (mean ± SD, n=3)

Method	Formulations	MMAD (μ)	GSD (μ)	FPF %	RF %	ED %
Physical Mixing	TER - A	4.77	1.50	62.48±0.11	65.3±0.07	95.69±0.21
	TER - B	4.15	3.10	67.42±0.14	69.6±0.04	96.86±0.12
	TER - C	3.19	2.30	75.96±0.21	78.1±0.12	97.25±0.05
	TER - D	3.26	2.44	78.41±0.03	80.3±0.13	97.65±0.06
	ITR - A	4.78	1.57	58.84±0.22	62.6±0.09	94.00±0.03
	ITR - B	4.52	2.96	63.35±0.04	66.2±0.16	95.70±0.21
	ITR - C	3.21	2.19	74.42±0.01	76.8±0.25	96.90±0.12
	ITR - D	3.35	2.08	73.84±0.12	77.0±0.17	95.90±0.04
	TER:ITR - A	4.35	2.26	56.94±0.11	60.3±0.12	94.42±0.12
	TER:ITR - B	4.54	2.09	61.95±0.16	64.1±0.05	96.65±0.24
	TER:ITR - C	4.25	1.85	63.70±0.25	66.9±0.02	95.22±0.11
	TER:ITR - D	4.26	2.80	66.30±0.11	69.4±0.13	95.54±0.13
Spray Drying	TER – A (sd)	3.53	1.94	71.86±0.04	75.1±0.05	95.69±0.21
	TER – B (sd)	3.45	2.25	69.45±0.03	74.1±0.03	93.73±0.07
	ITR – A (sd)	4.21	1.85	68.80±0.09	72.5±0.02	94.90±0.02
	ITR – B (sd)	4.05	1.98	69.20±0.13	73.3±0.06	94.40±0.04
	TER:ITR – A (sd)	4.12	2.63	66.35±0.15	69.8±0.07	95.06±0.13
	TER:ITR – B (sd)	4.03	2.83	69.53±0.04	72.6±0.08	95.78±0.18

MMAD-Mean Median Aerodynamic diameter, GSD-Geometric standard deviation, FPF-Fine particle Fraction, RF-Respirable Fraction, ED-Emitted Dose

20 capsules were randomly taken and the overall table of contents was taken way externally, shedding a bit much a part of the over shell as completely as possible (Rogueda and Traini, 2007). 20 capsules were weighed for content and determined using the following formulae.

Average fill weight (mg) = Content present in 20 capsules (mg)/20 ___(1)

Moisture content

In a 5 ml volumetric flask, 6-10 mg of sample was dissolved in methanol and hydranal KF reagent was filled in the reaction cell and test solutions were injected into it. The moisture content present in the sample was calculated by conducting all the experiments in triplicate (n = 3) (Meenach *et al.*, 2013). Moisture content of the sample was calculated using the formula

SF*100/W _____(2)

Where W = Coefficient the Sample, in mg, S = Volume of the KF reagent, in ml, F = the water compare factor of KF reagent, in mg.

Percentage Yield

Percentage yield was determined by taking the weights of reactants (drug and excipients) and products and calculated in line with the formula.

% Y = (Weight of Product / Weight of initial drug and excipients)*100 ____(3)

Drug Content

10 capsules were taken and transferred into a 100 milliliter volumetrically flask (Terbutaline dose equivalent to 50mg and Itraconazole dose equivalent to 500mg) and capsule was dissolved under sonication by adding the suitable volume of diluent (Water for Terbutaline sulphate and Methanol for Itraconazole), for about 10 minutes as well as intermittent quaking and final volume was made with diluents. Solution turned into selected through a 0.45μ membrane and estimated Terbutaline Sulphate at 276nm and Itraconazole at 264nm using UV spectrophotometer (2060 Plus UV-VIS Dual Beam, Analytical Technologies Pvt. Ltd.).

Scanning electron microscopy (SEM)

Hitachi S-4300 microscope was used to analyze the shape and morphology. Double-sided mucilaginous atomic number 6 directories have always been compensate alum stubs and samples were gold coated using Emscope SC400 coating system. Working distance with 13-15mm was set and a beam of electrons with fast electricity of 5-10 kV was used. Similar conditions were maintained for all the magnifications (Shekunov *et al.*, 2007).

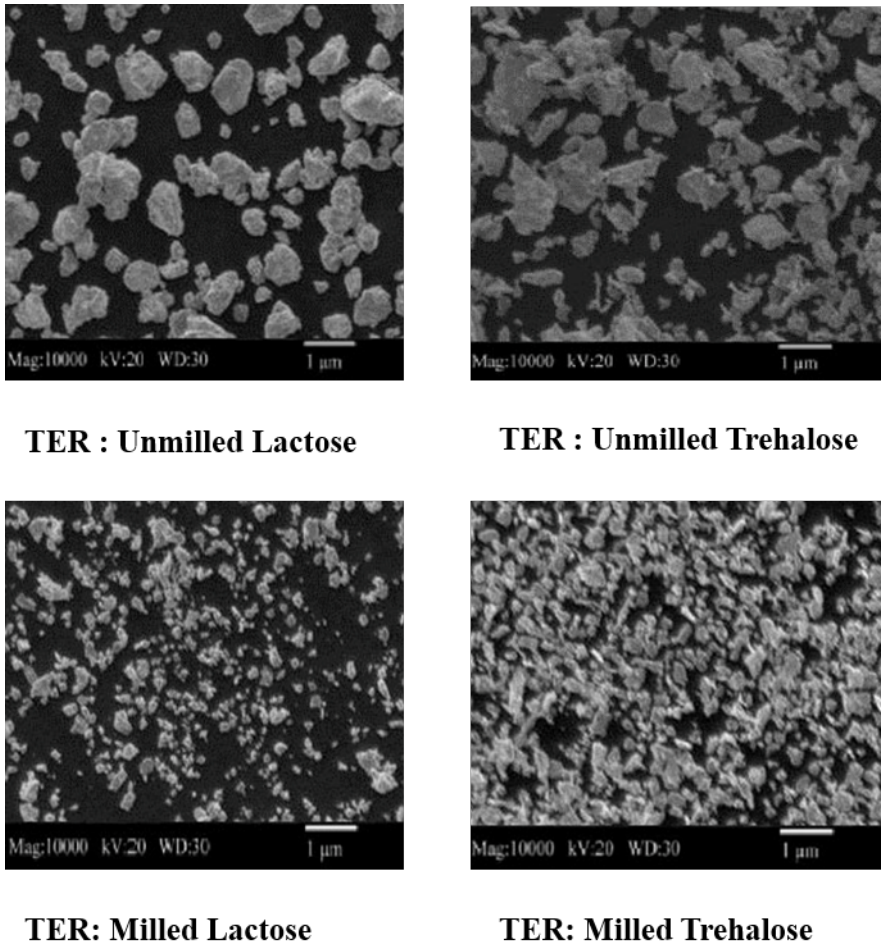

Figure 11: SEM of Terbutaline Sulphate formulations (Physical Mixing)

Size distribution using laser light diffraction

Shimadzu laser light diffractor was used to analyze the size plus filler redistribution of the particles in all the formulations. The samples were ultrasonicated for 10 min by dissolving the samples in chloroform. The dispersion was transferred into a measuring radical cell plus stored stirring. Volume-based measurements like Dv1mw980, Dv50, and Dv90 were used for the characterization of particles (Mansour *et al.*, 2013). The span value was calculated using the formula below (Zhang *et al.*, 2011; Mansour *et al.*, 2013).

((Dv90-Dv10)/Dv50) _____(4)

Particle Size and Zeta potential

Malvern zeta sizer was used to measure the electrophoretic mobility of the particles present in all the formulations by diluting the sample with water.

Determination of MMAD using cascade impactor

Seven ultimateness fall impactor was used to determine the MMAD. Randomly selected capsules (3 per each formulation) were needle pierced and was drawn into the cascade impactor with a controlled flow rate of 28 L/min with delay time of 10s. A total of 25.5mg (TER-A to TER-D) total per run, 100mg (ITR-A to ITR-D) total per run and 125.5mg (TER: ITR-A to TER: ITR-D) total per run. After deposition of DPI, Terbutaline Sulphate and Itraconazole content was determined in each chamber by UV Spectroscopy. Absorbance was detected at 276nm for Terbutaline Sulphate and 264nm for Itraconazole. MMAD and GSD at each stage for all the samples were calculated using MMAD calculated.

In vitro drug release studies

The dissolution studies are ordered palmy phosphate buffer with pH 7.4 at 37 °C using a rotating basket apparatus at 50rpm. The studies were performed with milled and spray-dried particles containing Terbutaline Sulphate and Itraconazole. At a predetermined time interval, 5ml aliquots had been withdrawn and a fresh 5 ml buffer was added simultaneously. Cumulative release of Terbutaline Sulphate and Itraconazole by UV/Vis-spectroscopy (λmax: 276 nm for Terbutaline Sulphate, λmax: 264 nm for Itraconazole) (Li *et al.*, 2014).

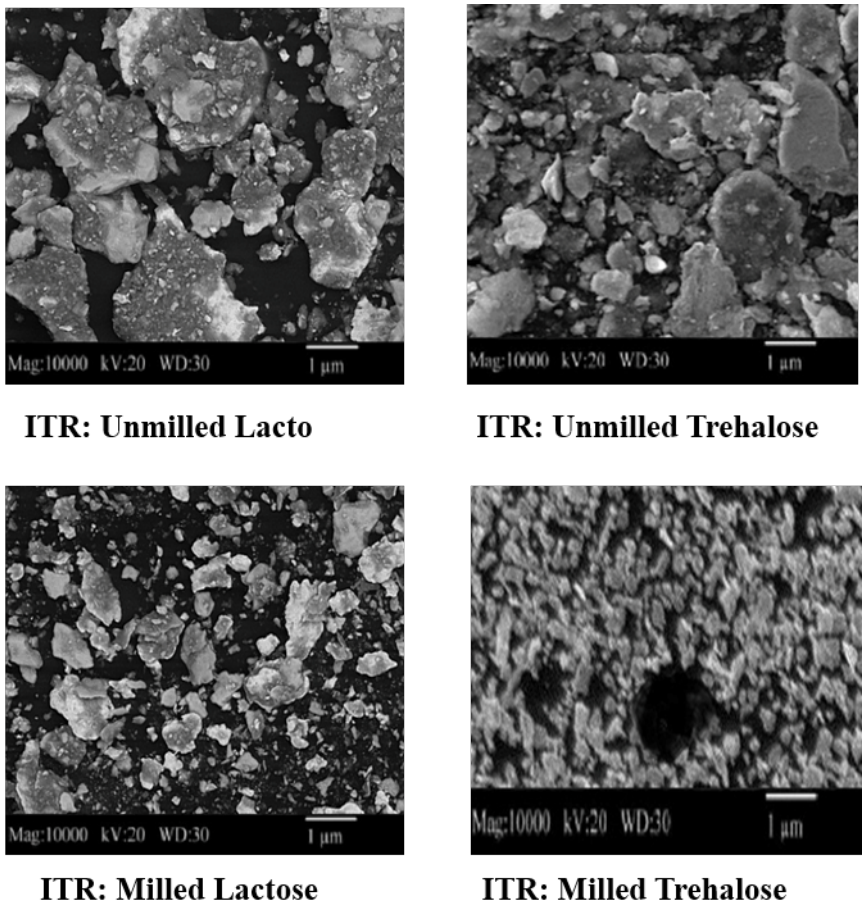

Figure 12: SEM of Itraconazole formulations (Physical Mixing)

RESULTS AND DISCUSSION

Preformulation

FTIR and DSC studies were performed for individual drugs and excipients. From the results, no incompatibility was observed between the drugs and excipients. The results were shown in Figures 1, 2, 3, 4, 5, 6, 7 and 8. All the drugs, excipients and formulations were subjected to various physical properties like Bulk Density, Tapped Density, Angle of Repose, Hausner's Ratio and Carr's Index to evaluate the density and flow of powder. Average fill weight also determined. All the formulations were found to have good flow properties when compared to plain drug and excipients. Due to the good flow property, all the formulations can be effectively delivered through the dry powder inhaler, which is very important in formulating as DPIs. Results were shown in Table 1 and Table 5.

Moisture Content

Moisture content for raw drugs and formulations was done by Karl Fisher serial dilutions. The residual water content for raw Terbutaline Sulphate and raw Itraconazole was found that one may be 4.41±0.18 and 7.62±0.11, respectively. Moisture content of all the formulations prepared by physical mixing and spray drying was decreased when compared to the raw drugs, which may be due to the general ubiety of lactose and trehalose in all the formulations.

Moisture content of formulations prepared by physical mixing ranges from 3.80±0.44 to 4.89±0.22. Formulations (Physical mixing) containing the combination drugs showed a slight increase, which may be due to the powerful ubiquity of Itraconazole (Fluffy Powder). Formulations prepared by way of atomizer brushing showed less moisture content when compared to the formulations prepared by physical mixing and ranges from 3.12±0.18 to 4.21±0.27. Results record in Figure 9 & Figure 10.

Percentage Yield and Drug Content

The spray-dried formulation showed less percentage yield (ranges from 77.50–88.75) when compared to milled formulations (ranges from 95.69–98.90). Less percentage yield for spray-dried formulations, when compared to milling, maybe due to the conditions used in the spray drying process. Drug content comes across in order to be within lim-

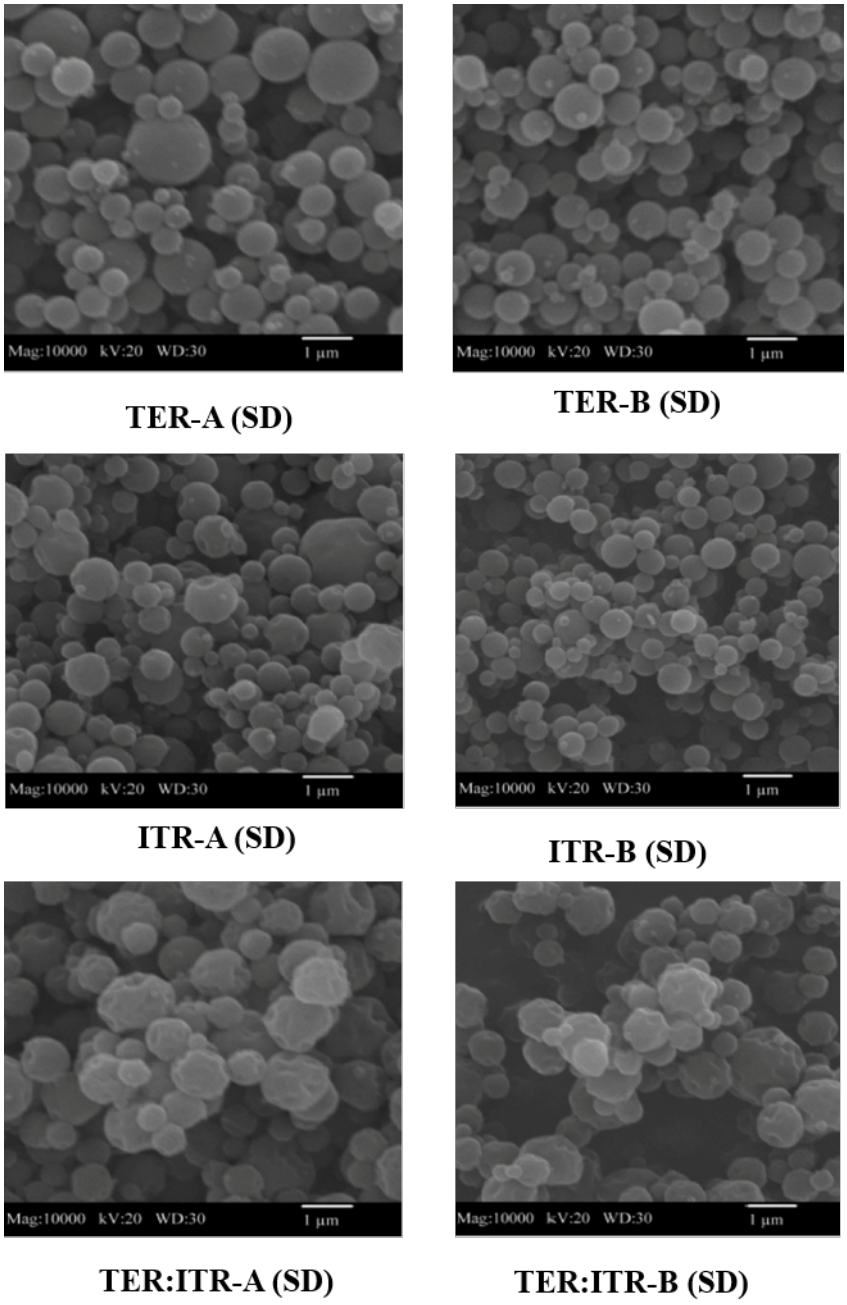

Figure 13: SEM of Terbutaline Sulphate and Itraconazole formulations (Spray Drying)

its (95.8±0.15 - 102.3±0.25) and results reflect in Table 6.

Scanning Electron Microscopy

The particle size of raw material was found to have a maximum particle size that may interrupt the respiratory passages. Hence the particle size has been decreased to the respirable-size using milling and spray drying. Particles were found that one may be smooth and spherical for spray-dried formulations. Formulations prepared through milling were found to have rough and irregular in shape. Results reflect in Figures 11, 12 and 13.

Particle sizing and Size distribution

All formulations tried and true nonparametric littleness distributions. The formulations prepared with trehalose as the carrier showed less D_{v90}, D_{v50} and D_{v10} values due to the fineness in the particles of trehalose when compared to lactose. The D_{v50} values were in the variety of 0.43-0.89 μm for all formulations. The D_{v10} values were in the range of mountains of 0.21–0.49 μm. This shows that all the particles were found planned in very particulate matter range and results reflect in Table 7 and Figure 14.

Zeta Potential

From the results, it was found that the formulations prepared by using milled trehalose as carrier attained less particle size when compared to milled lactose. Further, individual formulations attained less particle sizes when compared to the formulations in combination. Polydispersity index was found impending in a very range of mountains of 0.101 to 0.467, which explains the particle size distribution as monodisperse. Zeta potential was found so be between +17±0.13 to +32±0.12, which explains the particles as moderately stable. Results had been shown in Table 8 and Figure 15 &Figure 16.

Determination of MMAD (Mean Median Aerodynamic diameter)

Particle deposition on lower degrees containing ultimate twain totally that one may phase 7 (the lowest stage) is said. General, spectacular percent deposit towards phase a meg increased for unmilled formulations and formulations in which the drugs are given in combination. The exception to this, spray-dried formulations showed very slight differences in % deposition at stage 1. This trend was opposite for stage 4, where the amount of powder deposited on this stage increased in spray-dried systems when compared to physically mixed systems. From the results, it was found that significant deposition was seen in lower stages (Stages 4–7), which explains that the particle may deposit in the deep lung region, thereby increasing the therapeutic benefit. Results were shown in Table 9 and Figure 17.

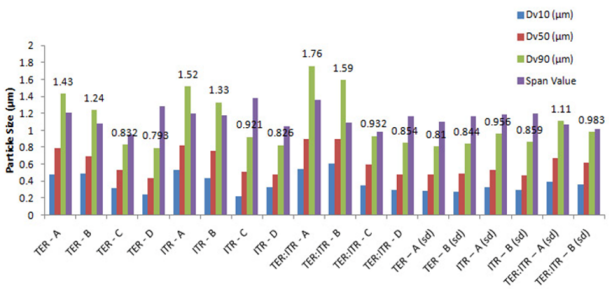

Figure 14: Laser light diffraction particle sizing and size distribution

***In-vitro* drug release studies**

Dissolution studies indicate that formulations prepared using milled trehalose release the drug at a faster rate due to its very fine particle size. TER-A(sd) and ITR-A(sd) was found that one may be the best formulations which released the drug upto 98.9% and 99.1% in 180 mts. All the formulations prepared viva atomizer drying has high % depositions from stage 2 to 7 when compared to other formulations, which made the spray-dried formulations the most effective drug delivery throughout the lung. Results were shown in Figure 18 & Fig-

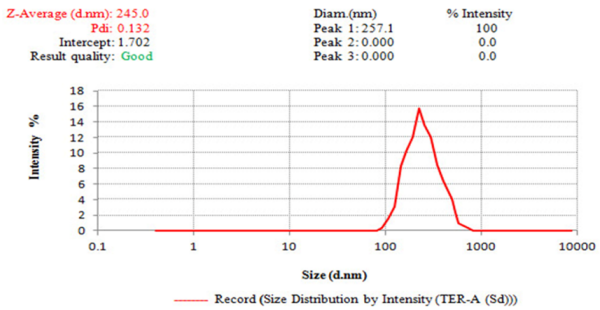

Figure 15: Size distribution by intensity (TER-A(SD))

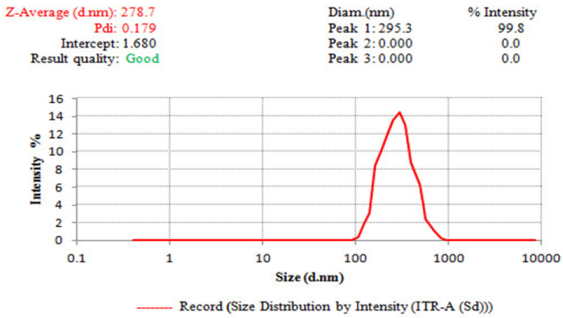

Figure 16: Size distribution by intensity (ITR-A(SD))

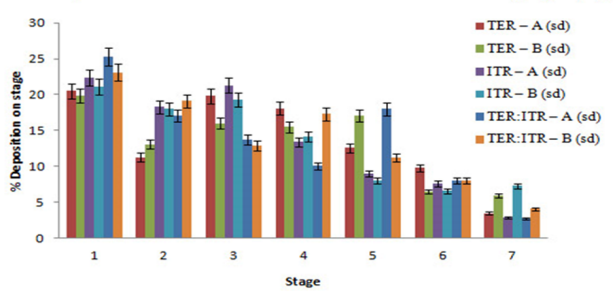

Figure 17: Dispersion Performance of Terbutaline Sulphate and Itraconazole Mixtures (Spray Drying)

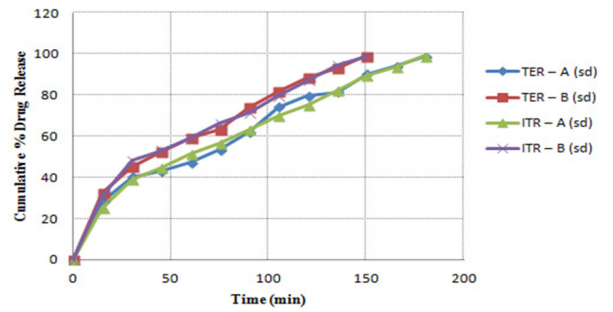

Figure 18: In-vitro Drug Release of Terbutaline Sulphate and Itraconazole nanoparticles (Spray Drying)

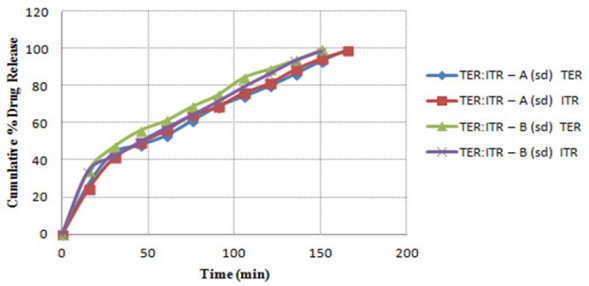

Figure 19: In-vitro Drug Release of Terbutaline Sulphate and Itraconazole nanoparticles incombination (Spray Drying)

ure 19.

CONCLUSIONS

Demanding tasks in formulating dry powder nanoparticles is achieving the respirable particle size that avoids the physical limitations of the general stroke and delivering the synergist to a powerful target site. From the results obtained, it was evident that the prepared formulations can be prepared as DPIs that releases the drug directly into the lung efficiently for the acupressure going from asthma. Spray drying was found to be the best method suitable for the readying containing dry powder nanoparticles when compared to physical mixing of milled drug and excipients. Combination foams could provide coeval delivery to the synoptical computer epithetical legal action maximizing the capability outcome in reference to the medicinal drugs.

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