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RESEARCH ARTICLE

Evaluation of Terbutaline Sulphate and Itraconazole Nanoparticle Formulation as Dry Powder Inhalers for the Treatment of Asthma

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ABSTRACT

In this study, new formulations of nanoparticles like dispersed liquid dosage forms (metered dose inhalers and nebulizers) or dry powders was found to be the best formulations for the treatment of pulmonary disorders [6]. Nanoparticles as drug carrier may reduce the toxicity of the incorporated drug. Nanoparticles in the treatment of pulmonary disorders gained much importance due to its unique features like surface to mass ratio, ability to absorb, creates a large surface area to carry various compounds [8]. The prepared formulations can be formulated as DPIs that releases the drug directly into the lung efficiently for the treatment of asthma. The formulations (TBS – A (sd), ITZ – A (sd), TBS: ITZ – A (sd)) were the best formulations based on MMAD values and *in-vitro* dissolution. Combination powders TBS: ITZ – A (sd) may provide simultaneous delivery to the same site of action increasing the potential effect of the drugs. The study compared different DPI formulations of Terbutaline sulphate and Itraconazole in single and combined formulation to analyze the in-vivo distribution characteristics and stability. Combination powders may provide simultaneous delivery to the same site of action increasing the potential effect of the drugs. The powders reported here offer a novel formulation for localizing potent drugs as single agents or in combination for the treatment of asthma.

Keywords: Terbutaline sulphate, Itraconazole, Nanoparticles, asthma

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1. Introduction

Terbutaline Sulfate: Terbutaline sulphate is a beta adrenergic agonist bronchodilator available as a sterile, non pyrogenic, aqueous solution in vials, for subcutaneous administration. β2 adrenergic receptor agonist, used as a reliever inhaler in the management of asthma symptoms and as a tocolytic (anti-contraction medication) to delay preterm labor for up to 48 hours. This time can then be used to administer steroid injections to the mother which help fetal lung maturity and reduce complications of prematurity [103-105].

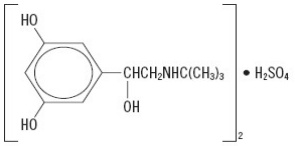


Figure 1

IUPAC Name: (±)-α-[(tert-butylamino) methyl]-3,5-dihydroxybenzyl alcohol sulfate. The molecular formula is (C12H19NO3)2, Terbutaline sulfate, is a white to gray-white crystalline powder. It is odorless or has a faint odor of acetic acid. It is soluble in water and in 0.1N hydrochloric acid, slightly soluble in methanol, and insoluble in chloroform. Its molecular weight is 548.65.

Itraconazole

Itraconazole is a synthetic triazole antifungal agent for oral use. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature

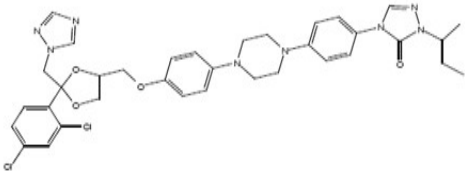
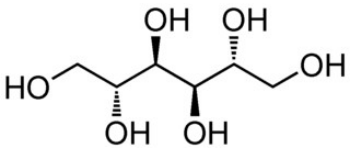


Figure 2

IUPAC Name: (±)-cis-4-[4-[4-[4[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-yl] methoxy] phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one. Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane [110-112].

Excipients

D-Mannitol



Nonproprietary Names: BP: Mannitol JP: D-Mannitol PhEur: Mannitol USP–NF: Mannitol

Synonyms: Compressol; Cordycepic acid

Chemical Name: (2R,3R,4R,5R)-1,2,3,4,5,6-Hexanehexol

Empirical Formula and Molecular Weight: $C_6H_{14}O_6$and 182.172

Functional category: Lyophilization aidplasticizing agent; sweetening agent; tablet and capsule diluent; tonicity agent.

Applications in pharmaceutical industry:

Mannitol is a polyol (sugar alcohol) and an isomer of sorbitol. Mannitol (C6H8(OH)6) is used in pharmaceutical products as a sweeting agent, tablet and capsule diluent, excipient for chewable tablets, a tonicity agent, and as a vehicle (bulking agent) for lyophilized preparations. Mannitol is industrially derived from the sugar fructose, and is roughly half as sweet as sucrose. Mannitol has a cooling effect often used to mask bitter tastes, and may be used in gums and candies.

Description:

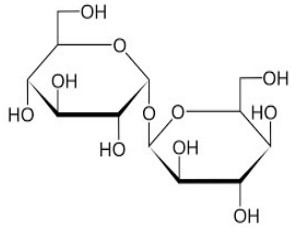
Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

Density: 1.514 g/cm3

Bulk density: 0.430 g/cm3, **Tapped density:** 0.734g/cm3,

Melting point: 166-168 °C.

Trehalose



Non-proprietary Names: Trehalose; D-Trehalose; Alpha, alpha-trehalose; Mycose;

Chemical Name: alpha-D-gluco-hexopyranosyl alpha-D gluco hexopyranoside

Empirical Formula and Molecular Weight: $C_{12}H_{22}O_{11}$. and 342.297 g/mol

Functional category: Diluents

Applications in pharmaceutical industry:

Trehalose has wide application in food products utilizing its unique properties of stability to heat and acid and non-reducing feature. Trehalose protects phospholipids, proteins and gells from damage by freezing and drying. This characteristic providing excellent restitution from freezing and drying is expected to increase its utilization in frozen and dry food products containing eggs and ground fish meat. Trehalose also suppresses unfavorable and bitter/astringent taste, and this distinction of trehalose, known as a masking effect, is a great help to improve quality of taste of food products.

Description:

White to off-white crystalline particles or powder. Trehalose is odorless and slightly sweet taste;

Density: 1.58 g/cm^3 at 24 °C,

Bulk density: 0.60 g/cm3, **Tapped density:** 0.92 g/cm3,

Melting point: 203 °C.

2. Materials and Methods

Development of standard curve of Terbutaline Sulphate [116]: An accurately weighed quantity of 100mg of Terbutaline sulphate was taken in a 100ml standard flask. To this equal volume of distilled water was added to standard flask and made up to the volume (Stock).From the standard stock 1,2,3,4,5,6,7,8,9,10ml was taken in a separate 100ml standard flask and the dilutions were made up to the volume using equal volume of distilled water to get 10,20,30,40,50,60,70,80,90,100µg/ml and these samples were analyzed by using UV spectroscopy at a wave length of 276nm.

Development of standard curve of Itraconazole [117]: An accurately weighed quantity of 50 mg of Itraconazole was taken in a 50ml standard flask. To this equal volume of methanol was added to standard flask and made up to the volume (Stock).From the standard stock 2,4,6,8,10ml was taken in a separate 100ml standard flask and the dilutions were made up to the volume using equal volume of methanol to get 20,40,60,80,100µg/ml and these samples were analyzed by using UV spectroscopy at a wave length of 264nm.

Formulation of Terbutaline sulphate & Itraconazole by Milling Method: 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 3 Hrs for nanosized particles and for 2 hours for fine particles. The 50mg: 2.5g terbutaline: carrier, 5 gm: 5 gm itraconazole: carrier, 50/5000mg: 7.5 gm 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. Formulations were shown in table 2. 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.

Table 1: List of Materials used

S.No	Materials	Gift sample/ Procured from
1	Terbutaline sulphate	Drugs India, Hyderabad
2	Itraconazole	Drugs India, Hyderabad
3	Lactose	Drugs India, Hyderabad
4	Trehalose	Drugs India, Hyderabad
5	Methanol	New Himalaya Scientific Company, Nellore
6	Sodium phosphate dibasic	New Himalaya Scientific Company, Nellore
7	Sodium hydroxide	New Himalaya Scientific Company, Nellore
8	Potassium phosphate monobasic	New Himalaya Scientific Company, Nellore

Table 2: Standard limits of angle of repose

S.No	Angle of repose	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Table 3: Standard limits of Carr's index

S.No	Carr'sindex (%)	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to Passable
4	23-35	Poor
5	35-38	Very poor
6	>40	Extremely poor

Table 4: 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)

3. Results and Discussion

Table 5: 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 6: 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^{0}c	166-170^0 c

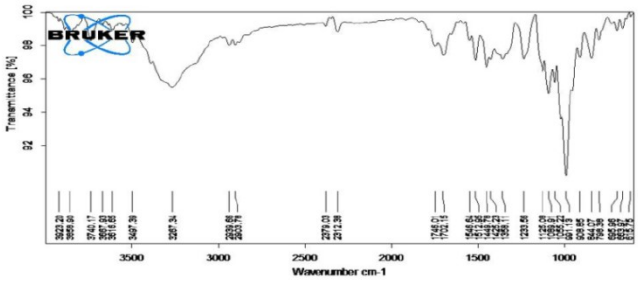


Fig 1: IR Spectrum - Terbutaline Sulphate

Table 7

Frequency (cm^{-1})	Bond/Functional 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

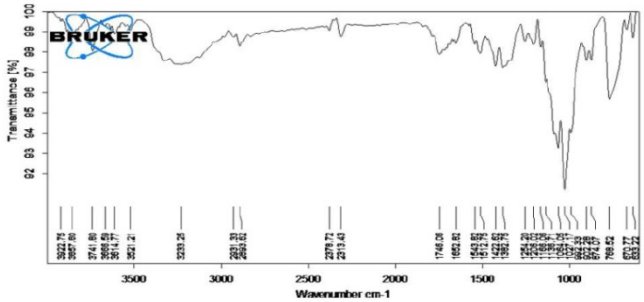


Fig 2: IR Spectrum - Terbutaline+ D-Mannitol

Table 8

Frequency (cm^{-1})	Bond/Functional 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

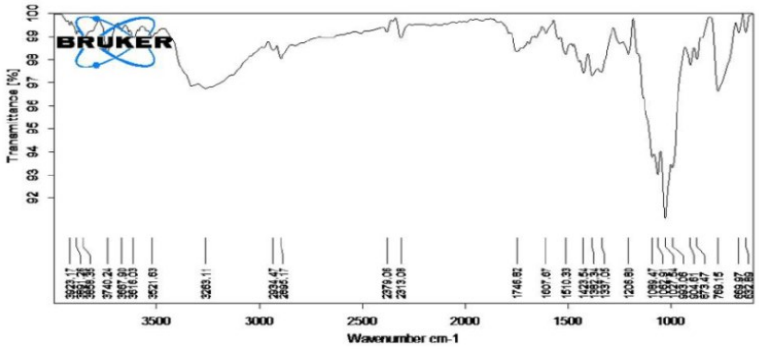


Fig 3: IR Spectrum - Terbutaline sulphate+Trehalose

Table 9

Frequency (cm^{-1})	Bond/ Funtional Group
1745	C=O
1607	C=C ring stretching
1607 and 1423	C-H bending of CH3 and CH2 group
1205	O-H bending
904	Substituted Phenyl ring
3300-3521	Broad Peak of OH and NH hydrogen bond
3263	Hydroxyl groups and Aromatic C-H stretching

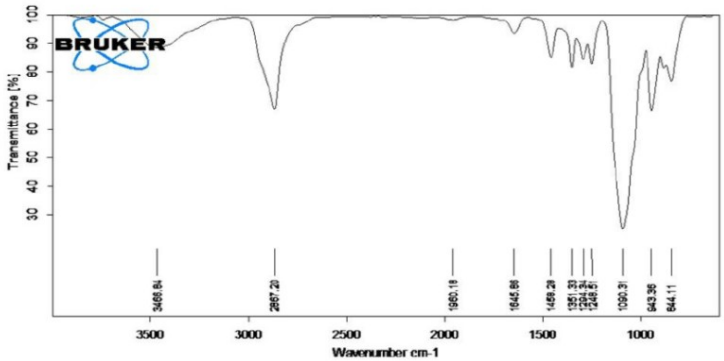


Fig 4: IR Spectrum – Itraconazole

Table 10

Frequency (cm^{-1})	Bond/Funtional Group
1645	C=O
1458	C=C ring stretching
3466	N-N or N=N
1090	C-O
1458	C-N Stretch

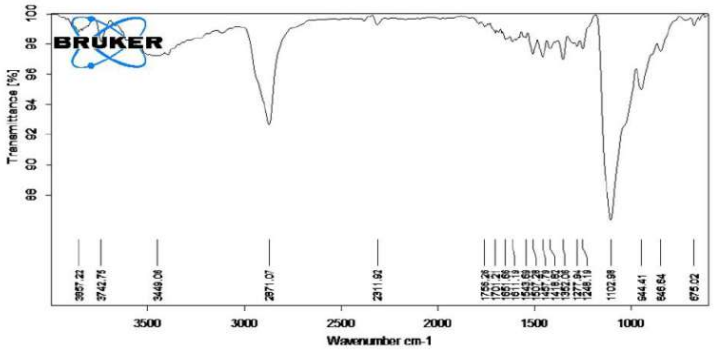


Fig 5: IR Spectrum - Itraconazole+ D-Mannitol

Table 11

Frequency (cm^{-1})	Bond/Funtional Group
1651	C=O
1457	C=C ring stretching
3449	N-N or N=N
1090	C-O
1458	C-N Stretch
1248	O-H bending
2971	Aromatic C-H stretching

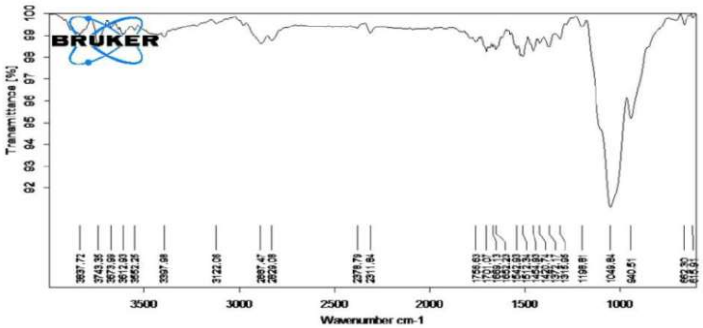


Fig 6: IR Spectrum – Itraconazole + Trehalose

Table 12

Frequency (cm^{-1})	Bond/ Funtional Group
1652	C=O
1420	C=C ring stretching
3397	N-N or N=N
1049	C-O
1454	C-N Stretch
1315	O-H bending
2997	Aromatic C-H stretching

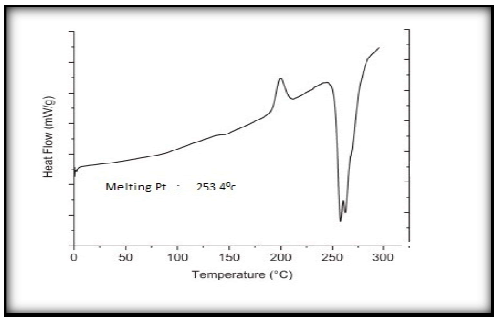


Fig 7: Differential Scanning Calorimetry Terbutaline Sulphate

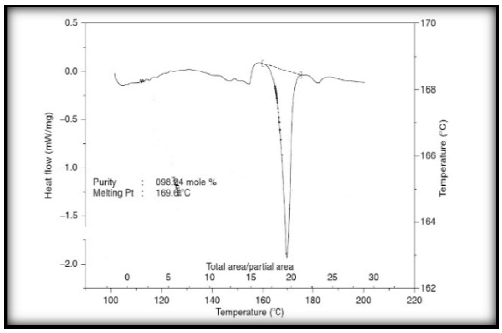


Fig 8: Differential Scanning Calorimetry Itraconazole

Table 13: Calibration Curve: Terbutaline Sulphate

S. No	Concentration(µg /ml)	Absorbance
1	10	0.076
2	20	0.152
3	30	0.228
4	40	0.305
5	50	0.398
6	60	0.420
7	70	0.525
8	80	0.611
9	90	0.667
10	100	0.734

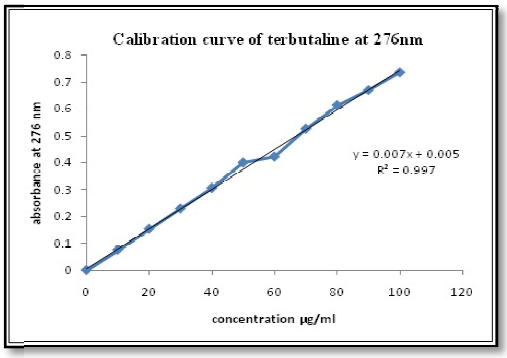


Fig 9

Table 14: **Calibration Curve: Itraconazole**

S. No	Concentration(µg /ml)	Absorbance
1	20	0.045
2	40	0.098
3	60	0.163
4	80	0.232
5	100	0.321

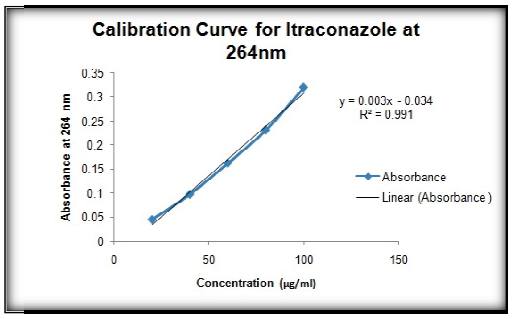


Fig 10

Table 15: Flow Properties

Property	Terbutaline Sulphate	Itraconazole
Bulk Density	0.48 gm/cm^3	0.24 gm/cm^3
Tapped Density	0.62 gm/cm^3	0.32 gm/cm^3
Angle of Repose	$26^0 .5^1$	$36^0 .1^1$
Hausner's Ratio	1.29	1.32
Carr's index	22.5 %	24.4 %

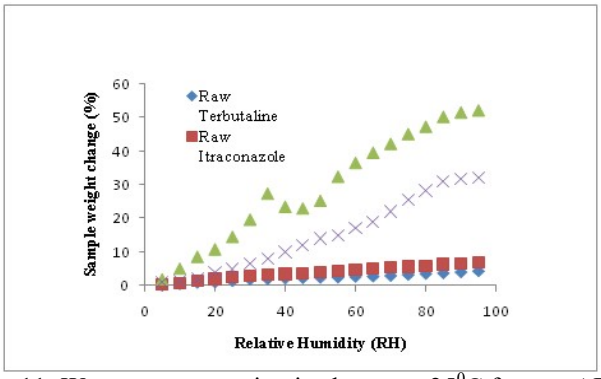


Fig 11: Water vapor sorption isotherms at 25^{0}C for raw API vs. milled

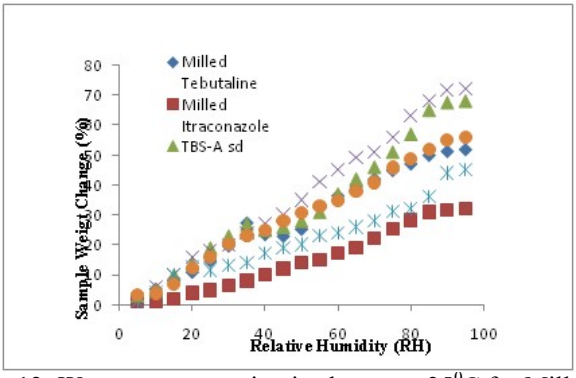


Fig 12: Water vapor sorption isotherms at 25^{0}C for Milled API vs. Spray Dried Formulations

Table 15: 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

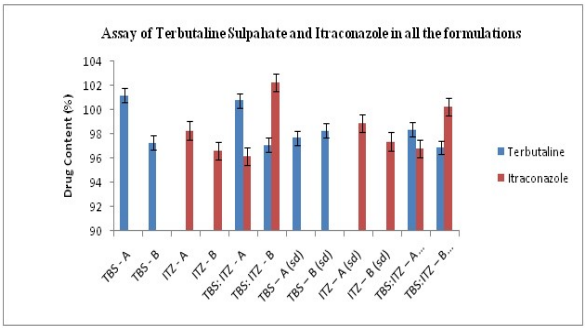


Fig 13: Assay of Terbutaline Sulpahate and Itraconazole in all the formulations

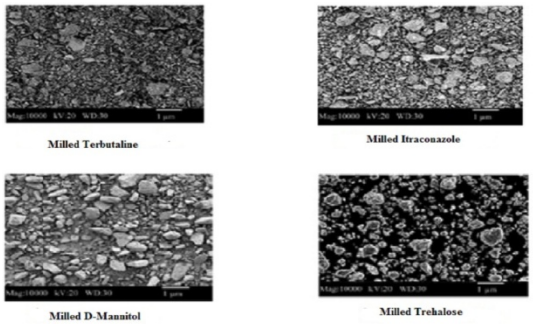


Fig 14: SEM of Milled drug and Milled Excipients

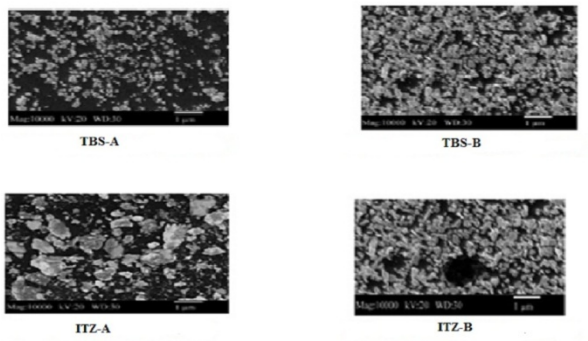


Fig 15: SEM of Milled formulations

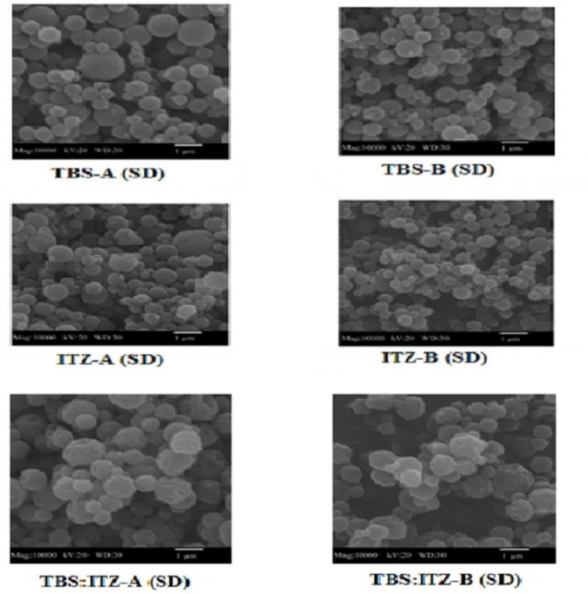


Fig 16: SEM of Spray dried formulations

Post formulation:

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. 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.

Moisture Content:

Moisture content for raw drugs and formulations was done by Karl Fisher titration. The residual water content for raw terbutaline and raw itraconazole was found to be 4.41±0.18 and 7.62±0.11 respectively. Moisture content of all the formulations prepared by milling and spray drying was decreased when compared to the raw drugs which may be due to the presence of D-manitol and trehalose in all the formulations. Moisture content of formulations prepared by milling ranges from 3.80±0.44 to 4.32±0.16. Formulations (Physical mixing) containing the combination drugs showed slight increase which may be due to the presence of itraconazole (Fluffy Powder). Formulations prepared by spray drying 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.

Percentage Yield and Drug Content:

Spray dried formulation showed less percentage yield (ranges from 77.50–88.75) when compared to milled formulations (ranges from 98.04 – 99.40). Less percentage yield for spray dried formulations when compared to milling may be due to the conditions used in the spray drying process. Drug content of all the formulations was found to be within the limits (96.2±0.14 - 101.2±0.31).

Scanning Electron Microscopy:

The particle morphology and surface morphology of all powders were visualized via SEM. The particle size of raw material for each sample was far beyond the maximum respiratory size for dry powder inhalation (DPI) to the lungs. Smooth and nearly spherical particles were produced for spray dried formulations. Formulations prepared through milling was found to have rough and irregular in shape.

Particle sizing and Size distribution:

The primary particle sizing and size distribution data of milled and spray dried particles of terbutaline and itraconazole are summarized in Table. All formulations had

unimodal size distributions. The formulations prepared with trehalose as carrier showed less D_{v90}, D_{v50} and D_{v10} values due to the fineness in the particles of trehalose when compared to D-mannitol. The D_{v50} values were in the range of 0.43-0.67 µm for all formulations. The D_{v10} values were in the range of 0.21–0.38 µm. Hence, the majority of solid-state particles had a primary particle size

Stability studies:

Stability studies were conducted for best formulations (TBS – A (sd), ITZ – A (sd), TBS:ITZ– A (sd)) according to ICH guidelines for Drug content and In-Vitro dispersion performance for 12 months as accelerated, intermediate and long term studies. From the results it was found that, drug content was decreased over 2% within 6 months when the formulations was stored at 40 ± 2^0Cand 75% ± 5% RH (Batch – 1). Drug content decreased partially when the formulations were stored at 30 ± 2^0C and 65% ± 5%RH, 25 ± 2^0C and 60% ± 5%RH (Batch – 2 and 3). The decrease in drug content for batch -1 may be due to accelerated stress of high temperature and relative humidity.

The results were shown in table. The aerosol dispersion properties of best formulations were evaluated using the Cascade Impactor coupled with a Rotahaler DPI device. The MMAD values ranged from 3.45 µm to 4.21 µm whereas the GSD values were 1.85–2.83 µm during normal conditions. The MMAD and GSD values were increased (from 4.67 µm to 6.32 µm whereas the GSD values were 2.24 –3.48 µm) on stress conditions during accelerated, intermediate and long term stability studies. The results were shown in table 5.28 – 5.29 and fig 5.40-5.42. Aerosol deposition on each stage is measurable and in particular, deposition on the lower stages of stage 2 all the way to stage 7 (the lowest stage) is observed. The % deposition on stage 1 increased for (Batch -1) when compared to other batches. Due to this the particles may deposit predominantly in the middle lung regions by sedimentation.

4. Conclusion

From the results it was evident that, the prepared formulations can be formulated as DPIs that releases the drug directly into the lung efficiently for the treatment of asthma. The formulations (TBS – A (sd), ITZ – A (sd), TBS: ITZ – A (sd)) were the best formulations based on MMAD values and *in-vitro* dissolution. Combination powders TBS: ITZ – A (sd)may provide simultaneous delivery to the same site of action increasing the potential effect of the drugs. The study compared different DPI formulations of Terbutaline sulphate and Itraconazole in single and combined formulation to analyse the in-vivo distribution characteristics and stability. Results conclude that, spray drying method is best suitable for the preparation of dry powder nanoparticles when compared to physical mixing of milled drug and excipients. Combination powders may provide simultaneous delivery to the same site of action increasing the potential effect of the drugs. The powders reported here offer a novel formulation for localizing potent drugs as single agents or in combination for the treatment of asthma.

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