

GENERAL REVIEW ON DRY POWDER INHALER FOR BRONCHODILATION IN PULMONARY DISEASE LIKE ASTHMA & COPD

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Abbreviation used-

COPD- Chronic obstructive pulmonary disease

AHR- Airway hyperactivity

DPIs- Dry powder inhalers

FDC- Fixed-dose combination

LABA- Long-acting b2 agonist

LAMA- Long-acting muscarinic antagonist

pMDI- Pressurized metered-dose inhaler

SABA- Short-acting b2 agonist

SAMA- Short-acting muscarinic antagonist

CFC- Chloro-fluorocarbon

HFC- Hydrofluorocarbon

Key word used:

Asthma, Dry Powder Inhalers, Nebulisers, Bronchodilation.

ABSTRACT

This article discussed the brief about the asthma pathophysiology, The working principle of DPIs and its mechanism of action. Inhalers have been developed because of difficulty of using the conventional metered dose inhaler (MDI) and because of the impending ban on CFC's. DPIs in general are easier to use than the MDI and cause fewer irritant effects. DPIs contain micronized drug which is <5µm in diameter. Unlike the MDI few patients develop a poor inhalation technique with continued use of DPI's. A report says the annual cost of treatment of asthma is more than 6 billion dollars per year in the United States of America, and the worldwide market for asthma medication is currently valued at 5.5 billion dollars each year. In this review paper the major discussion on asthma etiology, classification of drug used to treat asthma and brief on how DPIs works, marked product advantages over others.

INTRODUCTION

Pulmonary disease such as Asthma is a chronic respiratory disorder that can characterized by inflammation of air and obstruction in reversible airflow, (AHR) persistent airway hyperreactivity, and airway remodelling (1). An estimate has made i.e. approx. 15 million American citizens were affected by asthma and the mortality and morbidity associated with and it is mostly seen in increase in industrialized nations (2, 3). Unproportionately in morbidity is high among inner-city residents in America (4).

According to a report the annual cost of treatment of asthma is more than 6 billion dollars per year in the United States of America, and the worldwide market for asthma medication is currently valued at 5.5 billion dollars each year (5). It has been approximately 50 year of Dry Powder Inhalers (DPIs) available for commercially use

that is in early 1970s. The prototype was described earlier several decades before. So, basically the Dry Powder Inhalers (DPIs) is a device through which medication delivers to the lungs and the physical state is itself a dry powder. DPIs contain micronized drug which is $<5\mu\text{m}$ in diameter. And carrier mostly used is Lactose which is used in most of the formulation due to its excellent flow property. The role of the device is to disperse the powder and ensure some concentration should reach to the lungs.

ETIOLOGY

The asthma's etiology is multifactorial, also, very complex and involve interaction in between numerous environmental stimuli and genetic factor. Most of the data about the pathogenesis of asthma has concentrated on atopic(allergic) asthma and the unproportionate level between the Th-1 which also called as cell-mediated immunity and Th-2 also known as humorally mediated immunity phenotypes. However, asthma may also occur via nonallergic mechanism of inflammation. Genetically, uterine environment, infant diet respiratory infections, environmental exposures, and occupational exposure, all contribute to this in proper balance. The manner in which all these factors merge will determine whether the reaction of an individual subject's immune system resulting in airway remodeling and airway inflammation. A superabundance of factors that is favoring Th-2 phenotype may eventually lead to atopy (allergy). Although the Th-1/Th-2 balance providing the framework within which to understand the immune events that promote bronchial hyperreactivity and airway inflammation, this construct is clearly over simplified. The demonstrated figure below which cell is involved in the inflammation and the receptor which is affected during the asthmatic condition.

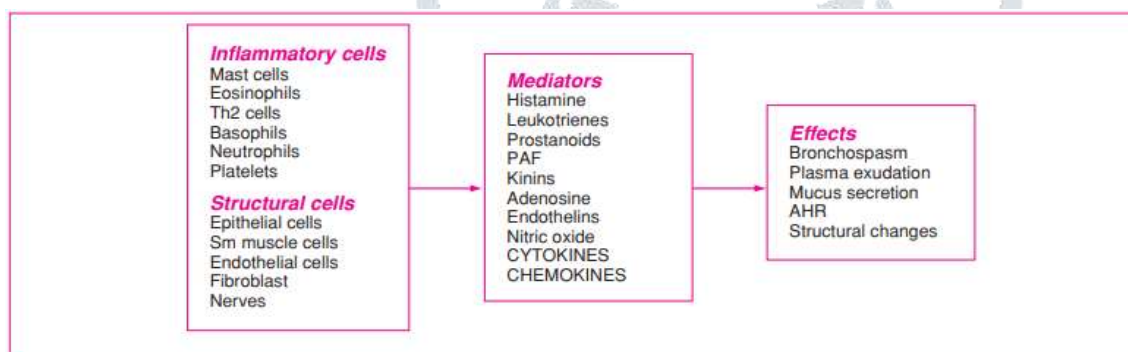


Fig. Many cells and mediators are involved in asthma and lead to several effects on the airways.(8)

Genetics

Classic Mendelian pattern for inheritance is not applicable to asthma but there is little bit of doubt that inheritance play an important role in asthma (9–12). Historically in 1860 familial aggregation for asthma was recognized (13).

DRUG CLASSIFICATION USED TO TREAT ASTHMA

There are class of drug used to treat asthma. Depending on the mode it is available in various formulation i.e for oral route, parenteral route or whether the route is inhalation. The medication available in market is in combination also depends upon the severity of the disease for example-Tablets, Capsules, I.V injections, Aerosol preparation, Nebulised based preparation, dry powder inhalers etc. And all forms of drug have their own advantages.

Table: Classification of drug

Function	Class	Examples
Bronchodilators	β -agonists	*(SABAs):albuterol,terbutaline, levalbuterol *(LABAs): salmeterol, formoterol
	Methylxanthines	Theophylline
	Muscarinic antagonists	*(SAMA):ipratropium*(LAMA): tiotropium
Anti-inflammatory agents	Mast cell degranulation inhibitors (chromones)	Cromolyn, nedocromil
	Antibodies	*Against IgE: omalizumab *Against interleukin (IL)-5: mepolizumab *Against IL-4 receptor: dupilumab *Against IL-5 receptor: benralizumab
Antileukotriene agents	Corticosteroids (CS)	Beclomethasone Budesonide,Flunisolide, Mometasone,Prednisone, Methylprednisolone
	Lipoxygenase inhibitors	Zileuton
	Leukotriene antagonists	Montelukast, zafirlukast

Beta2-adrenergic agonist agents

The beta2-agonist is most common in used for bronchodilator , and available in different form (e.g., metered-dose inhaler, solution for nebulization,and oral solution). It is most used in rescue therapy for symptoms of acute asthma and is used as needed and prescribed by physician. Tachyphylaxis may associates with prolong use and it is due to beta2-receptor down-regulation and hyposensitivity of receptors.

Types and administration**SABA:**

- Albuterol (inhalation, oral)
- Levalbuterol (inhalation)
- Terbutaline (oral, intravenous (IV))

LABA:

- Salmeterol, Vilanterol, Formoterol (inhalation)

Mechanism of action and effects

- They bind on the β -2 receptor.
- Effect: stimulates the cAMP in smooth muscle cells \rightarrow smooth muscle relaxation \rightarrow dilation of bronchioles
- **LABA:** duration up to 12 hours
- **SABA:** duration up to 4–6 hours and onset of action is within 5 minutes

Clinical uses**SABA:**

- Rapid action bronchodilator, it is used in acute asthma exacerbation of asthma.
- Oral form not recommended for acute exacerbation because it has longer onset of action, less effective bronchodilation.

LABA:

- Not recommended for monotherapy so the use is only with inhaled corticosteroids.
- Combined inhaled corticosteroids and LABA (low-dose inhaled CS-formoterol): can be used against acute symptom (Global Initiative for Asthma guidelines)
- Used during exercise- prevention of nocturnal symptoms and induce bronchoconstriction

Side effects

- The most common side effect is β 2-mediated skeletal muscle tremors
- Other effects are:

Tachycardia (cardiac β receptor stimulation),
Hypokalaemia,Hyperglycemia

Precautions

- Use is caution in CVS (arrhythmia, heart failure, coronary artery disease).
- May elevate intraocular pressure in glaucoma
- May increase glucose in diabetics

Muscarinic Antagonists

Types and administration

- SAMA: ipratropium bromide (inhalation)
- LAMA: tiotropium bromide (inhalation)

Mechanism of action and effects

- It competitively block muscarinic receptors, thereby preventing vagal-induced bronchoconstriction
- \downarrow cyclic (cGMP) \rightarrow \downarrow mucus secretion and \downarrow smooth muscle contraction.

Clinical uses

- Less effective than β 2-agonists for acute exacerbation.
- Long-term maintenance treatment in children $>$ 6 years of age and adults with severe symptomatic asthma uncontrolled with inhaled CS
- Also used in COPD

Side effects

*Minor atropine-like effects with high doses

*Few systemic effects because of poor absorption into the circulation

Precautions

*Use is caution in patient having glaucoma with narrow-angle (can increase intraocular pressure).

*Bladder neck obstruction/prostatic hyperplasia (may cause urinary retention)

Corticosteroids

Types and administration

- Inhaled corticosteroids (ICS): beclomethasone, budesonide, fluticasone, mometasone, triamcinolone
- Systemic corticosteroids:
- Oral CS: prednisone, prednisolone
- IV CS: hydrocortisone, methylprednisolone

Mechanism of action and effects

- Blocks the release of arachidonic acid (via phospholipase A2 inhibition), consequently halting the release of inflammatory mediators
- Effects:
- \downarrow airway hyperresponsiveness
- \downarrow airway mucosal edema
- \downarrow capillary permeability
- \downarrow leukotriene release

Clinical uses

- ICS: generally, the **most effective** anti-inflammatory agent for the treatment of asthma
- Drug of choice for long-term control of persistent asthma
- Short-term oral CS treatment ($<$ 7 days) of acute severe exacerbations
- Tapering required if oral CS $>$ 2 weeks

Side effects

- ICS:
- Less severe and fewer than those of systemic CS
- Local effects:
- Dysphonia: less common with devices that produce smaller-sized particles
- Thrush: can be avoided by a large-volume spacer with metered-dose inhalers (MDIs); rinsing of the oropharynx and spacer after inhalation also helps
- Much less common:
- Deceleration of growth velocity in children
- Adrenal suppression
- Cataracts
- Systemic CS side effects: adrenal suppression, weight gain, diabetes, hypertension, immune suppression, osteoporosis, and depression

Antileukotriene Agents**Types and administration**

- Leukotriene receptor antagonists (LTRAs): zafirlukast, montelukast (oral)
- 5-lipoxygenase inhibitor: zileuton (oral)

Mechanism of action and effects

- Zileuton: selective inhibition of 5-lipoxygenase (thus preventing conversion of arachidonic acid to leukotrienes)
- Zafirlukast and montelukast: inhibit leukotriene (LT)-D₄ receptors and LTE₄ receptors
- Effects (by targeting leukotriene):
- ↓ vascular permeability and mucus secretion
- ↓ smooth airway contraction
- Reduced activation of inflammatory cells

Clinical uses

- Exercise-induced bronchospasm
- Mild persistent asthma + allergic rhinitis
- Asthma and aspirin-exacerbated respiratory disease
- Additive benefit for moderate-to-severe persistent asthma
- Considered in patients with difficulty with compliance or inhaler technique (e.g., children)

Side effects

- Common: fatigue, headaches, dyspepsia
- Neuropsychiatric adverse effects: changes in behavior and mood (especially for montelukast)
- Zafirlukast and zileuton:
- Potentially hepatotoxic, which requires liver function test monitoring
- Drug interactions (including increased warfarin effect)
- Eosinophilic granulomatous polyangiitis can develop when antileukotrienes are given to patients with steroid-dependent asthma.

Precautions

- Zafirlukast and zileuton:
- Contraindicated in liver disease/hepatic impairment
- Monitor for mood and behavioral changes

Montelukast:

- Monitor for mood and behavioral changes
- Contains phenylalanine (not recommended for patients with phenylketonuria)

Clinical Relevance

Asthma medications are also used for the following conditions:

- Chronic obstructive pulmonary disease (COPD): a common chronic disease of the airways characterized by airflow limitation. Obstructive inflammation is noted in the small airways, lung parenchyma, and pulmonary vasculature. Patients usually present with dyspnea and chronic cough. Bronchodilators and corticosteroids are part of the regimen for treating COPD.
- Eosinophilic granulomatous polyangiitis (EGPA): vasculitis characterized by necrotizing granulomas, eosinophilia, and eosinophilic tissue infiltration. The vasculitis affects small- and medium-sized arteries. Multiple organs can be affected, including the pulmonary, renal, gastrointestinal, cardiovascular, and nervous system. Among the treatments is mepolizumab.
- Allergic rhinitis: a condition characterized by rhinorrhea, sneezing, and itching of nose, eyes, and palate. Allergens trigger an allergic nasal response where nasal mast cells release histamine and other mediators. Corticosteroid nasal sprays are commonly prescribed. Other less-used therapies available include cromolyn nasal spray, ipratropium nasal spray, and montelukast.

DRY POWDER INHALERS (DPIs)

Inhalable drug delivery medication for patients with COPD and asthma may confuses for patient and physician alike. The right one is difficult to choose from different sheer varieties of devices. But in all the type which is available in current generation, the one which has been proved highly valuable and much efficient for approximately all age group of patient with COPD or asthma is DPIs.

In an article which is in recent published journal for Advances in Therapy, where all the researchers were discuss how DPIs work, what makes them stand in the region of science, and what patients and prescribers should look in any device. (24)

The active drug in DPIs is composition of microparticles loaded onto larger carrier particles, which came back to the throat and let the active drug go inside the lungs. The unique design of DPIs convert inhalation into forces that deagglomerate the drug with carriers.

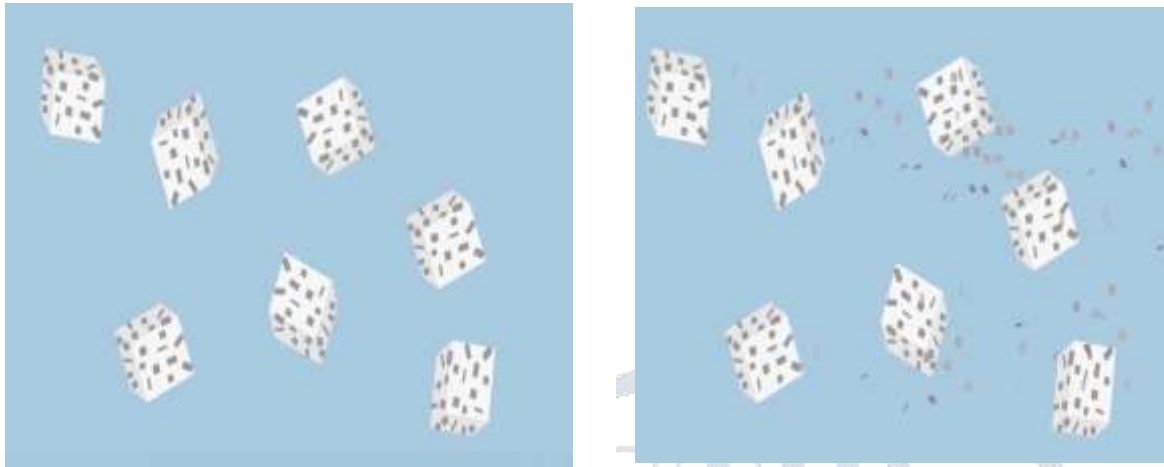


Fig- a representation that how the drug microparticle is binded with the carrier system and its release (23)

The particles of drug transported deep inside the lungs, and the larger carrier cling back to the throat and at the end swallowed there.

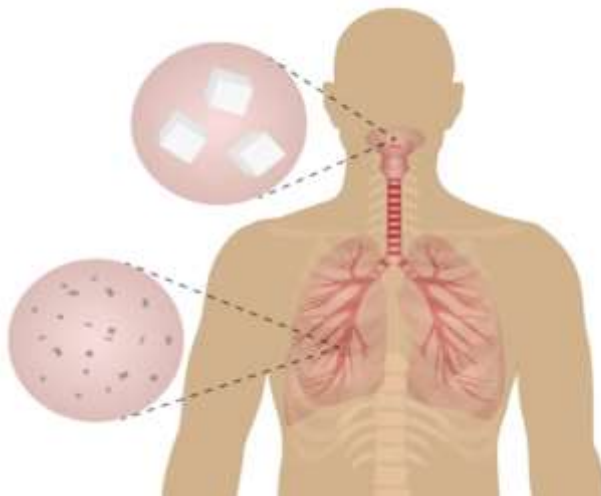
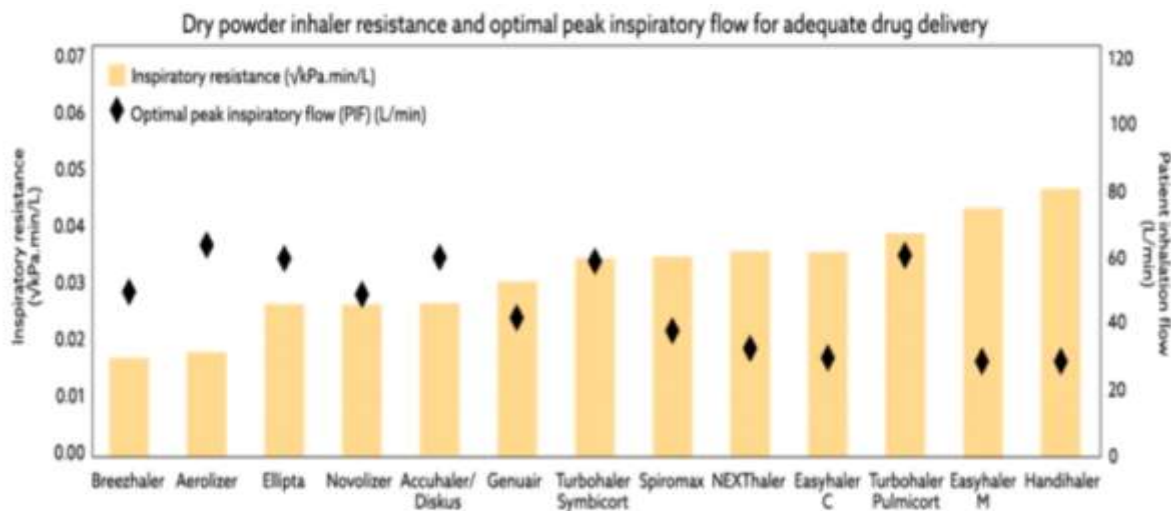


Fig-representationon how drug particle transported into lungs whereas the carrier cling back to throat

Dry powder inhalers do not requires propellants ,that are harmful to the atmosphere, such as CFC and HFC. Instead, the patient's breath is all that's required for activation.

Choosing the right from no of DPIs for patients never been easy.IN 2020 Preference is key so, nothing makes any sense if there is no preference given by the patient himself , because at the end that will determine patient adherence and treatmentnt sucess with DPIs. A graphical representation given below stated how different devices for dry powder specifically have different optimal inspiratory flow



Graph plotted on scale x-axis=optimal peak inspiratory flow in (L/min) Vs Y-axis=inspiratory resistance (kPa min/L) (24)

DPIs are of 3 types :

- 1-Unit-doses device system
- 2-Multi-unit doses device system
- 3-Reservoir device system

Unit-doses device system - In Unit-doses device system in a gelatin capsule or blister only single drug is present, and loaded by the patient immediately before use.

Multi-unit doses device system- In multi-unit doses device system there are series of capsule and blisters present.

Reservoir device system - In Reservoir device system the powdered drug is metered by the patient themself before inhalation from storage.

DIFFERENT TYPE OF DPIs: There are different DPIs available in market with different working mechanisms for treatment of Bronchial Asthma, COPD, as well as other respiratory diseases.

DPIs been classified into three throughout based on their use they are:

- The active device
- The breath-activated multi-dose
- The breath-activated single-dose

As the name indicating single dose device can only be used only once whereas the multi dose device can be re-use in which the drug can be loaded before administration by the patient themselves. The examples of the above stated belonging to each category are present in figure (2).

DPIs available in Market	Manufacturer	Available in form of
*ELIPTA	GLAXOSMITHKLINE	Strip pack
*TURBOHALER	ASTRAZENECA	Reservior
*EASYHALER	ORION PHARMA	Reservior
*EXUBERA	NEXTAR THERAPEUTICS PFIZER	Blister/air
*TAPER(3M)		Hammer impact
*CYLOHALER		Capsule
*SPINHALER		Capsule
*ACCUHALER	GLAXOSMITHKLINE	Strip pack

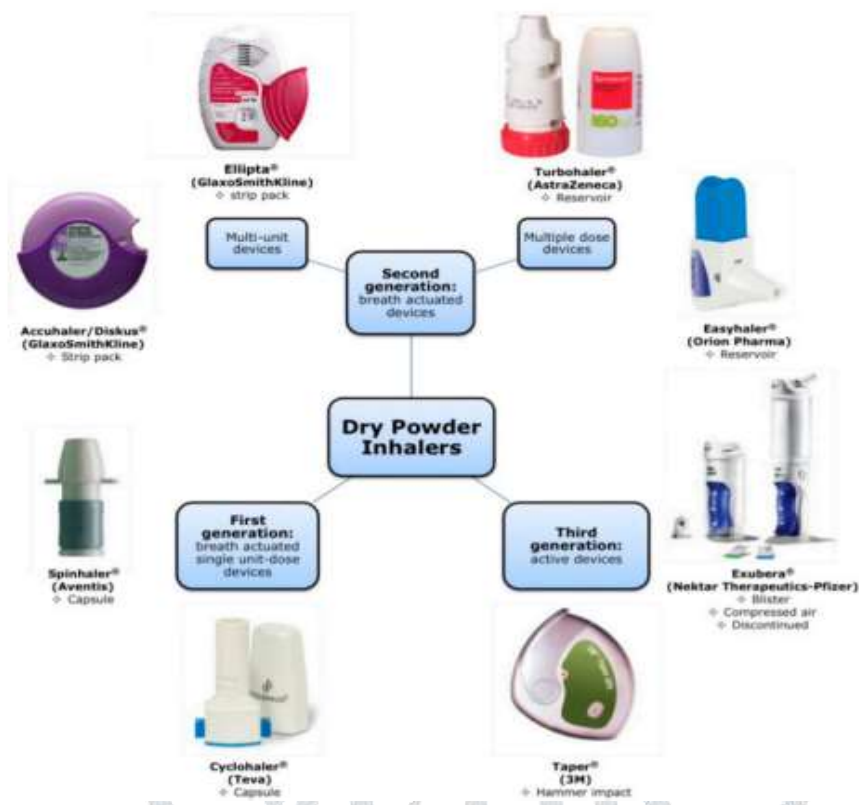


Figure-Types of dry powder inhalers (DPIs). Reproduced, with permission, from reference(7)

DEVICE:

DPI are free flowing drug powder formulation of drug which is prepared via micronization or spray drying technique of a blend consists of drug and an inert carrier Lactose (6), which is suitable for the formulation. In a result the drug should pharmacologically act locally in the upper respiratory tract or deep inside the lungs. The drug formulation delivered via a DPI device, DPI devices consist of various models depend on their mechanism as well as the nature of the drug that is, metering system, the DPI formulation, or an actuator. The bulk chamber contains of drug is covered by an over-cap other than that the dust cap is used to cover the mouth piece for the prevention of contamination.

ADVANTAGES OR DISADVANTAGES

Advantages:

- Dry powder inhaler contains powder drug which have special ability to adhering on the mucous membrane inside the lungs.
- Don't need to coordinate pressing the device and breathing in the machine.
- Cheaper than pMDI.
- No need to use a spacer.

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