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A Review on Dry Powder Inhaler

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ABSTRACT

This review focuses on the formulation and development process for dry powder inhalers (DPIs), which use larger carrier particles with micronized medication to improve flow, reduce agglomeration, and facilitate dispersion. The forces of contact and aerodynamic characteristics control fluidization, dispersion, transport to the lungs, and deposition in the peripheral airways. The formulation becomes fluidized when activated, and the drug particles split from the carrier particles and are transported deep into the lungs under inspiratory airflow. Low deposition efficiency may occur due to insufficient shear in the airflow to effectively separate the medication from the carrier particles. The analysis highlights the need for careful evaluation of the powder production process, formulation, and inhaler device for proper delivery of dry powder aerosols to the lung. The article also discusses advancements in high dosage powder pulmonary medication administration and new powder engineering techniques.

Keywords: dry powder inhalers, inhaler devices, micronization, powder formulation, Laser Diffraction

INTRODUCTION

Pharmacologically active medicines have long been delivered to treat respiratory disorders using inhalation medication administration. Pressurized metered-dose inhalers (MDIs) have been the mainstay of traditional asthma therapy, which mostly consists of bronchodilators, steroids, mast cell stabilizers, and anticholinergic medications. The environmental risks associated with chlorofluorocarbon (CFC) propellants are posing an increasing threat to the delivery system. Propeller-free alternatives like as dry powder inhalers are being researched and developed.[1]A wide variety of passive and active single or multiple dose DPI devices are available on the market.[2]Because they allow for direct delivery of medication into the patient's deep lungs by breathing, dry powder inhalers have an advantage over other pulmonary drug delivery techniques and are being investigated more and more for systemic drug delivery.[3] The medicine alone or in combination with a suitable carrier material (usually lactose) can be found in the DPI formulation. To increase flow characteristics and dose homogeneity, medication powders are administered into the deep lung via the dry powder inhaler (DPI).[1,4]It has been determined that lactose is the safest excipient for pulmonary administration. A well-controlled lactose mixture including a large size fraction (40-200 μm) and a fine size fraction (1-40 μm) should be utilized in formulations.[5]DPIs are complex systems whose performance depends on a number of technical factors, the most important of which are to take into account during their design and assessment.

- The aerosol generation process and the duration of the dose-containing aerosol's release are given priority in the inhaler design by the powder de-agglomeration principle.
- The formulation for the inhaler is dry powder.
- It is important to take into account the patient's air flow through the inhaler and the ensuing dynamics of particles and fluids in the respiratory tract.[6]

Advantage of Pulmonary Drug Delivery :[7]

1. The capacity to provide medications directly to the lungs is a benefit of pulmonary drug delivery.
2. Blood flow is not far from the statement.
3. Preventing the first pass hepatic metabolism is the aim.
4. When it comes to other oral routes, fewer doses are needed to provide the same therapeutic impact.

5. The medication acts quickly.
6. When taking various medications at the same time, this technique might be employed as an alternative to drug interactions.
7. This chemical has a localized effect on the respiratory system.
8. There is a lower dosage of the drug given.
9. This technique makes it easier to lessen the production of systemic negative effects.
10. The large alveolar surface area reduces extracellular enzyme levels compared to the gastrointestinal tract.

Disadvantages of Pulmonary Drug Delivery :[8]

1. To achieve effective drug deposition, the efficient aerodynamic filter present in the lungs must be overcome.
2. The mucous lining of pulmonary airways helps clear particles deposited in the throat.
3. Only 10-40% of the drug that exits the conventional inhalation device is typically deposited in the lungs.
4. The drug's short-lived duration is due to its rapid removal from the lungs or rapid drug metabolism.
5. Needs regular dosage.

Objectives :

1. The process of preparing an inhelar without a propellant.
2. The study's goal is to look at DPI's mode of action.
3. The formulation of DPI and development is a crucial aspect of any business strategy.
4. The study aims to explore various types of DPI.
5. The study aims to evaluate the effectiveness of DPI.

MECHANISM OF DRUG DEPOSITION:[1]

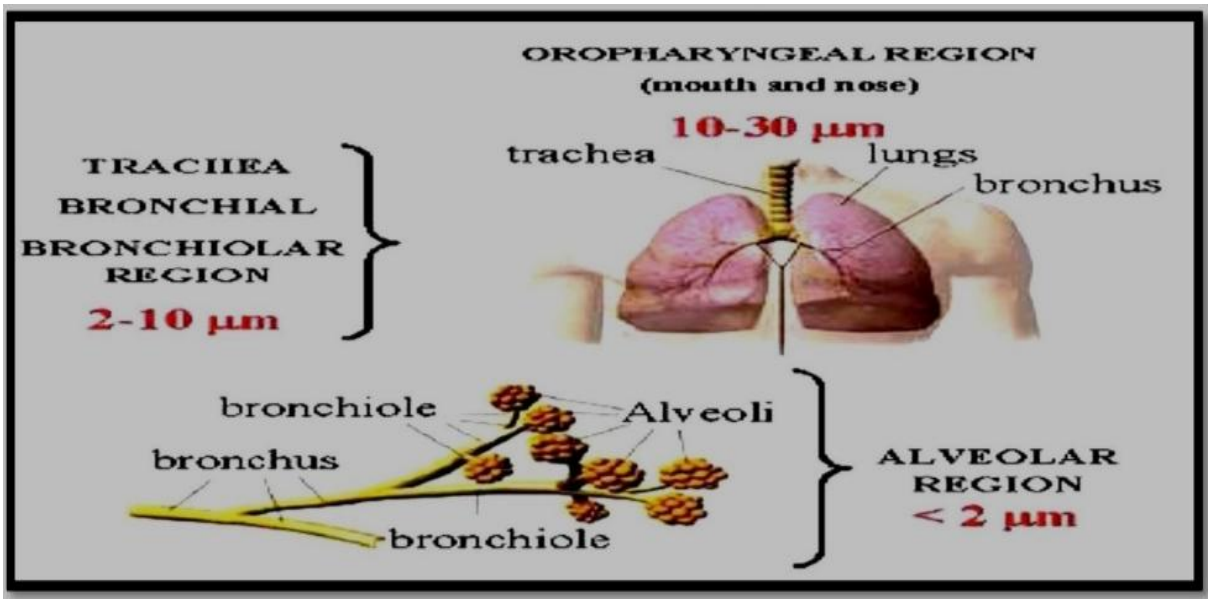

Fig.1 Pulmonary tract-Drug deposition characteristics

The process by which particles deposit in the respiratory tract includes

1. Inertial deposition
2. Sedimentation (gravitational deposition)
3. Brownian diffusion

1.Inertial deposition :

Impaction is the inertial deposit of a particle onto the surface of an airway, usually in the vicinity of airway bifurcations. When momentum, which increases with air velocity and particle size, stops particles from moving in regions where the direction of air flow is changing, it happens.

2. Sedimentation:

When air resistance is overcome by gravitational force, particles fall out of the air stream at a steady pace, a process known as sedimentation. In narrow, low-velocity airways, this is vital. The likelihWood of sedimentation decreases with breathing rate and is correlated with residence duration and particle size. When gas molecules and aerosol particles contact, diffusion takes place, producing random particles.

3.Brownian diffusion:
Brownian motion has a significant role in the deposit of particles in bronchioles, alveoli, and at the bifurcations of bronchial airways. Its efficacy is inversely related to the diameter of the particles, which are 0.5 μm. Particles with a molecular size can settle by diffusion in the trachea, bigger bronchi, and upper respiratory tract.

4.Interception:
For fibers and aggregates, deposition is important because particles may come into touch with airway walls even when their center of mass stays on a fluid streamline.

5.Electrostatic Attraction:
A lung deposition investigation employing the Twin Stage Impinger apparatus showed that electrostatic charges enhance attractive forces on airway surfaces, especially for new particles, boosting deposition.

6.Parameters Determining Particle Deposition In Deep Lung:[9]
Different biophysical factors influence the way drugs are deposited regionally in the human lungs:

- Behavior of aerodynamic particles
- The patient's breathing pattern
- When the aerosol pulse is injected into the respiratory cycle
- The respiratory tract's anatomy

The size distribution and size of aerosol particles have a major effect on aerosol deposition. Aerosol particles with different densities and shapes can be categorized according to their aerodynamic qualities; the aerodynamic particle diameter (AD) is equivalent to the diameter of a sphere with a density of 1 g/cm3.

7.Aerodynamic Particle Behavior:[10]
Particle size has an important effect on where they deposit, how they work, and how much of them enter the lungs. Aerodynamic diameter (AD), the equivalent diameter of a spherical particle with the same settling velocity from an air stream, is frequently used to quantify the size of aerosols. Particles with higher density have smaller real diameters and bigger geometric diameters. There are two types of aerosol size distributions: polydisperse (non-uniform) and monodisperse (uniform). By filtering inhaled particles bigger than 100 μm, the tracheobronchial tree and upper airways keep larger particles out of the respiratory system.The naso/oropharynx traps fine particles, defined as those with a diameter of less than 10 μm. Particles bigger than 10 μm affect the walls of the throat but do not enter the lung. Particles ranging in size from 2 to 0.05 μm are found in alveoli, and particles with a diameter of 5 μm to 0.5 μm are deposited in respiratory bronchioles. Aerosols that are therapeutic are transmitted by impaction, sedimentation caused by gravity, and diffusion via Brownian motion. For airborne exposure to be safe and effective, these systems are essential.

FACTORS AFFECTING DEVELOPMENT OF DRY POWDER INHELAR DEVICES

1. Humidity:
Drugs are delivered using dry powder inhalers (DPIs) as a result of interactions between excipient adhesives and active ingredients. Drug delivery is impacted by the morphologies of the micronized drug particle and carrier. Van der Waals and electrostatic forces are the main forces of adhesion. A high capillarity force results from capillarity condensation, which raises the overall adhesion force in humid situations. When the relative humidity (RH) is more than 50%, this force takes over.[11]

2. Interparticulate forces:[7]
Interparticulate force is the main factor influencing the flow and dispersion characteristics of micronized and microcrystalline powders used in inhalation treatment; thus, improvements in chemical and physical factors are necessary.

3.Particle size: [1]
Targeting certain lung locations using aerosol particle size control is possible, but patient dynamics and the complexity of the respiratory system must be taken into account. Particle size has an impact on therapeutic efficacy, emotional response, and deposition, according to clinical research.

4.Physical Properties of Powders:
DPI provides patients with aerosol medications that may be loaded or stored. To overcome cohesive and adhesive forces for dispersion, the powder needs to be fluidized and entrained into the patient's airflow. For the development of DPI, flow and dispersion must be optimized and controlled. Adhesive forces, physiochemical parameters such as density, size distribution, morphology, and surface composition, as well as features of the particle and powder all have an impact on the properties of particles.

5.Drug Carrier and Carrier Size:
Optimizing the interface between particles and inhalers is essential for effective medication delivery in powder formulations. For better powder flow, coarse inert carriers such as lactose are used with micronized powders. The number of carrier particles falls and the number of drug particles per carrier increases as carrier size increases. This results in a small increase in formulation removal efficiency because to higher velocity and less collisions.

6.Particle Engineering:
The creation of particles for precise medication doses is essential to the effectiveness of Direct Plasma Injection (DPI). The development of enhanced DPI performance by preformulation characterisation of drug carrier combinations utilizing Corrasion is highlighted in Staniforth's review.

FORMULATION OF DPI[12]

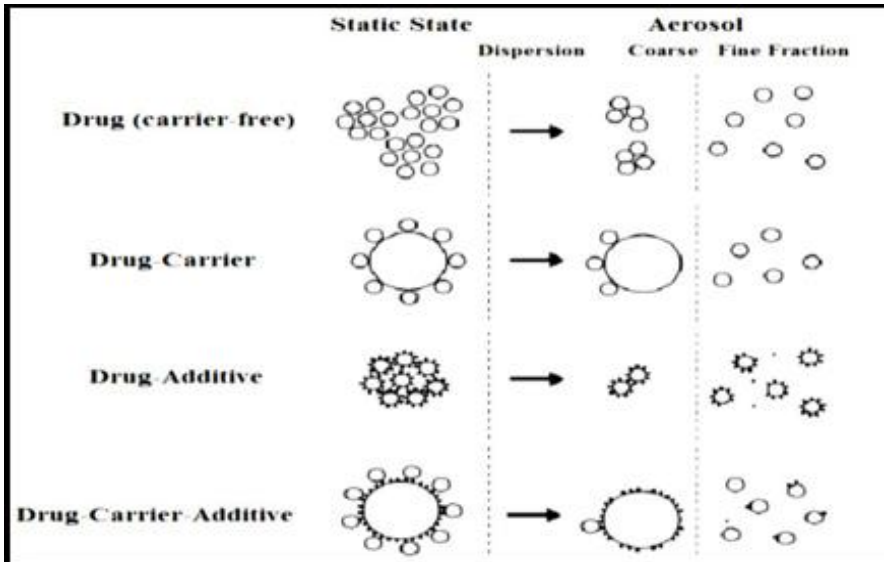

Fig.2 Different types of formulation strategies for Dry Powder

Three categories can be used to classify the DPI formulation:
1. API creation.
2. Formulation of API with or without carrier.
3. Combining the formulation with the apparatus.

All DPIs have 4 basic features:
1. A system for dosing metering.
2. A process for aerosolization.
3. A process for deaggregation.
4. An adapter to aim the spray directly into the patient's mouth.

Pre-formulated medication particles with an aerodynamic diameter of less than 5 μm are required for inhalation. The flow characteristics of the final formulation are impacted by fine particles' worse flow than coarse ones. Due to their difficulty in dispersing, small particles require special qualities in formulations. The bioavailability of the inhaled medication can be impacted by factors that alter its delivery, dispersion, and deposition in the respiratory tract.

1.Carrier Free system:
The carrier method needs inhaled medication particles that are either single compounds or encapsulated particles with an aerodynamic diameter less than 5 m.

2.Carrier Based system:
With benefits including better drug particle flow, precise dosing, minimal dosage variability, simplicity of handling, and enhanced breathing efficiency, lactose is a popular carrier in DPI formulations.
1. biocompatible, biodegradable, stable both chemically and physically.
2. compatible with a range of medications.
3. It needs to be inexpensive and inert.

Dry powder inhalers often employ alpha-lactose monohydrate as a carrier; however, because of their shortcomings, other carriers such as mannitol, glucose, sorbitol, maltitol, and xylitol are required. Because mannitol is hygroscopic, it

is the most promising carrier for DPIs. Lower adhesion and improved active ingredient release are provided by crystallized forms. Larger lactose carrier particles are combined with micronized medication to create DPI formulations.

TECHNIQUES FOR POWDER PRODUCTION FOR DPI's[1]

Lung-penetrating material production is essential to the fabrication of DPI powder. Spray drying, mixing, and micronization are some of the methods. Palletization or blending with bigger particles can reduce problems with fill, flow, and dispersibility.

1.Controlled Crystallization or Precipitation:
The process of crystallization involves generating particles from a material's solution in a solvent with the general goal of creating a stable, crystalline substance. However, reduction of big particle sizes is necessary in DPI goods.

2.Micronization:
Using high energy, micronization reduces the size of particles to less than 5 mm in diameter from coarse-diameter ones. Particles can be micronized using devices such as ball mills, jet or fluid energy mills, and others, which increases the difficulty of size reduction and encourages the spread of cracks.

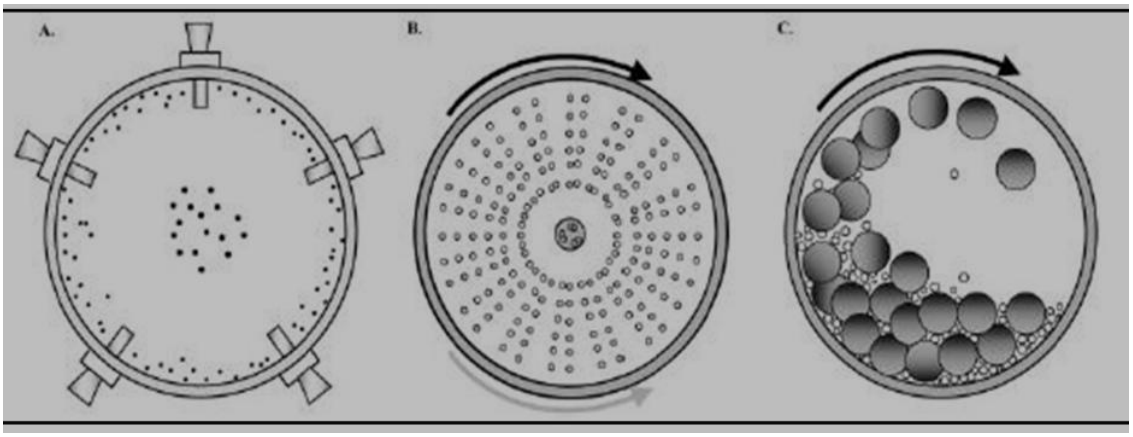

Fig .3 .micronization A: Jet mill. B: Pin mill. C: Ball mill.

3.Blending:
The creation of an ordered powder is achieved by blending pharmaceuticals with bigger excipient particles, which improves flowability, fillability, and dispersibility. For consistent particle behavior, further processing can be required. In order to ensure particle size deaggregation during aerosol medication administration, pelletization is the purposeful agglomeration of tiny drug material into bigger units. This is usually accomplished using vibratory sieving or tumbling powder.

4.Secondary Processing:
Water or solvents are usually eliminated from milling goods by encasing the material in a barrier, such as laminated aluminum foil, to minimize changes in crystallinity. Other methods involve creating a material that is 100% crystalline, which might need to be quarantined or annealed to allow it to equilibrate under controlled storage conditions.

5.Spray Drying:
Using hot air and spray drying, liquid droplets are turned into dry particles that are safe to breathe in. A few examples of the variables that might affect the size and distribution of the powder include the chemical makeup of the material, cyclone efficiency, spray temperature, and feed solution concentration. To guarantee uniform dispersion in the final powder, the initial step entails preparing a solution containing the medication and excipients. After that, the solvent is extracted from the drug solids by evaporating it.

TYPES OF DPI

There are three types of dry powder inhaler devices: multi-dosage reservoirs, single-unit dose, and multi-unit dose. For inhaled medications to reach the lungs and provide stability and consistent dosage, an inhalation apparatus is essential. It should retain a high fine particle fraction (FPF) of medications, be portable, and be simple to operate. Higher resistance devices, however, demand more inspiratory power from their users.[13] Depending on the kind of dose, dry powder inhaler devices are divided into three categories: single-unit dose, multi-dose reservoirs, and multi-unit dose.
They can be categorized as follows based on the metering system:

1. Single unit dose inhaler
2. Multiple dose inhaler
    a. Multi-unit dose devices
    b. Multi dose reservoir device

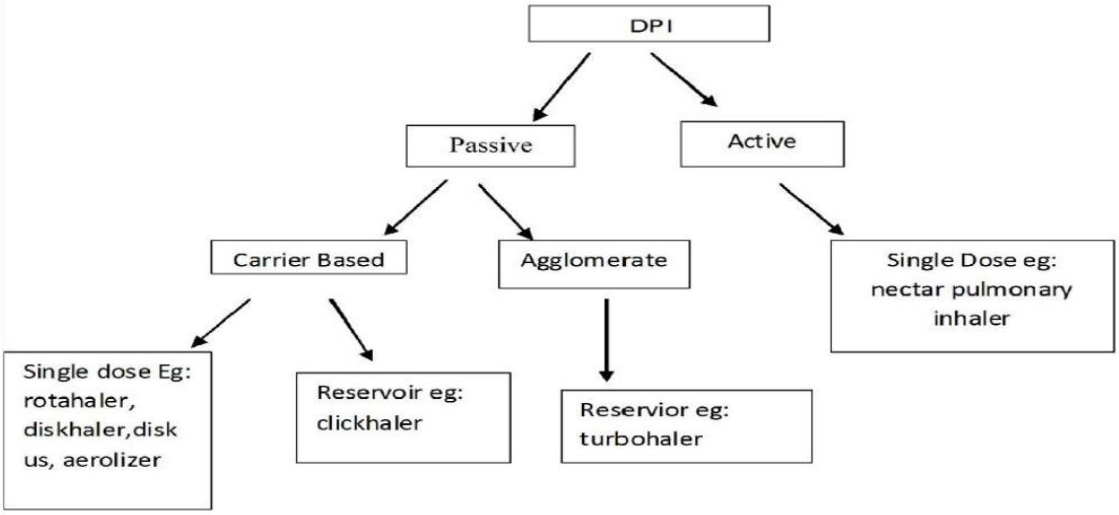

Fig 4.Types of DPI's

1.Single- unit Dose Inhale:
Bell and associates created the spin haler, the first capsule-based device, in the early 1970s to dispense sodium cromoglycate powder. The medication is given as single-use capsules that are put into the inhaler for one dose and then thrown away. The cap is kept to be disposed of, but the capsule body falls into the apparatus. Particle deaggregation results from the capsule's irregular motion during the patient's inhalation.

2.Multi-dose Devices:
There are two types of multi-dosage devices: multi-unit dose devices, which employ factory-metered and sealed doses packed to carry numerous doses without reloading, and reservoir type devices, which store formulation in bulk and include an integrated mechanism to meter individual doses. These gadgets are made to withstand environmental damage and provide sufficient dosage uniformity control. For both kinds, multi-dose DPIs have been created.

a.Multi-unit dose devices:
Single dosages are contained in blister packs on a disk cassette in these devices; upon piercing, inspiratory flow via the packing depression disperses the powder, and bypass flow enters via the mouthpiece holes, encouraging deagglomeration.

b. Multi dose reservoir device:
During inhalation and metering, the micronized medication pellets in the reservoir system break down into primary particles. The reservoir base may be twisted to distribute a single dose, and scrapers press the medication into conical perforations. Shear force causes fluidization, while turbulence causes particle deagglomeration.

EVALUATION

1. Appearance and Color:
The look of the closure system, including the valve and its parts, and the container indicate the integrity of the medicinal product. If color is detected, the early stage of the medication product's shelf life deterioration should be determined using a quantitative test with approved criteria.

2.Particle size analysis:
Particle size may be measured using a variety of techniques, the most often used being the light scattering decay method and the cascade impactor method. With an emphasis on lactose, the cascade impactor is a technique for analyzing particle size in inhalation goods. Particles are projected at a fast speed using a sequence of nozzles and glass slides; bigger particles are hit at lower stages and tiny ones are gathered at higher levels. Typically, a particle diameter of 1–5 microns is ideal for aerodynamics. A emerging method that offers a complete profile is laser diffraction.

3.Sieve analysis:
Several sieve analysis techniques, including air-jet sieving and ordinary sieves agitated on a seive shaker, can be used to quantify the lactose particle size. Weighing the material that is received on each sieve allows one to compute the particle size distribution. For coarse and granulated lactose, sieves are effective; however, air-jet sieving performs better for finer grades.

4.Laser diffraction:
A laser beam is used to measure powder by diffracting light in various directions, creating a scatter pattern that detectors record. There are theories that link the particle size distribution and scattering pattern quantitatively.[14]

5.Moisture Content:
For evaluating minute quantities of water in inhalation powder that impact capillary condensation, solid-state phase behavior, characteristics, and stability of pharmaceutical particles, the Karl Fisher technique is commonly used.

6.Flow properties of Powder:[15]
Carr's Flowability Index:
The flow properties of a DPI were measured by the Carr's method which involves following four tests:
1) Angle of repose
2) Compressibility
3) angle of spatula
4) uniformity coefficient

Hausner's Ratio-Hausner's ratio (HR):
The maximum and minimum bulk density values were determined using tapping.

Packing Properties of Dry Powder Inhalation:
The packing properties of the powder used in DPI were determined using Kawakita's equation, which indicates porosity.

7.Drug Content (Assay):
Even if it isn't directly connected to the performance of the inhaled aerosol, the drug concentration in the formulation should be evaluated analytically using a stability indicating method with high acceptance criteria to assure consistency in other factors like dosage content uniformity.

8.Net Content:
There are several ways to find out a container's net content. Weighing tared cans, distributing contents, and calculating the residual weight are a few of these. Opening and removing containers to optimize product distribution is one modification. These tests, however, do not represent the true net content of any container. Thus, to ensure proper product distribution, considerable thought and adaptation are essential**.**

9.Impurities and Degradation Products:[16]
Degradation product and impurity levels should be ascertained using stability indicating techniques, which also establish acceptable standards for both individual and aggregate degradation products and impurities. In the drug product specification, contaminants and degradation products that are present at 0.10 percent or more should be mentioned, either as identifiable or unidentified, and listed separately.

10.Microbial Limits:[16]
To ensure that the medication product doesn't promote the development of microorganisms, microbial quality in drug products should be regulated using tests and acceptance criteria for total aerobic count, yeast and mold count, and freedom from indicator pathogens.

11.Spray Pattern:
According to the study, spray patterns from various material batches or valves may be compared by impinging the spray on paper that has been treated with a dye-talc combination. Depending on the kind of powder, the dye used can be either water- or oil-soluble.

12.Extractables/Leachable:[16]
Valves and other non-compendial plastic and rubber container closing parts that come into touch with the formulation while being stored need to be investigated. It is necessary to ascertain the leachables profile and the extractables profile for rubber container closure components and compendial polymers. The drug product specification should include a test and limits for leachables, and safety evaluations should be carried out in accordance with established safety thresholds.

CONCLUSION

For medications that function systemically and for which the lung is the only point of entry into the body, as well as for pharmaceuticals to be supplied for local treatment in the lung, DPI might be viewed as an appealing drug delivery method. Their propellant-free nature, good patient compliance, high dosage carrying capacity, and medication stability are just a few of their many benefits. It is now being studied for the treatment of conditions including chronic obstructive pulmonary disease (COPD) and asthma.Drug and carrier particle engineering and formulation strategy changes are being used to enhance DPI inhalation performance. Future research will focus on targeted pulmonary drug deposition and intracellular drug delivery, while improving inhaler design for optimal therapeutic advantages.

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