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Formulation and Evaluation of Dry Powder Inhaler

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Abstract: ***This review focuses on the dry powder inhaler (DPI) formulation and development process. Most DPI formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. A combination of intrinsic physicochemical properties, particle size, shape, surface area, and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lungs, and deposition in the peripheral airways. When a DPI is actuated, the formulation is fluidized and enters the patient's airways. Under the influence of inspiratory airflow, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact on the oropharyngeal surfaces and are cleared. If the cohesive forces acting on the powder are too strong, the shear of the airflow may not be sufficient to separate the drug from the carrier particles, which results in low deposition efficiency. This review thus demonstrates that the successful delivery of dry powder aerosols to the lung requires careful consideration of the powder production process, formulation and inhaler device. The developments and improvements towards high dose powder pulmonary drug delivery are summarized and discussed here. It also throws light on the invention and improvement of novel inhaler devices as well as the further development of formulation principles and new powder engineering methods.***

I. INTRODUCTION OF DRY POWDER INHALER

Inhalation drug delivery has been used for many years for the delivery of pharmacologically active agents to treat respiratory disease .Traditional asthma therapy with bronchodilators, steroids, mast cell stabilizers, and anticholinergic drugs has primarily used the pressurized metered-dose inhaler (MDI). However, this delivery system is now under increasing threat because of the environmental concerns regarding chlorofluorocarbon (CFC) propellants. A range of alternative devices, such as dry powder inhalers, which do not contain propellants, are being evaluated and developed. [1] Dry powder inhalers contain the drug in a powder formulation, where drug particles (< 5 μm) are blended with a suitable large carrier (e.g. lactose) to improve flow properties and dose uniformity and drug powders are delivered into the deep lung via a device known as dry powder inhaler (DPI). Powder de-agglomeration and aeroionisation from these formulations are achieved by the patient's inspiratory airflow . In a DPI, the aerosol needs to be generated from the powder formulation by patient 'sown effort'. For achieving this, a high turbulence is needed to break the large agglomerates of the drug into smaller, finer and inhalable particles. Turbulence is generated by creating resistance to air flow in the DPI device and the effort required to generate adequate flow rates is dependent on the extent of resistance. Whereas the flow rates required to be generated vary among various available DPIs, a flow rate of 60-90 L/min is generally required. Pulmonary drug delivery by Dry Powder Inhalers (DPIs), by virtue of its propellant free nature, high patient compliance, high dose carrying capacity, drug stability and patent protection, has encouraged rapid development in recent past to realize full potential of lungs for local and systemic treatment of diseases. But DPIs are complex in nature and their performance relies on many aspects including the design of inhaler, the powder formulation and the airflow generated by the patient . In last decade, performance of DPIs has improved significantly through the use of engineered drug particles and modified excipient systems.

Exploration of inhalation aerosols for drug delivery has contributed vastly in treating pulmonary diseases for decades.Interestingly, inhalation of powders has been used for many centuries dating back to ancient times by the ancient Egyptians and Greeks. In the 19th century, Newton and Nelson each patented a DPI, after which the inhalation aerosol therapy took a detour away from DPI until 1948, when Abbott introduced Aerohalor for penicillin. Although drug delivery through inhalation was achieved many years ago, dose control was poor. When the pharmaceutical industry succeeded in delivering controlled doses of drug, there was no looking back. Treatment of pulmonary diseases, especially asthma, was revolutionized. Today, drug delivery has come a long way in successfully delivering drug to the lungs not only for local action but also for systemic application. Yet, inhalation aerosol drug delivery faces challenge in achieving consistent dose delivery and toxicity related to higher dosages delivered to the lungs. The four major classes of inhalation aerosol delivery systems are nebulizers, pMDIs and DPIs. Each has its own advantages, disadvantages and limitations in regard to the type of formulation that can be used, the types of drugs that can be used, and the amount of respirable dose that can be generated from these devices. In the past two decades, respiratory drug delivery has focused on two main aspects of drug delivery: replacing chlorofluorocarbon propellants and methodology to increase drug bioavailability.

Hydrofluoroalkane propellant and DPI have come to the rescue in replacing chlorofluorocarbon propellant, while nanotechnology continues to be explored for targeted pulmonary delivery. However, the challenge that still exists is achieving higher fraction of respirable drug and consistency in dose delivery. Part of the challenge stems from the operating principles of the devices. Other challenges are formulation optimization, patient noncompliance, incorrect handling of the inhaler device, wrong choice of treatment option and patient's personal preference to certain device type.[2]

A. Advantages

1) No propellants
2) Provides local action within the respiratory tract and are non-invasive
3) Avoids hepatic first-pass metabolism
4) Allows for a reduction in systemic side-effects
5) Provides rapid drug action
6) High drug dose carrying capacities, reproducibility (Monodisperse)
7) Breath actuated hence no hand-mouth co-ordination required
8) Minimal extra-pulmonary loss of drug due to low oropharyngeal deposition,
9) low device retention and low exhaled loss
10) Reduces extracellular enzyme levels compared to GI tract due to the large
11) alveolar surface area
12) Better patient compliance, simple to use and convenient to carry and do not require spacers[3]

B. Disadvantages

1) Deposition efficiency depends on patient's inspiratory airflow.
2) Greater potential problems in dose uniformity.
3) Less protection from environmental effects, Humidity may cause powders to aggregate and capsules to soften.
4) Dose lost if patient inadvertently exhales into the DPI
5) More expensive than pressurized metered dose inhalers.
6) Development and manufacturing are more complex than pMDI.[3]

C. Objectives

1) Preparation Of Inhelar Without Propellant.
2) To Study Mechanism Of Action Of DPI.
3) Formulation Of DPI And Development.
4) To Study Verious Types Of DPI.
5) To Study Evaluation Of DPI.

II.MECHANISM OF DRUG DEPOSITION:[4]

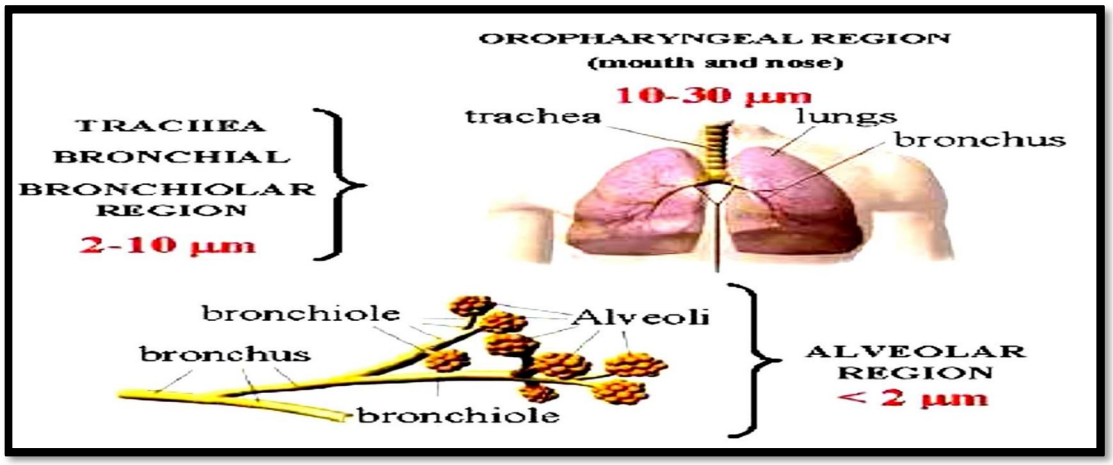

Fig 1. Pulmonary tract-Drug deposition characteristics.

Impaction The mechanisms by which particles deposit in the respiratory tract includes

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

A. *Inertial Impaction*

Defined as inertial deposition of a particle onto an airway surface. It happens principally close to the airway bifurcations of the large conducting airways.

Impaction occurs when a particle's momentum prevents it from changing course in an area where there is a change in the direction of bulk air flow. It is the main deposition mechanism in the upper airways, and at or near bronchial branching points. The probability of impaction increases with increasing air velocity, breathing frequency, and particle size.

B. *Sedimentation*

Sedimentation results when the gravitational force acting on a particle overcomes the total force of the air resistance. Inspired particles will then fall out of the air stream at a constant rate. This is an important mechanism in small airways having low air velocity. The probability of sedimentation is proportional to residence time in the airway and to particle size, and decreases with increasing breathing rate. Diffusion occurs when the collision of gas molecules with small aerosol particles exerts discrete non-uniform pressures at the particles' surfaces, resulting in random

C. *Brownian Motion*

The effectiveness of Brownian motion in depositing particles is inversely proportional to particle diameters of those particles, 0.5 μm, and is important in bronchioles, alveoli, and at bronchial airway bifurcations. Molecule size particles may deposit by diffusion in the upper respiratory tract, trachea, and larger bronchi.

D. *Interception*

is important only for fibers (asbestos) and aggregates. For such particles, deposition may occur when a particle contacts an airway wall, even though its centre of mass might remain on a fluid streamline.

E. *Electrostatic Attraction*

Electrostatic charges enhance deposition by increasing attractive forces to airway surfaces, in particular for fresh generated particles. Lung deposition study is carried out by Twin Stage Impinger apparatus.

F. *Parameters Determining Particle Deposition In Deep Lung.*[5]

Different biophysical parameters determine regional drug deposition in the human lungs:

- Aerodynamic particle behavior
- Breathing pattern of the patients
- Time of aerosol pulse injection into the breathing cycle
- Anatomy of the respiratory tract

Of these factors, aerosol particle size and size distribution are the most influential on aerosol deposition. The aerodynamic particle diameter (AD) is the diameter of a sphere with a density of 1 g/cm3 that has the same aerodynamic behavior as the particle which shall be characterized. In that way, aerosol particles with different density and shape can be characterized depending on their aerodynamic properties.

G. *Aerodynamic Particle Behavior*

The size of the particles is a critical factor affecting the site of their deposition, since it determines operating mechanisms and extent of penetration into the lungs. Aerosol size is often expressed in terms of aerodynamic diameter (AD). The aerodynamic diameter is defined as the equivalent diameter of a spherical particle of unit density having the same settling velocity from an air stream as the particle in question. Thus, particles that have higher than unit density will have actual diameters smaller than their AD .Conversely, Particles with smaller than unit density will have geometric diameters larger than their AD.

Aerosol size distributions may be characterized as practically monodisperse (uniform sizes) or polydisperse (non-uniform sizes). The upper airways (nose, mouth, larynx, and pharynx) and the branching anatomy of the tracheobronchial tree act as a series of filters for inhaled particles. Thus, aerosol particles bigger than 100 µm generally do not enter the respiratory tract and are trapped in the naso/oropharynx. The particles must be very fine, for example having a aerodynamic diameter of less than 10 µm. Particles having aerodynamic diameters greater than 10 µm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5 µm to 0.5 µm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 2 to 0.05 µm are likely to be deposited in the alveoli15*).*Particles in the ambient air are transported by different physical mechanisms. The relevant mechanisms for therapeutic aerosols are diffusion by Brownian motion (particles in the size range of <0.5 µm), sedimentation by the gravitational force (particles in the size range of >0.5 µm) and impaction (size range >3 µm). [6]

III.PRINCIPLE OF OPERATION[7]

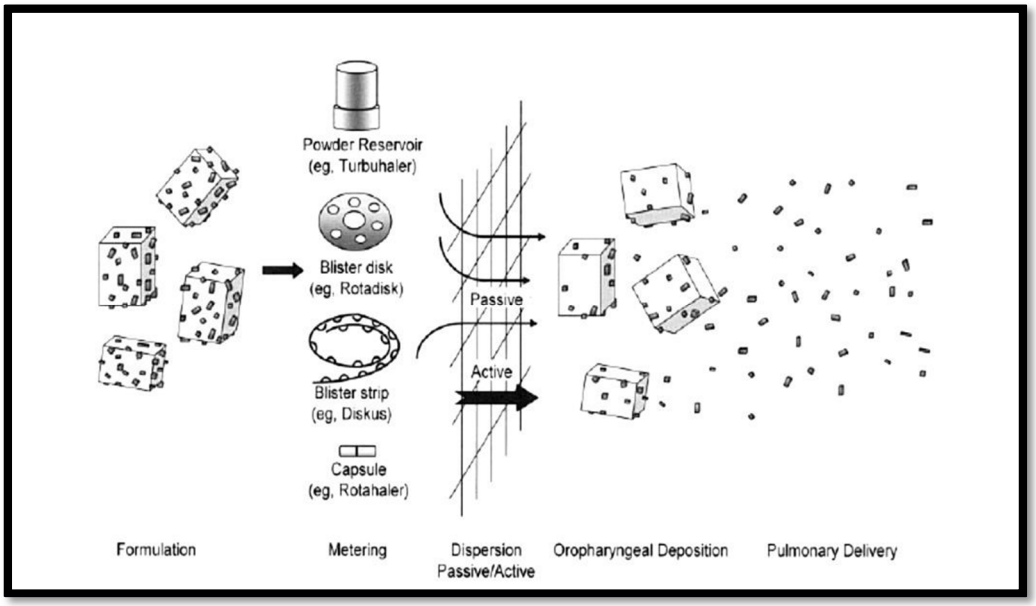

Fig. 2 Principle of dry powder inhaler design.

The formulation typically consist of micronized drug blended with larger carrier particles, dispensed by metering system entrains the particles into the patient's airways. Where drug particles separate from the carrier's particles and are carried into the lungs.

Figure shows the principles of DPI design. Most DPIs contain micronized drug blended with larger carrier particles, which prevents aggregation and helps flow. The important role these carrier particles play is discussed later in this article. The dispersion of a dry powder aerosol is conducted from a static powder bed. To generate the aerosol, the particles have to be moved.

Movement can be brought about by several mechanisms. Passive inhalers employ the patient's inspiratory flow. When the patient activates the DPI and inhales, airflow through the device creates shear and turbulence; air is introduced into the powder bed and the static powder blend is fluidized and enters the patient's airways. There, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharynx and are cleared. Thus, deposition into the lungs is determined by the patient's variable inspiratory airflow. Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency en countered with DPIs. Dose uniformity is a challenge in the performance of DPIs. This is a greater concern with powders than with liquids because of the size and discrete nature of the particulates. Various dispersion mechanisms have been adopted for DPIs. While most DPIs are breath-activated, relying on inhalation for aerosol generation, several power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are currently under development. These devices are being considered for the delivery of systemically active drugs that have narrow therapeutic windows. It is important to note that these "active" inhalers are not subject to the same limitations as passive inhalers and have a different advantage/disadvantage profile.

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Moreover, it has been suggested that if shear and turbulence could be standardized by using a dispersion mechanism that is independent of the patient's breath, high delivery efficiency and reproducibility might be might provide formulation independent delivery. There are no commercially available active dispersion DPIs.[8][9]

IV.FORMULATION OF DPI's:[11]

The formulation of DPI can be classified into three categories:

1) API production.
2) Formulation of API with or without carrier.
3) Integration of formulation into device.

All DPIs have 4 basic features:

- A dose metering mechanism.
- An aerosolization mechanism.
- A deaggregation mechanism.
- An adaptor to direct the aerosol into patient mouth.

To introduce the drug particle into the lungs, they must be <5μm in aerodynamic diameter. This is achieved by milling the powder prior to formulation. An important consequence of fine particle requirement for the inhalation arises from the fact that powder flow properties are dependent on the particle size distribution; fine particles generally flows less well than coarse ones. The final formulation must flow sufficiently well either to be dispersed from the bulk reservoir to give an adequately responsible dose or be capable of being handled well on automatic filling machine to produce the unit dose form for use in device. Small particles are also notoriously difficult to disperse must therefore be formulated to have appropriate properties such as reasonable flow ability and high dispersibility.3 major processes are involved in delivery of drug particles from the carrier, their dispersion in the air flow and deposition in the respiratory tract. Thus, any factor that affects any of these processes could ultimately influences the bioavailability of the inhaled drug.

A. Carrier Free system

In this carrier strategy, the drug particle which is to be inhaled must have aerodynamic diameter less than 5 μm and present either in the form of single compound or as an encapsulated particles.

B. Carrier Based system

Lactose is the most common and frequently used carrier in DPI formulations,

Carrier particles offers several advantages like: improve drug particle flow ability, improved dosing accuracy, minimum dose variability, ease of handling during manufacturing operations, inhalation efficiency increases etc

Carrier particles should have several characteristics such as

1) Physically and chemical stable, biocompatible and biodegradable,
2) Compatible with the various drugs
3) Must be inert and economical.

Alpha-lactose monohydrate is typically used as 'the' carrier in dry powder inhalers. There is an urgency to find suitable alternative carriers due to several drawbacks of lactose and modified lactose as a carrier for dry powder inhalers like mannitol, glucose, sorbitol, maltitol and xylitol.

From all the sugars, mannitol pretends to be most promising carrier for DPIs as compared to sorbitol, maltitol and xylitol sugars due to their hygroscopic nature. Carriers like crystallized mannitol (Pearlitol 110 C), spray-dried mannitol (Pearlitol 100 SD), crystallized maltitol (Maltisorb P90) etc were used, it was found that crystallized forms of the carrier are better than spray-dried forms as it offers lower adhesion and better release of the active ingredient.

By mixing micronized drug with larger lactose carrier particles DPI formulations are basically prepared. It is prepared in such a way that results in good blend uniformity and better flow characteristics. It is most important that, when the formulation is delivered to the patient via an inhalation device the drug particles are released to provide a safe and efficacious dose to the patient[i] .

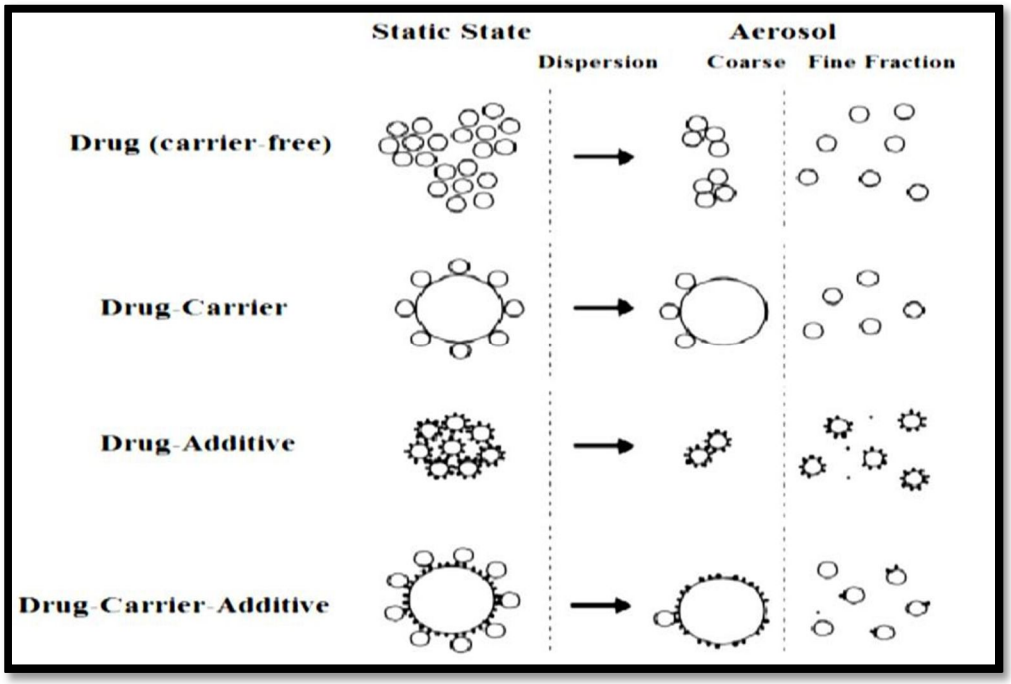

Fig.3 Different types of formulation strategies for Dry Powder

V. TECHNIQUES FOR POWDER PRODUCTION FOR DPI's

The primary factor influencing the manufacture of DPI powders is the need to produce material that can penetrate into the lung. Development of various approaches to the controlled production of fine particle, primarily depending on the nature of the drug. Of the processes micronization and blending and, more recently, spray drying is used most often. Problems such as poor flow ability, fill ability, and dispersibility can be minimized by blending with larger, less cohesive excipients particles such as lactose or palletisation of the individual drug.[8]

A. Controlled Crystallization or Precipitation

Crystallization, or precipitation, is the process by which particles are produced from solution of the material in a suitable solvent. The formation of a stable, crystalline material is normally the target of this final step .In the production of materials for use in DPI products, however, the particle size of the crystallized product is normally too large. Subsequent reduction in particle size is then necessary and can significantly alter the physical nature of the material.

B. Micronization

Micronization is a high-energy particle-size reduction technique that can convert coarse-diameter particles into particles of less than 5 mm in diameter. Different types of equipment can micronize particles, for example, jet or fluid energy mills[13] and ball mills. All techniques involve applying a force on the particle, typically in the form of a collision, either particle–particle or particle–equipment. The force acts at imperfections in the crystal surface, initiating crack propagation through the particle. As the size of the particle decreases, the number of imperfections decreases, thereby making the task of reducing particle size more difficult.

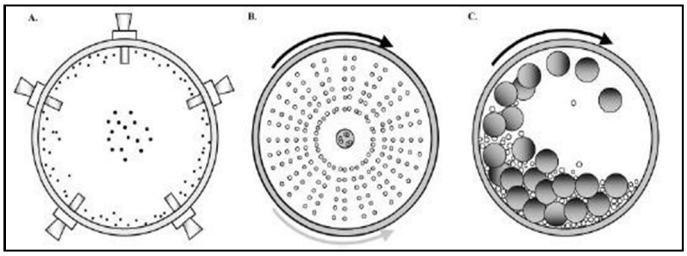

Fig 4. .micronization A: Jet mill.[13] B: Pin mill.[14] C: Ball mill.[15]

C. Blending

The most commonly used method for improving the flowability, fillability, and dispersibility of small cohesive particles is blending the drug with excipient particles, most commonly lactose, of considerably larger particle size. The objective of the mixing process is to produce an ordered powder in which the small particles attach themselves to the surface of larger ‘‘carrier’’ particles. During formulation feasibility, the blends are made by mortar and pestle and/or geometric mixing in a tumbling blender. For high-volume production, the process generally involves a high-shear mixer.

The final product performance of a powder blend in a DPI is ultimately dependent on the individual drug and carrier properties as well on the process by which they are blended. Secondary processing may be required to ensure that carrier particles behave consistently from batch to batch.

Steps that involve transport or storage of the finished blend should be monitored closely to avoid segregation, which occurs when the drug separates from the carrier or when carriers of different sizes separate. Segregation can be minimized by the careful selection of formulation and process equipment.

For example, hopper design can play a significant role in minimizing sagragation.[10] **6.4 Pelletization:**

The process involves deliberate agglomeration of the fine drug material into less cohesive, larger units. Pelletization is usually achieved by vibratory sieving or any process that tumbles powder. The resultant pellets must be used in a system capable of de aggregating to an appropriate particle size for aerosol drug delivery.[10]

D. Secondary Processing

The technique generally used to minimize the degree of change in crystallinity of the milled product is to eliminate the water or other solvents from the product, usually by packaging the material within a suitable barrier (for example ,aluminum foil laminate). Other techniques include the production of a 100% crystalline material, which may eliminate the effects of moisture. This technique, however, may require a secondary production stage of annealing or a quarantine period to allow the product to equilibrate under controlled storage

E. Spray Drying

Spray drying involves converting the atomized liquid droplets into dry powders by hot air. This one-step process is capable of making particles of size suitable for inhalation.

The particle size and size distribution of the powder can be manipulated by the concentration of the feed solution, the spray temperature, cyclone efficiency, and chemical nature of the feed. A typical first step involves creating a solution of the excipients and drug.

Dissolving the excipients and drug ensures a uniform distribution of all the excipients and the active drug in the finished powder in contrast to the heterogeneous nature of blended powders. The solution is then atomized and mixed with a drying medium, usually air, or an inert gas if the feed consists of an organic solvent. The solvent is evaporated and removed from the drug solids.[10]

VI. ADVANCES IN FORMULATION OF DPI:[16]

Research into dry powder formulations has been an area of growth in recent years. Various techniques are used to made advances in dry powders formulation for inhalation involves either, micronization via jet milling, precipitation, or spray drying using various excipients, such as lipids and polymers, or carrier systems like lactose. A) **Lactose carrier systems**:

To overcome the problem of poor flow of cohesive powders, pulmospheres are the new type of aerosol formulation is the large porous hollow particles. They have low particle densities, excellent dispersibility and can be used in both MDI and DPI delivery systems. These particles can be prepared using polymeric or non-polymeric excipients, by solvent evaporation and spray-drying techniques. Pulmospheres are made of phosphatidylcholine, the primary component of human lung surfactant. The large size of pulmospheres allows them to remain in the alveolar region longer than their nonporous counterparts by avoiding phagocytic clearance.

A. Biodegradable Polymers Biodegradable Polymer

Microspheres are currently being studied as sustained release pulmonary drug carriers. Polymers such as polylacticacid and poly glycolic acid have been investigated for pulmonary drug delivery. Although a limited amount of research has been published in this area, the sustained-release profiles achieved with corticosteroids appear promising.

B. Liposome's and Nanoparticles Liposome's:

As a pulmonary drug delivery vehicle, have been studied for years and used as a means of delivering phospholipids to the alveolar surface for treatment of neonatal respiratory distress syndrome. More recently, they have been investigated as a vehicle for sustained-release therapy in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases.

VII.TYPES OF DPIs[17]

Dry powder inhaler devices are classified by dose type into single-unit dose, multi-dose reservoirs, and multi-unit dose, as illustrated schematically in Fig. The inhalation device is important in achieving adequate delivery of inhaled drug to lungs. The device should be easy to use, in expensive and portable. The device must provide an environment where the drug can maintain its physicochemical stability and produce reproducible drug dosing. The device should be designed to deliver high fine particle fraction (FPF) of drugs from the formulations. However, devices with higher resistance need a higher inspiratory force by the patients to achieve the desired air flow. [12] Dry powder inhaler devices are classified by dose type into single-unit dose, multi-dose reservoirs, and multi-unit dose.

Based on the metering system, they can be classified as

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

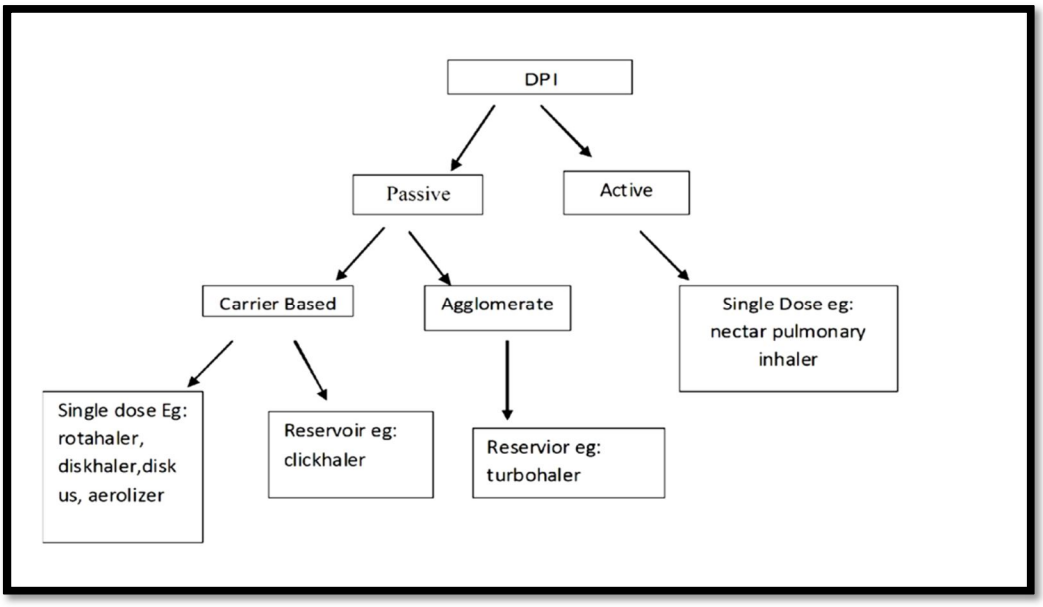

Fig 5.Types of DPI's

A. Single- unit Dose Inhaler

The concept of first capsule-based device (the spin haler) was described in early 1970s, by Bell and colleagues, who had developed this device for administration of powdered sodium cromoglycate.

In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual capsules, which are then inserted into the inhaler for a single dose and removed and discarded after use. The capsule body containing the dose falls into the device, while the cap is retained in the entry port for subsequent disposal. As the patient inhales, the portion of the capsule containing the drug experiences erratic motion in the airstream, causing dislodged particles to be entrained and subsequently inhaled. Particle deaggregation is mainly caused by turbulence promoted by the grid upstream of the mouthpiece.

Example: Rotahaler® (GlaxoSmithKline), Aerolizer® (Novartis), Handihaler® (Boehringer Ingelheim) etc.

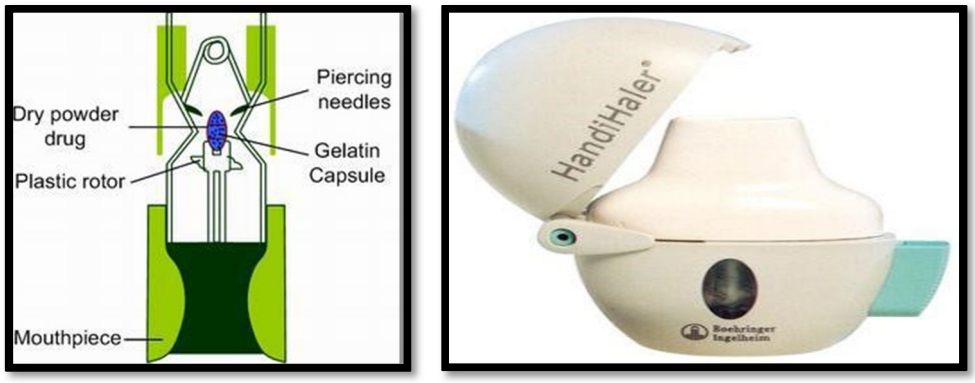

Fig **6**. Schematic presentation of the Spinhaler

B. Multi-dose Devices

There are two types of multi-dose devices, reservoir type devices and multi-unit dose devices. The multi-dose reservoir type device stores the formulation in bulk, and has a built in mechanism to meter individual doses from the bulk upon actuation. The multi-unit dose device uses factory metered and sealed doses packaged in a manner that the device can hold multiple doses without having to reload. Typically, the packaging consists of replaceable disks or cartridges, or strips of foil-polymer blister packaging that may or may not be reloadable. This pre-packaged does have the advantage of being protected from the environment until use, and ensuring adequate control of dose uniformity. Multi-dose DPIs have been developed, either as multi-unit dose or as multi-dose reservoir devices.

1) Multi-unit dose Devices

In this type of devices individual doses packaged in blister packs on a disk cassette. Following piercing, inspiratory flow through the packaging depression containing the drug induces dispersion of the powder. The aerosol stream is mixed with a bypass flow entering through holes in the mouthpiece that, gives rise to turbulence and promotes deagglomeration.

Example: M® (Boehringer Ingelheim), Diskhaler® (GlaxoSmithKline), Diskus® (GlaxoSmithKline) etc. Fig 4. Diskus www.wjpps.com Vol 4, Issue 11,
2015. 649 Thorat et al. World Journal of Pharmacy and Pharmaceutical Sciences

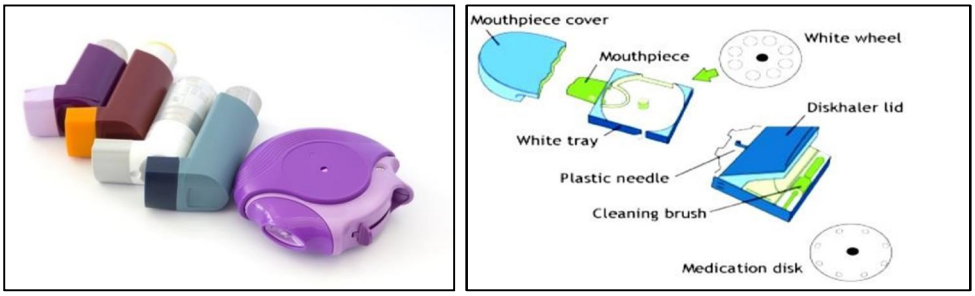

Fig 7. Schematic presentation of the Diskhaler [ii].

2) Multi-dose Reservoir Devices

It contains multiple doses of small pellets of micronized drug that disintegrate into their primary particles during metering and inhalation. One dose can be dispensed into the dosing chamber by a simple back-and-forth twisting action on the base of the reservoir. Scrapers actively force drug into conical holes which cause the pellets to disintegrate. Fluidization of the powder is done by shear force as air enters the inhaler. Particle deagglomeration occurs by turbulence. The advantages of the reservoir systems are their relative ease and low cost of turbulence.[17]

VIII. FACTORS AFFECTING DEVELOPMENT OF DRY POWDER INHELAR DEVICES:[18]-[22]

A. Humidity

In the dry powder inhalers (DPIs), due to the interactions between the active substance and the excipient adhesion results. The delivery of the drug is believed to be affected by the morphologies of the carrier and the micronized drug particle. Van der Waals and electrostatic forces are the primary adhesion forces for a dry uncharged particle on a dry uncharged substrate. The total adhesion force increases in humid environments due to capillarity condensation which leads to rise to a very large capillarity force. The capillarity force dominates when the RH is above 50% [18]

B. Interparticulate Forces

Flow and dispersion properties of the micronized and microcrystalline powders (particles smaller than 5μm), used for inhalation therapy are predominantly influenced by the Interparticulate force. Chemical and physical of the bulk drug, have been attempted in order to enhance inhalable dose performance.

C. Particle Size

It is assumed that by controlling the particle size, aerosols may be targeted to a particular lung site .However, the complexity of the respiratory tract and the patient's respiratory dynamics cannot be ignored. Regardless, there are several clinical studies which established the importance of particle size on deposition and affective clinical response. The effectiveness of the inhaled drug inside the human respiratory tract is also affected by the size, shape and density of the inhaled particles.[19]

D. Physical Properties of Powders

DPI provides powder pharmaceuticals in aerosol forms to the patients. The powdered drug is either loaded by the user into the DPI before use or stored in the DPI. To generate an aerosol the powder in its static state must be fluidized and entrained in to the patient's inspiratory air flow. The powder is subjected to numerous cohesive and adhesive forces that must be overcome to get dispersed. Optimization and control of flow and dispersion (deaggregation) characteristics of the formulations is of critical importance in the development of DPI. These properties are governed by adhesive forces between particles including vanderwall forces, electrostatic forces and surface tension of absorbed liquid layers. These forces are influenced by various physiochemical properties like particle density, size distribution, particle morphology and surface composition. Several cohesive and adhesive forces are exerted on particle on particles characteristics such as size, shape and crystalline form and powder characteristics such as packing density and equilibrium moisture content.[20]

E. Drug Carrier and Carrier Size

Optimization and control of particle–particle and particle –inhaler interaction is of critical importance in the development of efficient DPI's. A complicated situation exists in powder formulations- drug particles less than 5 μm aerodynamic diameter to ensure efficient drug deposition but should also exhibit acceptable flow properties required for accurate dose metering. Thus micronized powders are also blended with coarse inert carriers like lactose to improve powder flow. Lactose is often selected as carrier/excipients because of several advantageous properties like low reactivity and toxicity, low water content and its low costs. The number of carrier particles per formulation mass decreases as the carrier size increases, and also the number of drug particles per carrier increases. Furthermore, this carrier size increment results in an increased momentum and reduced number of collisions between carrier–carrier and carrier–device. The increased momentum of larger carriers is the reason for the slight increase in formulation removal efficiency. [21]

F. Particle Engineering

One of the most important factors involved in evaluating DPI performance is the engineering of particles required to produce powder formulation that delivers accurate and uniform doses of drug. In a review Staniforth has outlined the development of improved performance of DPI by preformulation characterization of drug carrier combinations. Staniforth explained the Pascal system which is an example of carrier formulation technology using a novel single step process called as Corrasion. This is a simultaneous milling, mixing and surface modifications of mixtures of 98-100% α lactose monohydrate and 0-2% of amino acid L-leucine.[22]

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IX. EVALUATION

A. Appearance and Color

The appearance of the content present in the container and the appearance of the container and closure system (i.e., the valve and its components and the inside of the container) should comply with their respective descriptions as an indication of the drug product integrity. If any colour is present with the formulation (either present from initial stage or form due to degradative processes occurring during shelf life), then a quantitative test with relevant acceptance criteria should be established for the drug product.[23]

B. Particle size Analysis

Many methods have been developed for the particle size measurement. Cascade impactor and light scattering decay method have been used to greater extent. The cascade impactor operates on the principle through a series of nozzles and glass slides stream of particles projected at high velocity, the smaller particles pass on and are collected at higher velocity stages while the larger particles are impacted on the lower velocity stage. The optimum aerodynamic particle diameter for most inhalation products has generally been recognized as being in the range of 1–5 microns. Sieve analysis and laser diffraction are used for the particle size analysis for lactose used in inhalation products. Laser diffraction is a fastest growing technique that describes almost the full profile while sieve analysis gives only a limited amount of data.[23]

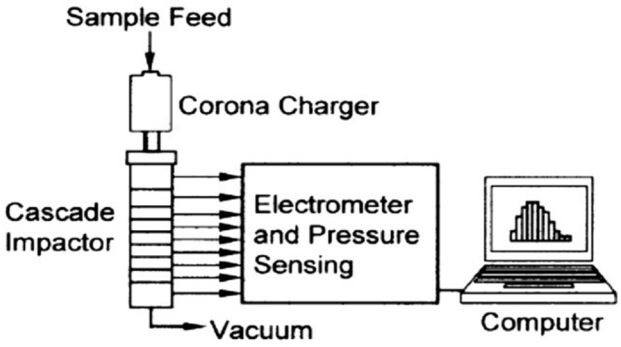

Fig 8.the electrical low-pressure impactor

1) Sieve Analysis

Sieving could be done by using nest of standard sieves shaken on a sieve shaker or with air-jet sieving. By weighing the material received on each sieve the particle size distribution can be calculated. To know particle size distribution sieves can be calibrated with reference materials. Sieves works well for coarse as well as granulated powder. Fine powders may often lock the holes present in the sieves. Therefore for finer lactose grades air-jet sieving works better but it has a disadvantage that only one sieve screen at a time can be operated.[24]

2) Laser Diffraction

In the Unites States Pharmacopeia (USP) General Chapter <429> (4) it is stated that laser diffraction involves the measurement of "a representative sample, dispersed at an adequate concentration in a suitable liquid or gas". For the measurement the powder is passing a laser beam. The light of the laser beam is diffracted in different Directions and the scatter pattern is recorded by detectors. The scatter pattern is strongly related to the particle size and the size distribution of the particles. Theories have been developed which quantitatively relate the scattering pattern to the particle size distribution.[26]

The result of laser diffraction techniques is often expressed as a volume distribution. These parameters are often linked to product performance. For inhalation lactose the most common laser equipment's used are supplied by Sympatico and Malvern.[24]

C. Moisture Content

The Karl Fisher method has been accepted to a greater extent for the measurement of small amounts of water present in the inhalation powder which has important effect on capillary condensation, solid-state phase behaviour, solid-state properties, and solid-state stability of pharmaceutical particles in the solid-state.[25]

D. Flow Properties of Powder

The flow properties of a DPI were measured by the Carr's method which involves following f our tests:

- Angle of repose
- Compressibility
- Uniformity coefficient
- Hausner's Ratio (HR).[25]

E. Packing Properties of Dry Powder Inhalation

The packing properties of the powder used in DPI were determined with the tapping method by utilization of Kawakita's equation for indicating porosity.[25]

F. Drug Content (Assay)

The drug concentration present in the formulation (in the entire container) should be determined analytically with a stability indicating method. The acceptance criteria should as high as possible to ensure conformance in other related aspects (e.g., dose content uniformity). Although this test may not be directly related in terms of performance of inhalation aerosols, it provides assurance of consistency concerning the manufacture of the drug product. (e .g. formulation, filling, crimping, and sealing).[26]

G. Net Content

Several methods can be used to determine whether sufficient product has been placed into each container. The tared cans that have been placed onto the filling line are weighed again and the difference in weight is equal to the net contents. The other method is a destructive method and consists of weighing a full container and then dispersing the contents. The contents are then weighed with provisions being made for the amount retained in the container. Other modifications consists of opening the container and removing as much as the product as possible. These tests are not indicated in determining the actual net content of each container as related to the amount that can actually be dispensed.[25]

H. Impurities and Degradation Products

By means of stability indicating methods the levels of degradation products and impurities should be determined. Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance .If the individual impurities or degradation products appearing at levels 0.10 percent or greater it should be specified. Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification.[24]

I. Microbial Limits

The microbial quality should be controlled by suitable tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator pathogens. Furthermore, proper testing should be done to show that the drug product doesn't support the microorganism's growth and that microbial quality is maintained throughout the expiration period.[24]

J. Spray Pattern

Comparison of spray pattern obtained from different batches of material or through the use of different valves should be used. The method of comparison is based on the impingement of the spray on a piece of paper that has been treated with a dye-talc mixture. Depending on the nature type of powder, oil soluble or water soluble dye is used.[25]

K. Extractable/Leachable

For non-compendial plastic and for rubber container closure components that are in contact with the formulation during storage (e.g., valves), a study should be conducted to determine the extractible profile. It should be determined whether any of the extractables or leachables presents in the formulation at the end of the shelf life of the product. The leachables profile should also be determined for compendial plastics and rubber container closure components. Identification should be attempted for compounds that appear as leachables and also safety assessments should be conducted in accordance with sufficient established safety thresholds.

Depending on the levels and types of compounds detected, consideration should be given to including a test and limits for leachables in the drug product specification.[24]

X. CONCLUSION

DPI can be considered as an attractive drug delivery system, both for drug that are to be administered for local therapy in the lung, as well as for drugs that act systematically and for which the lung is only port of entry to the body. They have several advantages like propellant free nature, high patient compliance, high dose carrying capacity and drug stability. It has become subject of interest for the treatment of diseases like: asthma, chronic obstructive pulmonary disease (COPD). Currently, the inhalation performance of DPIs is being improved by changing formulation strategy, drug and carrier particle engineering. The future research in DPIs will thus aim to assimilate drug in a matrix particle to achieve specific pulmonary drug deposition and probably to achieve intracellular drug delivery especially, proteins, peptides, plasmids, DNA etc. The design of inhaler needs improvement to meet requirements of an ideal inhaler. A better understanding of the influencing properties of powder on the performance of DPI will help to address the challenges in the development of DPI formulation and inhaler devices for optimum therapeutic benefits.

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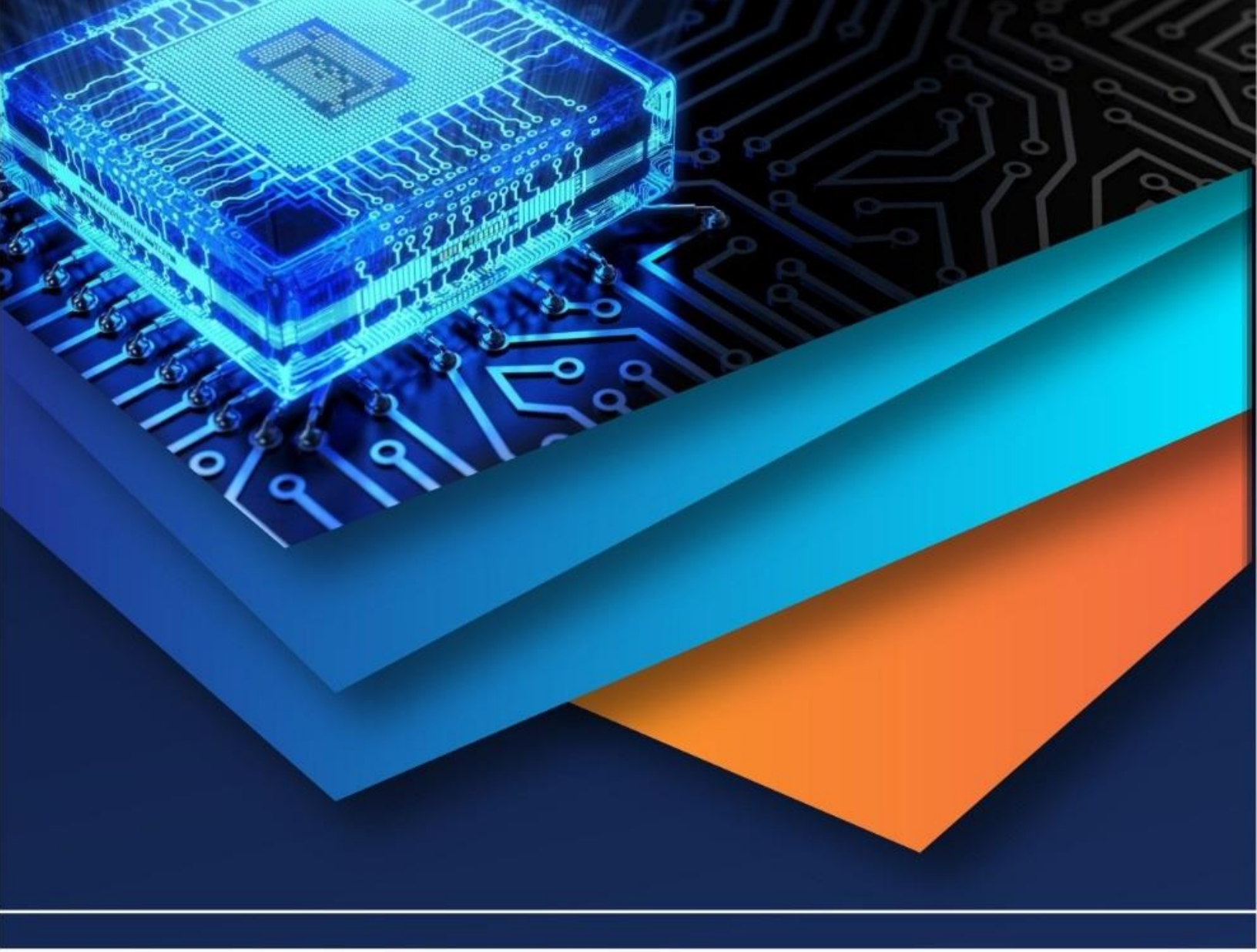

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