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Inhalers: Back to the Future

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Abstract: An inhaler is a device holding a drug that you take by breathing in (inhaling). This allows the drug to be delivered directly into the lungs where it is needed, meaning that people need much smaller doses than if the drug was taken by mouth. Inhalers were developed in the 1778 by an English physician named John Mudge and were associated with lung complaints. It wasn't until the 20th century that they became connected with asthma treatment. Today varieties of dosage forms are employed for different indications and demographics including pressurized or propellant-driven metered dose inhalers, dry powder inhalers, and nebulizers/nebules. Research and development in this field has shown remarkable innovation in the past decade. Important new drug products for the treatment of asthma, chronic obstructive pulmonary disease, cystic fibrosis, diabetes, and a range of neurological disorders have been developed. New devices in each of the dosage form categories also have been developed, and new formulation technologies have been adopted.
Key words: Inhaler; metered dose inhalers; dry powder inhalers; nebulizers

Introduction

At beginning ancient Indians burned cigarettes with dried and crushed strammonium used for inhalation. Later inhalers were developed in the 1778 by an English physician named John Mudge and were associated with lung complaints[1]. It wasn't until the 20th century that they became connected with asthma treatment. The first inhalers were based on a pewter tankard and Mudge used it to inhale opium vapor for cough treatment (fig1).During the 1800s ceramic pots such as Dr. Nelson's inhaler started being used to inhale plant or chemical substances and then in the early 1860's[1], Dr. Siegle developed a steam spray inhaler[3]. This treatment atomized liquid medication and was the beginning of nebulizer therapy. Nebulizers are commonly used today for asthmatics that have severe asthma attacks but cannot inhale as quickly and deeply as is required when using a pressurized inhaler. The first nebulizer was actually produced in 1858 by a French inventor named Dr. Sales-Girons. His nebulizer was unique in that it had a pedal that acted like a bicycle pump, and when pulled up air was forced through an atomizer and a mist was created to be inhaled. Later in the 19th century many devices developed includes[3-5]

Silbe Atomizer: A hand held nebulizer with a bulb syringe that had to be squeezed
Colossol Nebulizer: A glass nebulizer with a rubber squeeze ball
Volatilizer Inhaler: Dr. Coulter's vaporizer and inhaler w called the champion Volatizer. It was steam powered and made of copper, brass and nickel plate

Fig1: John Mudge inhaler1778

Fig2: Dr. Siegel inhaler1872

Fig3: Sales-Gironnebulizer (1858)*

Fig4: Silbe hand-held rubber bulb nebulizer **Fig5:** Glass Collosol Nebulator **Fig6:** Dr Coulter's inhaler1892

The pressurized inhalers we recognise today were developed until 1955, when American doctor George Maison invented a pressurized metered dose inhaler (MDI). Today many inhalers present in the market. Which are Nebulizers; metered dose inhalers (MDIs); and dry powder inhalers (DPIs).

Nebulizers

Nebulizers are the oldest pulmonary drug delivery devices used to convert liquids into aerosols of a size that can be inhaled into the lower respiratory tract. From the beginning two types of Nebulizers are widely using includes pneumatic nebulizers and ultrasonic nebulizers. The process of pneumatically converting a bulk liquid into small droplets is called atomization. Pneumatic nebulizers have baffles incorporated into their design so that most of the droplets delivered to the patient are within the respirable size range of 1–5 mm. Ultrasonic nebulizers use electricity to convert a liquid into respirable droplets. Although the first choice of aerosol generator for the delivery of bronchodilators and steroids is the metered dose inhaler, nebulizers remain useful for several reasons. First, some drugs for inhalation are available only in solution form. Second, some patients cannot master the correct use of metered-dose inhalers or dry powder inhalers. Third, some patients prefer the nebulizer over other aerosol generating devices. The physiologic benefits of metered-dose inhalers and nebulizers are virtually equivalent [3,4] and the choice of device is often based on clinician or patient preference rather than clear superiority of one approach over the other. Although cost savings have been suggested with the use of metered-dose inhalers compared to nebulizers, these benefits may be overestimated.

Pneumatic Nebulizers

Nebulizers are the oldest form of aerosol generation. Although they have been commonly used for many years, their basic design and performance has changed little over the past 25 years. Nebulizers are most commonly used for bronchodilator administration, and it is well established that nebulized bronchodilators produce a physiologic response. Because bronchodilators are relatively inexpensive, there is little market pressure to improve nebulizer performance. In fact, the market generally prefers an inexpensive nebulizer rather than a high-performance neb ulizer for bronchodilator administration. However, there are newer drugs available for inhalation that are expensive and for which precise dosing may be important. These include dornasealfa, tobramycin, and pentamidine.

Principle of Operation

The operation of a pneumatic nebulizer requires a pressurized gas supply as the driving force for liquid atomization[6] (Fig. 7). Compressed gas is delivered through a jet, causing a region of negative pressure. The solution to be aerosolized is entrained into the gas stream and is sheared into a liquid film. This film is unstable and breaks into droplets because of surface tension forces. A baffle is placed in the aerosol stream, producing smaller particles and causing larger particles to return to the liquid reservoir. More than 99% of the particles may be returned to the liquid reservoir. The aerosol is delivered into the inspiratory gas stream of the patient. Before delivery into the patient's respiratory tract, the aerosol can be further conditioned by environmental factors such as the relative humidity of the carrier gas. Nebulizer nozzles are of two types[8]. With the internal mixing design, gas flow interacts with the solution prior to leaving the exit port. With external mixing, gas and the solution interact after both leave the nozzle. Modifications on these designs are used by nebulizer manufacturers, without clear superiority of one approach over the other.

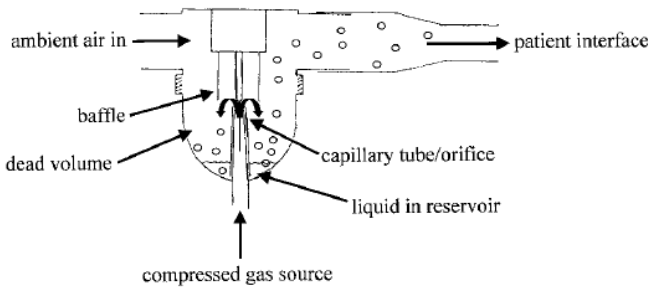

Fig 7: Basic components of the design of pneumatic nebulizers

Breath-Enhanced Nebulizers

The traditional nebulizer design incorporates the nebulizer sidestream to the air flow of the patient. Some newer nebulizers use a mainstream design with valves. In this valved open-vent design, the patient breathes through the nebulizer during inspiration, which enhances the nebulizer output. During the expiratory phase, a one-way valve directs patient flow away from the nebulizer chamber (Fig. 8). This design has been evaluated in several studies, which have reported greater pulmonary deposition with this design than with a conventional nebulizer[9-10].A potential advantage of the open-vent nebulizer design is an improvement in nebulizer output with an increase in inspiratory flow. Coates et al[11] reported a greater output of tobramycin with increased inspiratory flow, using an openvent nebulizer, whereas changes in inspiratory flow did not affect the output of the conventional nebulizer. As with conventional nebulizers, performance differences between breath-enhanced nebulizers have been reported.

Fig 8: Schematic representation of the function of a breath-enhanced nebulizer

Breath-Actuated Nebulizers

Aerosol waste during the expiratory phase can be eliminated if the nebulizer is only active during the inspiratory phase. Methods to manually actuate the nebulizer during the inspiratory phase have been available for many years[12]. It is also of interest to note that this design is commonly used in mechanical ventilator-actuated designs[13-14]. Both pneumatically and electronically controlled breath-actuated nebulizers have recently become commercially available. Their role in clinical application is yet to be determined.

Continuous Nebulization

Since the late 1980s, there has been considerable clinical and academic interest in the use of continuous aerosolized bronchodilators for the treatment of acute asthma[14-16]. These studies suggest that this therapy is safe, at least as effective as intermittent nebulization, and may be superior to intermittent nebulization in patients with the most severe pulmonary function. Several configurations have been described for continuous nebulization. These include frequent refilling of the nebulizer, use of a nebulizer and infusion pump, and use of a large-volume nebulizer. Berlinski et al reported a consistent and adequate aerosol production by a large-volume nebulizer over a 4-hour period of operation. Reisner et al, however, reported a more consistent aerosol delivery with a small-volume nebulizer attached to an infusion pump than with a large-volume nebulizer. A commonly used large-volume nebulizer for this therapy is the High-output Extended Aerosol Respiratory Therapy (HEART) nebulizer. Raabe et al reported a detailed evaluation of the performance of the HEART nebulizer. At a flow of 10–15 L/min, the aerosol output was 38–50 mL of aerosolized drug per liter of gas flow, and the solution output was 30–56 mL/hr. McPecket al[17] compared the HEART nebulizer to a conventional small-volume nebulizer in a model of adult and pediatric breathing. With the adult breathing pattern they reported similar aerosol delivery from the HEART nebulizer and small-volume nebulizer. For the pediatric breathing pattern the aerosol delivery from the small volume nebulizer was greater than from the HEART. Both Raabe et al and McPeck et al reported an MMAD of about 2 mm with the HEART nebulizer. An important finding of McPeck et alwas that the albuterol delivery from the HEART nebulizer was significantly less than the target dose from the manufacturer's recommended setup.

Nebulizers for Specific Applications

Specially constructed small-volume nebulizers should be used when contamination of the ambient environment with the aerosolized drug needs to be avoided. The most common example is aerosolized pentamidine[18]. The nebulizer is fitted with one-way valves and filters to prevent gross contamination of the environment. Examples of these devices include the Cadema Aero-Tech II and the Respirgard II. These devices produce a very small particle size, with an MMAD of about 1–2 mm, which is necessary to improve alveolar deposition of the drug. The Small-Particle Aerosol Generator is used specifically to aerosolize ribavirin (Virazole)[19].The device consists of a nebulizer and a drying chamber. The drying chamber reduces the MMAD of particles to about 1.3 mm. There are concerns about the potential adverse effects of this drug on health care workers when ribavirin is used. For this reason, a scavenging system should be used when ribavirin is administered. This is a double-enclosure system, with a ribavirin administration hood or mask inside a tent. Two high-flow vacuum scavenging systems aspirate ribavirin from the system through high-efficiency particulate air filters.

Ultrasonic Nebulizers: Ultrasonic nebulizers have been clinically available since the 1960s.[20-21] Small-volume ultrasonic nebulizers are commercially available for delivery of inhaled bronchodilators. Although several studies

reported greater bronchodilator response with ultrasonic nebulizers than with other aerosol generators, this has not been confirmed in other studies. Large-volume ultrasonic nebulizers are used to deliver inhaled antibiotics in patients with cystic fibrosis (eg, tobramycin). Ultrasonic nebulizers have also been used during mechanical ventilation, where they have an advantage in that they do not augment tidal volume, as occurs with pneumatic nebulizers. A potential issue with the use of ultrasonic nebulizers is the possibility of drug inactivation by the ultrasonic waves, although this has not been shown to occur with commonly-used nebulized medications. The ultrasonic nebulizer uses a piezoelectric transducer to produce ultrasonic waves that pass through the solution and aerosolize it at the surface of the solution. The ultrasonic nebulizer creates particle sizes of about 1–6 mm MMAD, depending on the manufacturer of the device. The volume output of the ultrasonic nebulizer is about 1–6 mL/min, depending on the manufacturer of the device. An ultrasonic nebulizer has 3 components: the power unit, the transducer, and a fan. The power unit converts electrical energy to high-frequency ultrasonic waves at a frequency of 1.3–2.3 megahertz. The frequency of the ultrasonic waves determines the size of the particles, with an inverse relationship between frequency and particle size. The frequency is not user adjustable. The power unit also controls the amplitude of the ultrasonic waves. This is user adjustable, with an increase in amplitude resulting in an increase in output from the ultrasonic nebulizer. The transducer vibrates at the frequency of the ultrasonic waves applied to it (piezoelectric effect). The transducer is found in two shapes, concave (focused) and flat (unfocused) [22]. Concave transducers produce a higher output but require a constant level of solution for proper operation. The conversion of ultrasonic energy to mechanical energy by the transducer produces heat, which is absorbed by the solution over the transducer. In some ultrasonic nebulizers, the solution to be nebulized is placed directly over the transducer. In others, the solution to be nebulized is placed into a nebulization chamber and a water couplant chamber is placed between the transducer and the medication chamber. A fan is used to deliver the aerosol produced by the ultrasonic nebulizer to the patient, or the aerosol is evacuated from the nebulization chamber by the inspiratory flow of the patient.

Metered-Dose Inhalers

In the first half of the 20th century, inhaled drugs for the treatment of asthma and chronic obstructive pulmonarydisease (COPD) were mostly delivered via hand-held, squeeze-bulb nebulizers. These devices were fragile, andsince the dose varied with hand pressure; they did not provide consistent drug delivery. The Riker Laboratories set out in the mid-1950s developed formulations of bronchodilator drugs in pressurized containers, providing greater convenience and a more reliable dose. This development followed the introduction of proprietary cosmetic aerosols as pressure-packs, and coincided with the invention of a metering valve capableof providing the patient with at least 100 precise doses. The pressurized metered-dose inhaler (pMDI, Fig. 9)quickly became the most important device for delivering inhaled drugs, and today approximately 500 million are produced annually.[23] Initially, they were given the acronym “MDI,” but the term “pMDI” is preferable, in order to distinguish them from dry powder inhalers (DPIs) another nonpressurized devices, some of which also have amulti-dose capability.

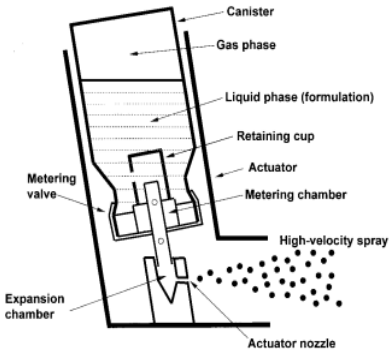

Fig 9: Pressurized metered dose inhaler

Breath-Actuated pMDIs

The concept of a breath-actuated pMDI is a good one, because it solves the problem of patient coordination of actuation with inhalation. Breath-actuated inhalers sense the patient’s inhalation through the actuator and fire the inhaler automatically in synchrony[24]. Patients seem to find breath-actuated pMDIs easier to use than conventional MDIs and may prefer them over other devices. Some breath-actuated inhalers are described below, and several others are currently in development.

Autohaler

An early model of the Autohaler breath-actuated device was described over 30 years ago, but it operated noisily and some patients could not generate the necessary flow to trigger the device. The current Autohaler device (3M Pharmaceuticals, St Paul, Minnesota) overcomes these limitations, since it is quiet and can be triggered by a flow of only 30 L/min (Fig. 10). A lever on the top of the device is raised, and then inhalation triggers a vane mechanism,

which results in the pMDI being actuated automatically bya spring. This device gave good lung deposition, even with patients who habitually exhaled immediately after firing aconventional pMDI.[25]

Easibreathe

The Easibreathe is a pMDI actuator, originally developed by Norton Healthcare (London, United Kingdom).[24]In some ways it resembles the Autohaler, but is simpler touse because opening the mouthpiece automatically preparesthe device for inhalation. The Easibreathe contains a pneumatic system, which restrains the operating spring. Actuation occurs in synchrony with inhalation at only 20L/min.

K-Haler

With the K-Haler breath-actuated device (Clinical Designs, Aldsworth, United Kingdom), the dose is actuated into a kinked tube, which is straightened by a breath operated lever, which releases the dose.[26] Opening the device's dust cap kinks the tube and depresses the pMDIvalve stem.

MD Turbo

The MD Turbo (Respirics, Raleigh, North Carolina) is abreath-actuated inhaler that can accommodate variouspMDI products. It incorporates "i-Point" technology, with which actuation only occurs at a pre-determined inspiratory flow.

Xcelovent

Another breath-actuated pMDI device, the Xcelovent, designed by Meridica (Melbourn, United Kingdom), delivers an HFA formulation containing budesonide and formoterol. Xcelovent may in the future be developed by Pfizer (Sandwich, United Kingdom).

Smartmist

A sophisticated microprocessor-controlled pMDI actuator device, the Smartmist (Aradigm, Hayward, California), accommodates a standard pMDI canister. A pneumotachograph reads the inhaled flow rate and volume, and a microprocessor actuates the pMDI only when a preprogrammed combination of flow and volume is achieved. While this device may be too complex and too expensive for routine pMDI use, it could provide a valuable function in controlled clinical trials by helping to ensure correct pMDI technique.

Breath-coordinated devices

Easidose

The Easidose (Bespak, Milton Keynes, United Kingdom) has been described as a breath-coordinated device, rather than a breath-actuated device. Inhaled air can pass through it only when the pMDI is depressed, so the patient's inhalation should be coordinated with actuation.[27]

Breathe Coordinated Inhaler

The Breath Coordinated Inhaler (Aeropharm, Edison, New Jersey)[28] is designed to coordinate the inspiration with the release of the dose. The device controls the inhalation flow rate through the actuator, so the patient has more time to actuate the pMDI reliably during inhalation.

Other Novel Devices

Breath-actuated inhalers and breath-coordinated inhalers do not attempt to solve the cold-Freon effect problem, but devices with slower spray velocity are likely to help. At least one device is already marketed, and several others are in development. In 1989, Byron et al[29] reported that it is possible to reduce the non respirable fraction by placing baffles near the actuator nozzle, to intercept large, rapidly moving droplets. However, no devices based on this principle seem to be in development.

Spacehaler

The Spacehaler (Celltech Medeva, Slough, United Kingdom)[30], formerly known as the Gentle haler (Schering-Plough, Kenilworth, New Jersey), is a compact, low-velocity- spray pMDI, 7.5 cm in length. The device produces a rapidly spinning vortex at the actuator nozzle, which reduces the initial spray velocity to approximately 2 m/s, which decreases or pharyngeal deposition and probably provides better lung deposition than a standard pMDI.

Tempo

The Tempo device, currently in development (Map Pharmaceuticals, Mountain View, California, formerly Sheffield Pharmaceuticals, St Louis, Missouri), contains a novel mechanism to manipulate the plume and reduce momentum of the spray. Some of the inhaled air is entrained to blow in the opposite direction to that of the spray plume. Both in vitro and in vivo data show that the Tempo may be associated with less or pharyngeal deposition and better lung deposition than a standard pMDI. This device also includes a breath-actuated capability.

BronchoAir

Broncho Air (Broncho Air Medizintechnik, Munich, Germany), a novel actuator, has a series of air jets that surround the valve-stem induction port, but the effect of this device on fine-particle dose seemed to vary between pMDI formulations[31]. pMDIs are sometimes regarded as old-fashioned inhalers that have changed little in half a century. However, this is only partly true. While the basic press-and-breathe pMDI is actually much the same as it was in the 1950s, apart from replacement of CFCs with HFA propellant formulations, there have been great strides in pMDI design relating to both devices and formulations. These technologic improvements should mean that pMDI

therapy can continue successfully well into the 21st century and provide many opportunities for inhalation therapy that are not confined to the traditional uses in the management of asthma and COPD.

Fig 10: MDI in the market

Dry Powder Inhalers

Dry powder inhalation 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.

Principles of Operation

The DPIs contain micronized drug blended with larger carrier particles, which prevents aggregation and helps flow. 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 air-flow. 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[32]. Figure 11 shows the principles of DPI design.

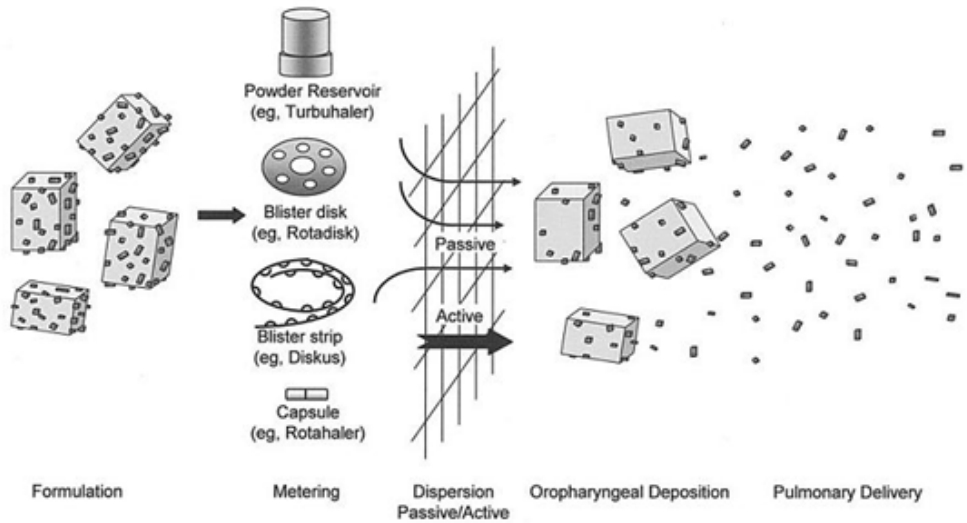

Figure 11: Principle of dry powder inhaler design

The formulation typically consists of micronized drug blended with larger carrier particles, dispensed by a metering system. An active or passive dispersion system entrains the particles into the patient's airways, where drug particles separate from the carrier particles and are carried into the lung.

Formulation Aspects

Dry powder formulations either contain the active drug alone or have a carrier powder mixed with drug. Particle size of drug should be less than 5 μm. It should be in the range of 2-5 μm. Generally the drug particle size is not well controlled during bulk drug production. The drug particle size must be reduced in a separate unit operation. There are various size reduction techniques such as milling, spray drying, and supercritical fluid extraction. There are various types of mills used for size reduction of drugs but few of them are suitable for DPI to reduce the size in the range of 2-5 μm such as fluid-energy mills, such as the jet mill; high-peripheral-speed mills, such as the pin-mill; and the ball mill[33]. The requirement to use micronized drug with small(ideally less than 5 μm) particle achieved good aerodynamic properties of the dispersed powder is confounded by the need to develop formulation that fill easily and accurately.It is also important that changes in the physical nature of the formulation on transportation and storage not adversely affect during formulation development. The inclusion of carrier can aid in the handling of the formulation and may impart some aerodynamic benefits also. The goal of delivering micronized powders is a challenging one. Because, these type of powder are highly cohesive. Their high interparticulate forces make them difficult to deaggregate, hence need for high inspiratory flowrate and turbulent airflow within DPI.Incorporation of carrier may aid the deaggregation process, but it can also lead to problem absorption of atmospheric moisture. Controlled temperature and humidity studies of salts form and lactose (or other suitable carrier) combination are essential during formulation development. Various techniques were developing to improve formulation performance by development of tertiary excipient like magnesium stearate and leucine. The inclusion of magnesium stearate in the DPI formulation as a ternary additive helped in improving the performance of the formulations. Magnesium stearate can form film layers which can adhere to drug-excipient particles and can interfere with inter-particle bonding as a result of hydrophobic coating [35]. The use of leucine also in the DPI formulation as a ternary additive has helped in improving the performance of the DPI formulations. This is possibly due to antiadherent action of the material.

Carriers Used in Dry Powder Inhaler

Carrier particles are used to improve drug particle flow ability, thus improving dosing accuracy and minimizing the dose variability observed with drug formulations alone while making them easier to handle during manufacturing operations. With the use of carrier particles, drug particles are emitted from capsules and devices more readily, hence, the inhalation efficiency increases. Design of the carrier particle is important for the development of DPIs.Carrier particles should have several characteristics such as physico-chemical stability, biocompatibility and biodegradability, compatible with the drug substance and must be inert, available and economical.[35]Lactose is the most common and frequently used carrier in DPI formulations accordingly nowadays various inhalation grades of lactose with different physico-chemical properties are available on the market. The advantages of lactose are its well-investigated toxicity profile, physical and chemical stability, compatibility with the drug substance, its broad availability and relatively low. Lactose, in particular alpha-lactose monohydrate, is typically used as 'the' carrier in dry powder inhalers. Due to several drawbacks of lactose and modified lactose as a carrier for dry powder inhalers, there is an urgent need to find suitable alternative carriers for better drug dispersibility in DPI.Alternative carriers like mannitol, glucose, sorbitol, maltitol and xylitol as potential carriers in DPI formulations. Of all the sugars evaluated, mannitol seemed to be a promising carrier for DPIs whereas sorbitol, maltitol and xylitol sugars were not able to generate desirable FPF due to their hygroscopic nature [36]. Carriers‟ like. crystallized mannitol (Pearlitol 110 C), spray-dried mannitol (Pearlitol 100 SD), crystallized maltitol (Maltisorb P90) and spray-dried lactose (Lactopress SD 250) for two drugs: micronized terbutaline sulfate and micronized formoterolfumarate,it was found that crystallized forms of the carrier offered lower adhesion and better release of the active ingredient than spray-dried forms. The crystallized mannitol produced maximal fine particle dose.

Basic Design of Dry Powder Inhaler Devices

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. This could be difficult for patients with severe asthma and for children and infant. In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual gelatine capsules, which are then inserted into the inhaler for a single dose and removed and discarded after use. 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. Newer devices of this type attempt to address issues such as reducing the flow rate dependent dose emission and of moisture ingress into the reservoir from patient exhalation or environmental humidity during the life of the product as these are common issues with the reservoir

type device. 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. A comprehensive and comparative review of commercially available DPIs and their classification is give below.

Unit-Dose Devices

Spinhaler®

The Spinhaler® (Aventis) was the first dry powder device, described in 1971. It has a mechanism for piercing the capsule. The cap of the capsule fits into an impeller, which rotates as the patient breathes through the device, projecting particles into an airstream. Shear force and relative motion are the predominant mechanisms of powder deggregation.

Rotahaler®

A similar DPI, the Rotahaler® (GlaxoSmithKline) has a mechanism for breaking the capsule into two pieces. 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 dug 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. A FPF of 26% has been reported for this low resistance device.

Aerolizer®

In the Aerolizer® (Novartis), the capsule is pierced on each side by four piercing pins. During inhalation, the capsule whirls and the particles are dispersed by turbulence generated by a spinning motion. Deagglomeration of the powder occurs through its passage through a plastic grid.

Handihaler®

The Handihaler® (BoehringerIngelheim) operates by dispensing drug contained in a capsule via a rumbling motion once the capsule has been opened by piercing pins. The particles are dispersed through the turbulence generated by a plastic grid at the time of inhalation. This device seems more complex as it requires at least 7 distinct steps to deliver the dose. For some patients, 2 inhalations are required to completely empty the capsule and achieve the therapeutic dose.

Multi-Dose Devices Multi-dose DPIs have been developed, eitheras multi-unit dose or as multi-dose reservoir devices.

Inhalator M®

Inhalator M® (Boehringer Ingelheim) has a rotating drum magazine for the storage of six capsules. The capsule is pierced at both ends and remains stationary while emptying occurs by fluidization due to the high pressure drop across the capsule. Deaggregation is caused by shear stress and collision.

Diskhaler®

The Diskhaler® (GlaxoSmithKline) employs 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 two holes in the mouthpiece that, together with a grid, gives rise to turbulence that promotes deagglomeration.

Diskus®

The Diskus® (GlaxoSmithKline) is quite similar except that it contains a foil strip with 60 single dose blisters. FPF have been reported to be approximately 23-30% for these two low resistance devices.

Turbuhaler®

One of the more sophisticated multi-dose reservoir systems is the Turbuhaler® (AstraZeneca). It contains 200 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 (Fig.12).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 (from a series of tortuous channels), impaction on the bottom of the mouthpiece and high shear stress in the swirl nozzle of the mouthpiece. This device of medium resistance has presented an FPF of 39-45%. The advantages of the reservoir systems are their relative ease and low cost of manufacture and the ease of including a large number of doses within the device.

Novel Dry Powder Inhalers

The large dependence on high inspiratory flow rates for the operation of the first dry powder inhalers led to the development of new technologies based on passive and active powder dispersion mechanisms. In both cases, the objective is to facilitate de-agglomeration of drug particles, resulting in greater lung deposition. Devices using passive mechanisms include Novolizer® (Meda, Sweden) and Airmax®(Yamanouchi, Netherlands)The air classifier technology has been described as the most efficient passive powder dispersion mechanism currently used in dry

powder inhalers.In this case, multiple supply channels generate a tangential airflow that results in a cyclone within the device during inhalation. Novolizer® uses this technology and, when compared to Turbuhaler®, showed a greater degree of budesonide deposition in the lung and lower drug deposition rates in the oropharynx. A similar mechanism is used in the Airmax®. This inhaler has a separator within which the airflow generates a cyclone similar to that observed in the Novolizer®, and this device also has greater efficacy than Turbuhaler®with respect to total drug that is delivered to the lungs, according to studies with salbutamol and budesonide.

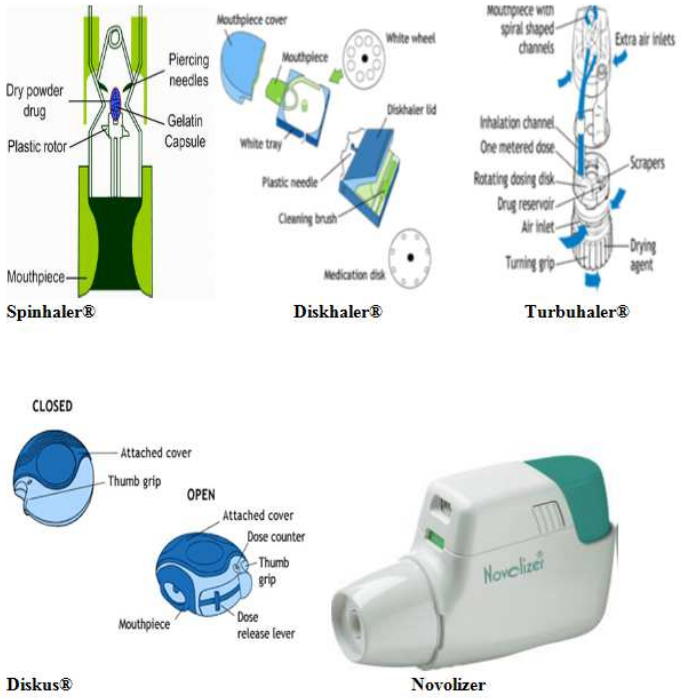

Fig.12: DPI's in the market

The technology of dry powder inhalers has developed to use energy as a key element in the process of particle de-agglomeration. Storage of mechanical energy in systems based on springs or compressed-air chambers was one of the alternatives found in some devices. Exubera® (Nektar Therapeutics, USA), for example, uses an air chamber that is actuated by the patient through a kind of manual pump. The effectiveness of this device, which was designed for aerosolizing insulin, Battery-powered, electrically driven systems have also become attractive options. Spiros®is a dry powder inhaler that operates appropriately even at very low inspiratory flow rates, exactly because it uses this principle to operate a twin-blade impeller that aerosolizes the drug. Advancements in these inhalers also include new types of powdered formulations of drugs through the production of microparticles by spray-drying techniques, resulting inporous particles, with low geometric diameter and high potential for lung deposition. Similar porous particles may be coupled to long-sized carrier molecules to reach the lungs with similar efficacy.Drug encapsulated liposomes are also a prospect of further improvement of drugs used in these devices[39].

Table 1: DPI devices currently available on the market[40]

Device	DPI type	Company	Drugs
Aspirair	Multi-dose	Vectura	ApomorphineHCl
JAGO	Multi-dose	Sky-pharma	Salbutamol sulphate
Airmax	Multi-dose	Norton-healthcare	Formuterol,budesonide
MicroDose	Multi-dose	3M	Insulin
Cyclovent	Multi-dose	Pharmachmie	Morphine
Technohaler	Multi-dose	InnovetaBiomeds Ltd	Sodium cromoglycate
Spiros	Multi-dose	Dura	Albuterol sulphate
Bulkhaler	Multi-dose	Astamedica	Albuterol sulphate
Omnihaler	Single dose	InnovetaBiomeds Ltd	ApomorphineHCl
Actispire	Single dose	Britania	ApomorphineHCl
Turbospin	Single dose	PH&T	Formuterol
Microhaler	Single dose	Harris pharmaceuticals	Sodium cromoglycate

Future Inhalers

Today the most wide spreading therapy in pharmaceutical industry is inhalations, this may be due to many reasons including faster onset of action, better bio availability and easy administration. However there is a need of implementation in these devices includes cost efficient, reducing lung depositions and device monitoring. With advanced technologies like adaptive aerosol delivery device (AAD – HaloLite) the nebulisers were developing in the way to reduce variability of the environment and facilitate monitoring of compliance with patient therapy. The device detects the pressure changes during tidal breathing and adapts to the inspiratory and expiratory flow patterns. The devices like aeroneb, eFlow, I-neb includes this type of technology. In the case of metered dose inhalers many devices like Onbrez, Breezhaler (indacaterol maleate) and Seebri® Breezhaler® (glycopyrronium bromide/NVA237) by Novartis which are in progress. The drypowder inhalers are most emerging devices in the field of medicine, however there may be great challenges need to overcome in case of these products including pressure monitoring, lung depositions and problems faced with CFC-propellents. These problems can be overcome in future devices with use of hydrofluoro alkanes and newer devices like microdose DPI's.

The future inhalers may be advanced with merging technologies in electronics and software and the imagined product may design as below:

- Inhaler usage history and spirometry data are wirelessly transmitted to the electronic copy of the patient's chart, viewable by both physician and patient.
- Inhaler calls your mobile phone as a reminder to take a dose.
- Inhaler tells patient when it's time to clean the device.
- Inhaler's dose counter triggers the inhaler to call to the pharmacy to order a refill pack.
- An inhaler with a built-in air quality monitor. Data from the device would be aggregated with data from other devices and plotted in Google Maps to show inhaler usage as a function of air quality and geographic area.
- Portable inhaler that can deliver both rescue and maintenance medications, at patient's selection

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