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Metered Dose Inhalers (MDI'S) for High-Performance Pulmonary Drug Delivery in Assistance to Nanotechnology

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Respiratory infections pose a severe danger to public health's morbidity and death on a global scale. Delivery via the lungs can be accomplished using several drug delivery tools, including nebulizers, MDI's and dry powder inhalers. Metered dosage inhalers are the most intriguing and the clinician's first preference out of all of them. This review emphasized based on metered dose inhalers for the delivery of pulmonary drugs. This study focuses on the provision of various therapies employing lipid nanocarriers, polymeric nanoparticles dendrimers & micelles, among others, using metered dose inhalers, liposomes, solid lipid nanostructures, nanostructured lipid carriers, and other topics were thoroughly explored. The market scenario for different MDI's as well as information on digital metered dose inhalers is also covered in this review.

Keywords: Cancer; Drug Delivery; Metered Dose Inhalers; Nanocarriers; Pulmonary Delivery.

A significant global hazard to morbidity and mortality in public health is posed by respiratory illnesses. The world's 2 billion people are exposed to environmental pollutants from a variety of sources, such as smoking cigarettes, incinerators, fireplaces for heating and cooking, etc. In addition, 40 lakh people die from chronic respiratory disorders worldwide. According to The Forum of the International Respiratory Society, there are five main respiratory diseases, or the "Big 5," which include lung cancer, acute lower respiratory tract infections, COPD & asthma
Out of these "major 5," over 65 million individuals have COPD, and 3 million people pass away from it every year, making it the 3rd greatest cause of mortality globally. Around 14% of children worldwide have asthma. Millions of people worldwide lose their lives to pneumonia each year, with pneumonia being the top cause of mortality in children less than the age of five. Around 10 million people are infected with TB each year, and 1.4 million of them pass away from it, making it among the most prevalent and deadly infectious diseases. The deadliest malignancy, lung cancer, claims over 1.6 million lives annually [1].

Although these respiratory disorders have a significant global impact on death and there hasn't been enough public awareness of and focus on morbidity. In comparison to other disease entities including diabetes, Alzheimer's disease, cancer,

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cardiovascular disease & stroke, research funding has likewise not accelerated considerably[2,3 4].

Over the previous two decades, devices to treat respiratory disorders have been developed using nanotechnology and nanoparticles to deliver drugs more effectively.

Nanoparticles have attracted attention in numerous fields during the last two decades, including semiconductor, medicinal, chemical, and environmental[5]. Due to the supremacy of the quantum effect & a significant increase in surface area, nanoparticles with sizes less than 100 nm exhibit unique features that make them appropriate for cutting-edge applications in electronics, defence, communication, energy, and biomedicine, including drug administration[5 6].

According to the Noyes-Whitney equation and the Ostwald-Freundlich equation, the huge surface area boosts dissolution kinetics & enhances saturation solubility.[7 8]

Because of the wide surface area, the medication is released fast from the concentration of the drug at the absorption site. Numerous methods, including chemical modification, stability of amorphous particles, canonization, and emulsion formulation, have been devised.

Numerous administration methods, including intravenous, oral, transdermal, & ocular, utilize nanoparticles. However, pulmonary delivery is uncommon. Unlike other routes of administration, pulmonary distribution offers certain advantages such as avoiding first-pass hepatic metabolism and lowering dose and side effects. Additionally, it enables the administration of medications for conditions like cystic fibrosis, COPD, and asthma. Fast absorption is made possible by the huge surface area of the lungs, thin epithelial layer, and abundant blood flow, which makes pulmonary delivery appealing. Due to its non-invasive nature, patients are more willing to comply[9].

Pulmonary drug delivery

For many years, the medication for asthma and COPD has benefited greatly from pulmonary medication delivery [2]. It is amongst the most crucial areas for research and development because it provides patients with the highest level of therapeutic effectiveness by quickly acting on drugs that target the lungs directly[10]. When compared to oral formulation, the overall dose is decreased. Salbutamol dosages, for example, are decreased by a factor of 10 to 20.[11].

Maximum lung specificity also minimizes the undesirable systemic effects [12]. There are several therapeutic inhaler devices on the market, including Dry Powder Inhalers, Nebulizers, Soft Mist Inhalers, and pressurized metered dose inhalers (pMDIs)[13 14]. As long as they are used properly, comprehensive reviews and meta-analyses of the evidence have shown that nebulizers, pMDIs, and DPIs have roughly equivalent effects for delivering glucocorticoids and bronchodilators [1516].

Types of inhalers

Dry Powder Inhalers

Bell and colleagues unveiled the first inhaler device that utilized DPI technology in 1971[17]. Then, sophisticated DPI devices were created for COPD & asthma patients. Inhaled dry powder formulations are loose agglomerates of micronized aerodynamically small medication particles less than 5ìm. Drug particles that have been micronized and adhered to large lactose carriers are combined in carrier-based interactive mixes. Aerosolization of the powder formulation is done using a DPI device, which de-agglomerates or separates the drug particles from the carrier before delivering the dose to the patient's lungs. DPI is categorized generically into 3 types: single-dose DPIs, active or power-assisted DPIs & multiple-dose DPIs[18]. Breath activation is used with single-dosage DPIs, which have buttons that are perforated with needles inside the device. Drug delivery is dependent on the patient's respiratory system. DPIs with many doses are an alternative to DPIs with a single dose. Devices with multiple doses are also those with multiple doses and several units of DPI [19]. Power-aided DPI devices have been created to address the issue of COPD patients not receiving enough inhalation therapy. These devices have low-flow activation capabilities and enhance lung deposition. Piezoelectric crystals that vibrate and battery-powered impellers are used to spread the medication. The main advantages of DPIs are that they don't require hand strength or coordination of inhalation with activation. DPIs must be primed and loaded in elderly individuals who have Parkinson's disease, joint discomfort, and stroke-related problems. Clinical research also demonstrates high patient compliance [20].

Nebulizers

Nebulizers are crucial for treating conditions where patients are unable to obtain the required flow rates and substantial pulmonary dosages are required. There are three different types of nebulizers depending on how the drug solution is converted into aerosol: Vibrating mesh, Jet & Ultrasonic[21]. Jet nebulizers are frequently used to turn liquid medications into aerosol particles using compressed gas. Limitations include longer treatment times, mechanical force, and noise. Portable and silent, ultrasonic nebulizers function. However, because ultrasound heats the medicine, it is incompatible with thermally sensitive medications like protein[22]. The newest technology, the vibrating mesh nebulizer, offers benefits such as a short treatment time, little leftover volume, and increased aerosol delivery[23]. The main obstacle is the price. Since all of these devices continuously create an aerosol, a significant proportion of medication is lost during exhalation. The main drawbacks, however, are that they are heavier, require more time for administration, and have a poorer delivery efficiency[24]. Philips I-Neb® & Activaero AKITA® nebulizer systems, two newly created and commercially accessible advanced technology-based nebulizers, are just two examples[25,26].

Soft MIST Inhalers

Microelectronic dosimetric systems are included in soft mist inhalers (SMI, such as Respimat). A fixed volume of a solution of the drug is sucked up into the dosing system when an SMI is manually primed through a nozzle with 2 condensed outlet channels that were carved using microchip technology. Soft mist inhaler aerosol outperforms a pMDI in terms of sustained duration, low velocity, and high fine particle fraction[27,28]. Compared to a pMDI, the SMI version has two to three times as much pulmonary deposition[29,30].

Metered Dose Inhalers(MDI's)

MDI's are the most promising pulmonary medication delivery method available. Metered dose inhalation therapy can now be used more effectively thanks to recent advancements in the fields of Nanotechnology, Biotechnology Particle engineering, Material sciences, and related sciences[29,30]. Metered dose inhalable formulations based on nanoscience serve to enhance therapy outcomes and reduce negative side effects[31]. To study the pulmonary delivery mechanism and therapeutic effect, a variety of drug delivery systems, including polymeric nanocarriers[32] that include polymeric nanoparticles, dendrimers, micelles & lipid-based nanocarriers[33,34], have been integrated with MDI.

Nanocarriers

Polymeric Nanocarriers

One of the extensively researched nanocarriers for a variety of drug delivery applications, such as cancer, HIV, COVID-19, & Inflammatory Bowel Disorder (IBD), is polymeric nanocarriers[35,36]. Micelles and polymeric nanoparticles are the two most prevalent polymeric nanocarriers. Polymeric nanoparticles have received substantial research because of their tremendous potential as Drug Delivery systems for treating a variety of ailments[37]. Before creating nanoparticles, polymers can be modified and functionalized to create functional polymeric nanoparticles. Through encapsulation into the polymer, Drug & therapeutic agents can be delivered to the exact site of action (deep lungs). It is possible to create drug-loaded nanoparticles by encasing the drug in a polymeric matrix[38,39]. The polymers that have received the most attention for research include cyclodextrins, polyanhydrides, poly (ortho-esters) , polyhydroxyalkanoates, poly-(lactic-co-glycolic-acid) (PLGA), poly(lactic acid), chitosan & poly (phosphonates). Polymers can be easily changed to respond to stimuli by adding the right chemical linkages [40,41]. Compared to inorganic nanoparticles, polymeric nanoparticles demonstrated less toxicity[42]. Controlling the physicochemical parameters of the polymer allows one to alter the kinetics of drug release. Widely employed in metered dosage inhalation-based medication delivery are polymeric nanoparticles. [43] developed and studied cross-linked chitosan-based NP's based pMDIs to transport small molecules to the peripheral airways to address this problem[44]. Using polyethylene glycol (PEG) 1000 (30%), sodium tripolyphosphate (1%) & cross-linked chitosan (5%) NP's were mostly produced. Cross-linked chitosan NP's were also mixed with the propellant hydrofluoroalkane (HFA) 227 to create pMDIs. The spherical, smooth-surfaced NP's had a Hydrodynamic diameter of 193.3 nm and a Zeta Potential of +28.2 mV. Cationic crosslinked chitosan PEG 1000 NP's did not assemble at the

lung pH. When dispersed in propellant HFA-227, Cross-linked chitosan PEG600 & 5000 NP's rapidly sedimented or creamed, whereas cross-linked chitosan PEG1000 NP's displayed good physical stability and dispersibility. Before being dispersed in HFA-227, the PEG incorporation during NP's formation changed the surface characteristics of the NP's and provided effective steric stability[41,44]. Additionally, the dispersion characteristics of crosslinked chitosan NP's are enhanced by the amphiphilic character of PEG with an appropriate Molecular Weight. To comprehend the aerodynamic performance, cross-linked chitosan nanoparticles were tagged with Fluorescein-5-Isothiocyanate (FITC). The Cross-linked chitosan NP's that were FITC-labelled showed dimensional Hydrodynamics and Zeta Potential measurements of 203 nm and +24 mV, resp. The work briefly highlights the potential of crosslinked chitosan-PEG 1000-based NP's as carriers for the delivery of small molecules & medicinal agents to the peripheral airways[44]. Currently, chemotherapy, radiation therapy, surgery, immunotherapy, and/or a combination of these are frequently used to treat lung cancer. Chemotherapeutic drugs' systemic delivery to the lung tumour is the main obstacle. Utilizing the method of precipitation and the Schiff base re-arrangement methodology, the pH-sensitive mPEG-1K DOX conjugated NPs were created[45,46]. The NPs had average particle sizes of 104 nm and DOX loadings of 32.7%, respectively. When placed in an acidic environment (pH 5.5 lysosomal pH/endosomal), as opposed to the physiological environment(pH 7.4), mPEG-1 K DOX linked NP's with pH sensitivity demonstrated increased DOX release (85%). Human lung Adenocarcinoma cells were used in in-vitro cytotoxicity research, and NPs displayed IC50 values that were roughly 24-fold lower than those of NPs made using mPEG-5 K. Additionally, the rate and extent of NP's internalization within cells follow a similar trend. Additionally, to create pMDIs, mPEG-1 K DOX linked NPs with pH sensitivity were distributed into the propellant HFA 227 with ethanol acting as a cosolvent. FPF and MMAD of NP's during in-vitro aerodynamic analysis were 63.5% and 1.6 m, respectively[45]. The physical and biological characteristics of the NP's were significantly impacted by the mPEG molecular weight (1K, 2K, and 5K Da). Cellular Internalisation, In-Vitro release rate, & In-Vitro destructive ability of NP's to lung cancer cells all increase with a shorter PEG chain. The pMDI formulations of NP's with shorter PEG chains also display better & more Aerodynamic performance & dispersibility. Therefore pulmonary administration of polymer-based pMDI offers great promise for use in clinical settings when treating lung cancer[45]. Recently, cinnamaldehyde, cineole, and citral were said to be used for stabilization. Thymopentin NP's-based pMDI was created by [47] and its aerosolization performance was carefully examined. Thymopentin NP's were made by bottom-up, freeze-drying Lecithin & Lactose in a water co-solvent system/tert-butyl alcohol, then centrifuging the excess lecithin out of the lyophilized matrix [43]. Polydispersity index and particle size of NP's were significantly influenced by lecithin concentration & the water content. Thymopentin NP's with an average particle size of 150nm & a polydispersity index of 0.1 was created using small, spherical-shaped water molecules that made up 33.3%(v/v) of the co-solvent system & 20.0%(w/v) of the organic phase. Fabricated thymopentin NP's were introduced to a glass container with a plastic coating and a 50 mL valve before HFA 134a propellant was added. Finally, cineol mixture/n-heptane was added to give suspension-type pMDI an excellent dispersibility[43]. During aerosolization studies using a Twin stage impinger(60 L/min), Thymopentin NP's pMDI demonstrated FPF greater than 55% with little deposition on the pMDI actuator. After 26 weeks of storage, the Thymopentin NP's pMDI had a relative thymopentin concentration of more than 97% with FPF 47%. The Thymopentin NP's were largely deposited to an area matching the lower pulmonary airways, indicating a favourable pulmonary drug delivery alternative, according to the Performance during aerosolization and pMDI suspension's stability over six months of storage[43]. Several polymeric micelles are being developed for preclinical and clinical usage in the delivery of anticancer medications. Comprehensive documentation of a review of micelles made with polymers for pulmonary medication administration was provided by [10]. Conventional and functional polymeric micelles are the two main types of polymeric micelles. The functional characteristics of polymeric

micelles, such as targeting, cell penetration, stimuli responsiveness, & mucoadhesive, were demonstrated. Direct dissolving, o/w emulsification, solvent evaporation/thin-film hydration, freeze-drying & dialysis are all methods for creating polymeric micelles[48]. Polymers with properties such as the composition of both hydrophobic & hydrophilic segments, biocompatibility, a low critical micelle concentration, high water solubility, biodegradability, non-toxicity & non-immunogenicity are suitable for the synthesis of micelles for pulmonary drug delivery. [10]. provided a table-format summary of the literature on the use of MDI's to deliver several drugs utilizing polymeric micelles[10]. Nanoparticles of Anhydrous reverse micelle were created by [45] to address the unstable sedimentation of pressured metered dosage inhalers containing peptides. Micelles are created by Lipid inversion & Freeze-Drying. Synthesized anhydrous reverse micelles had a polydispersity index (PDI) of 0.152 and a size of 147 nm. They demonstrated an appropriate 46.99% fine particle fraction for MDI's. They demonstrated a 12-week sedimentation stability of 4-6°C[45]. There is a lot of room to investigate the use of micelles in MDI therapy for pulmonary diseases.

Dendrimers

Branching macromolecules with monodispersed topologies makeup dendrimers. Dendrimers are made up of a core, internal layers, and a terminal functional group, which are three different structural components. Click chemistry, multicomponent processes, and cycloaddition techniques can be used to create dendrimers[46]. Dendrimer-based drug delivery and targeting have advanced significantly in recent years. The use of dendrimers in the monitoring, therapeutics, diagnosis, imaging, & treatment of many diseases is widespread[48]. Due to their high density and surface functional group, poly(amidoamine) (PAMAM) dendrimers are extensively researched as nanocarriers. Drug solubility and bioavailability were improved by dendrimer conjugation[49]. To investigate the effectiveness of siRNA aerosol formulations in pMDI and in-vitro transfection within a pulmonary epithelium, [50] created triphenylphosphonium (TPP) adorned Fourth Generation (G4) poly(amidoamine) dendrimers. TPP and the G4-dendrimer were joined utilizing while chemistry is taking place, whereas siRNA & the TPP-G4-dendrimer were joined using electrostatic contacts (dendriplexes). TPP density & N/P ratio had a striking impact on the effectiveness of siRNA's invitro transfection[50]. 12 TPP molecules conjugated to Dendriplexes & a 30 N/P ratio demonstrated the best in-vitro gene knockdown efficacy when used with lung alveolar epithelial (A549) cells in the current investigation. In-vitro siRNA transfection efficacy was significantly improved by dendriplexes over unmodified dendriplexes by a factor of two. Dendriplexes showed zeta potentials of 40mV, 363nm & 0.36, resp., for their Hydro-dynamic diameter & Polydispersity Index. Using mannitol as a carrier, Spray-drying was used to create inhalable dendriplexes microparticles[50]. Spray-dried nano complexes with a smooth, spherical form and geometric and solvated diameters of 2.4 and 4.2 ìm, resp. demonstrated good yield (76%) and strong loading efficiency. Using the Andersen Cascade Impactor (ACI) at 28.3 L/min, nano complexes pMDI (63L metering valve) were created using the HFA-227 propellant and displayed MMAD & FPF of 3.8ìm & 50.3% respectively. When compared to nano complexes DPI, the pMDI showed a significant 1.3-fold improvement in FPF. As a result, the TPP conjugate G4-dendrimer provides a special stage to enhance the biological effectiveness of siRNA during pulmonary distribution[50]. Using poly(D, L-lactide-co-glycolide), [51] created core-shell structures with 3-amine-terminated poly (amidoamine) dendrimers (PLGA). The airway epithelial cell line from the humans (Calu-3) model & aerosol characteristics by multistage cascade impactor were used to methodically evaluate dendrimers for in-vitro cellular transport & absorption. With the use of isothiocyanate chemistry, fluorescein isothiocyanate (FITC) was first attached to dendrimers & then those Dendrimers were loaded into PLGA's biodegradable polymeric matrix using a solvent for core-shell nanoparticles[51]. Lyophilized core-shell NP's (245nm) in smooth spheres had a loading efficiency of 7.8% & Zeta Potential of 10 mV. An in vitro experiment using core-shell NP's in 1X mucus with Hank's Balanced Salt solution (pH 7.3) showed persistent release that could be attributed to diffusion processes from PLGA polymeric matrix. After 2 days of exposure, core-shell NP's had no harmful effects on the

Digital device	Pharmaceutical Organization/Device Developer	Digital device details	Publication approval year
Nebulizer Chronolog[81].	Advanced Technology Products, Inc	It is a small electrical device that connects to the MDI device and logs the time & date of each actuation.	1982
Doser™[81]	Meditrack Inc.	An MDI device is used to track drug usage. It has a flexible grasping cup that fits the MDI device's top with ease. The internal microcomputer of the DoserTM counts & displays the number of doses left in the MDI.	1994
Smart Mist® [81,82]	Aradigm Corporation	Because of their unique shape, they effectively cover the entire MDI gadget. Without requiring any modifications, the MDI device(actuator & canister) can be installed within the Smart Mist®. It has a micro-processor that can measure the flow rate and volume of inhaled air.	1996
MDILog™ [81,82]	Medtrac Technologies	This tiny device is affixed to the actuator permanently. An actuator-to-actuator switch links the canister during an actuation.. Each actuation's shaking, date, and time are recorded. A built-in thermistor also recognizes the patient when they make an effort to inhale.	1997
VeriHaler[79,83]	Sagentia Innovation	To gather crucial information about how the device is used, it has a condenser microphone built into the device's case that uses a proprietary algorithm to filter out distracting surrounding noise. It can be used with both DPI's & MDI's.	2010
T-Haler[81,83]	Cambridge Consultants	It is an inhaler with instructions and geographic awareness. It records how the user operates the inhaler using onboard sensors and Wi-Fi and displays real-time directional feedback on a computer monitor.	2012
Propeller[79,84]	ResMed	A computerized tool called Propeller records medicine use and provides user-specific data to help lessen & manage symptoms.	2014
CareTRx [81,85]	Teva Pharmaceutical Ltd.	Patients with COPD and paediatric asthma who use a cloud-based smart inhaler attachment are better able to follow their treatment regimens.	2014

eMDI[86]	H&T Presspart & Cohero Health	Real-time updates on prescription use, Customized reminders, alerts, reports, as well as weekly and monthly summary reports, are all made possible with its help. Both MDIs and DPIs can be used with it because of its modular design. The BreatheSmart app is used with it.	2016
Inspair[79,87]	Biocorp	The gadget fits MDI mouthpieces and has electronic cards and miniature sensors. Every day's inhalations are automatically tracked, the canister is properly prepared (shaken before use), the coordination of inhalation & actuation is evaluated ("hand-mouth" coordination) & helpful instructions are given at each stage of the inhalation process.	2016
Intelligent Control Inhaler (ICI)[88]	3M Drug Delivery Systems	Patients do not need to time their in-breath with the device's triggering because the gadget is designed to deliver the medication automatically at the proper inspiratory flow. Together with the device, a companion app was created that reminds users to take the right amount and renew their prescriptions and offers feedback on their technique to help them use the right technique.	2016
Hailie®[89]	Adherium Ltd.	MDI is immediately enveloped in the apparatus. Data on medicine use is gathered by its cloud-based platform using Bluetooth sensors. It is used with the Hailie® app.	2018
HeroTracker® Sense [79,90]	Aptar Pharma and Cohero Health	Provide real-time feedback while keeping an eye on the pharmaceutical process. It delivers warnings about the environment, regular reminders, and health-related information to keep you and your carers informed. With the BreatheSmart® app, it is utilized.	2018
FindAir ONE[91,92]	FindAir	It is small enough to fit on the tip of an inhaler and collects information on every medicine use, including the date, location, and specifics of each exacerbation.	2019
Adhero[79,93]	Aptar Pharma & Lupin Limited	Reusable Bluetooth-enabled smart gadget that is designed to fit on top of an MDI. It works with the "My Adhero" app.	2019
CapMedic™[94]	Cognita Labs	An audio, visual, and haptic coach built into the apparatus aids in measuring all crucial MDI usage phases. It evaluates seven use-related processes or faults, including crucial factors like coordination, inspiration, and orientation. It is usable even without an app.	2020

monolayers of Calu-3 cells[51]. The airway epithelial model revealed that core-shell NP's appeared to be permeable, the same as a paracellular marker (dextran). Dendrimer's pattern of cellular internalization and transport are both influenced by core-shell NP's. Throughout the trial, which lasted for 5 hours, core-shell NP's effectively crossed the lung epithelium. ACI(28.3 L/min) successfully generated MMAD (3 ìm) & FPF (55%) for the pMDI(HFA 227) of the core-shell NP's aerodynamic study. In conclusion, core-shell NP's pMDI is an essential option to control cellular absorption & movement of therapeutic substances & may be investigated to achieve desired local or systemic drug administration[51]. Polyester dendrimers with G3(0.8nm) & G4(1.3nm) FITC conjugations displayed Zeta potentials of 2.3mV & 1.3mV, resp. G4 polyester dendrimers that had been PEGylated (PEG 1000) displayed average particle sizes & Zeta potentials of 4.2nm and 0.0mv, resp. PEGylated G4 polyester dendrimers did not significantly degrade in physiological buffer solution(pH 7.4) until day 5 & after 30 days, the dendrimer displayed a degradation profile comparable to the unchanged dendrimer[52]. The increased solvation of the dendrimers by the HFA utilized to prepare pMDI is responsible for the good aerodynamic characteristics. In a nutshell, PEGylation of polyester dendrimers has a major impact on aerodynamic performance, cellular uptake, and degradation. These combined biological and aerodynamic findings support the use of dendrimer synthesis and PEGylation to alter their interaction with the Pulmonary Epithelium & to formulate them for use in portable pMDI delivery systems[52]. Additionally, pMDIs based on acid-labile G3-NH2-PEG1000-DOX dendrimers were investigated for Pulmonary Drug Delivery[53]. The degree of PEGylation can be employed to adjust the carrier characteristics during pulmonary medication delivery. Being able to effectively limit lung retention time, PEGylated Dendrimer Conjugate is a useful treatment option for primary lung cancer with metastatic locations, lung metastases, & primary non-metastatic cancer[53]. Dendriplexes microparticles demonstrated GSD(3.8) FPF(48.9%) & MMAD(2.6im) adequate for pulmonary delivery during aerodynamic evaluation utilizing ACI (28.3 L/min). These findings demonstrated that the strategy using dendriplexes microparticles had a higher potential for transporting biological materials to the pulmonary airways[54].

Lipid-based Nanocarriers

Lipid-based nanoparticles have certain characteristics that set them apart from other nanocarrier systems. Numerous lipid nanoparticles exist, including self-emulsifying drug delivery systems, solid lipid nanoparticles, nanostructured lipid carriers, and liposomes.[55]. Lipid bilayers make up the vesicular carriers known as liposomes. The liposome-encapsulated medication provides a longer therapeutic effect because of its depot action. The versatility of liposomes allows for the loading of both lipid- and water-soluble medicines as well as gene delivery[56]. Liposomes exhibit up to a 24-hour retention period in the lungs. Interleukin 2, Catalase, Budesonide, Insulin, Rifampicin, 9NC & polyethyleneimine-p53 DNA are all delivered to the lungs using liposomes[57]. However, clearing the respiratory tract of the particles is also more crucial. Particle physicochemical characteristics affect particle clearance. The main factors that affect how effectively deposited nanoparticles are cleared are age, exercise, influenza, and pneumonia [58]. Nanocarriers made of solid lipids are the most intriguing. The 1st Generation of solid lipid nanoparticles was created in the 1990s by research teams led by [59]. The drug is put into the lipid matrix of SLN's, which is stabilized with an emulsifier or surfactant. SLNs have a size range of 40 to 1000 nm.

The main benefits of SLNs include physical stability, drug degradation prevention, regulated release, and minimal cytotoxicity[60]. Due to their favourable tolerance in the airways, SLNs are attractive for pulmonary administration. SLNs have deep lung deposits that are simple to aerosolize. Due to the accumulation, adhesion, & holding of the SLN's in the lungs, the medication is released slowly, reducing the need for dosing[32]. Over the past 20 years, business interest in nanostructured lipid carriers has grown significantly. When delivering cancer chemotherapeutics, NLCs are more efficient. If have reasonable tissue toxicity, targetability, stability, specificity, and steadiness[32]. To manufacture surfactant-coated Plasmid DNA nanoparticles for gene delivery using a pressurized metered dose inhaler, [61] created a unique low-energy nanotechnology approach. Using ethanol

as a cosolvent and hydrofluoroalkane 134a as a propellant, lyophilized pDNA was added to pMDI. Utilizing transfection analysis, in-vitro toxicity assay results revealed no appreciable loss of biological functionality & cell viability[61].

Biologics

Due to their use in treating serious respiratory illnesses like cancer, cystic fibrosis, and tuberculosis in the previous years, pulmonary administration of biological substances(e.g., siRNA, RNA, proteins, DNA & peptides) has attracted significant attention[62,63]. [64] study of this application focuses on inhaled antibody systems. To enhance the Immunoglobulin G's aerodynamic qualities, Immunoglobulin G powder was created using the spray drying procedure & added to pMDI.

Miscellaneous pMDI Formulations

Other formulations were examined for medication delivery using MDI in addition to the drug delivery systems already mentioned. Using pMDI, [65] created assemblages of microcrystals & designed microparticles to distribute medication actives (formoterol fumarate dihydrate, mometasone furoate & glycopyrrolate) effectively and consistently. Spray drying was initially used to create phospholipid/calcium chloride porous microparticles, whereas air jet milling was used to create drug microcrystals. Microcrystals of mometasone furoate (1.0ìm), Glycopyrrolate (1.7ìm) & Formoterol Fumarate Dihydrate (1.4ìm), revealed mean particle sizes adequate for pulmonary drug delivery, as did spray-dried porous microparticles (2.3ìm). A layer with a thickness of about 100nm was created by an amphiphilic particle surface, and designed microparticles also displayed a corrugated surface. In conclusion, co-suspension technology-based dual or triple combination pMDI is effective for treating respiratory diseases[65]. The total dose of Sibenadet Hydrochloride pMDI (1–25 mg) did not significantly affect the FPF, according to an aerodynamic study. Relative interparticle interactions with the micronized carrier particles contributed significantly to the decreased aerosol performance of sibenadet hydrochloride with binary particulates. [66]. Surface energetics of the drug & carrier are responsible for controlling particle cohesion/adhesion, interparticle interactions & sedimentation rate of formulations.[66]. To treat pulmonary hypertension, [67] created cyclodextrin (CD)-based sildenafil citrate pMDI. Dried ethanol and HP-CD, CD, and CD were predominantly used in the production of the sildenafil-CD (1:17) combination.

Due to the unequal distribution of the pMDI clouds over the blood artery & difficulty in achieving precise control on the spraying region, compared to sildenafil complex pMDI, sildenafil complex intravenous injection exhibited better interaction with blood vessel smooth muscle cells. [67]. In short, CD-based pMDI is an important step toward effective pulmonary medication delivery.

Treprostinil MDI (2–3 puffs) was inhaled as a whole, causing selective pulmonary vasodilatation that peaked after 30–45 minutes and continued to have an effect on hemodynamic for the remaining two hours. Treprostinil MDI demonstrated satisfactory results in the medication of pulmonary hypertension; nevertheless, a controlled clinical trial is required to investigate several important concerns, including ease of handling, device size & patient autonomy & the formulation's long-term efficacy [68].

The atomized Clarithromycin particles which were collected from stage 4 of the cascade, had a corrugated spherical shape because of the quick evaporation of the propellant and co-solvent after actuation, in contrast to the raw clear Clarithromycin particles, which had columnar surface morphology. Furthermore, the fact that the deposited clarithromycin particles have no clearly defined angular morphology confirms the material's indeterminate(amorphous) character. Additionally, the Clarithromycin pMDI formulation had good aerodynamic properties and was physically stable for a month(storage at 4 & 37°C). In essence, the study suggested that lung inflammatory illnesses may be treated by creating a solution-based pMDI that contains low-dose macrolide[69].

The MMAD & FPF of low-dosage diclofenac pMDI were lower, at 9.94 ìm & 7.1% respectively. Additionally, pro-inflammatory cytokines IL-6 and IL-8 significantly decreased during the evaluation of the anti-inflammatory action in the airway cell culture models of the Cystic Fibrosis (CuFi-1) & Normal Lung (NuLi-1) caused by the Air Liquid interface. In short, the current study suggests that aerosolized low-dose diclofenac pMDI may be an effective inhalation anti-inflammatory medication for the medication of cystic fibrosis[70].

In comparison to the tablet (2.5mg), the HFA 134a-based Zolmitriptan pMDI demonstrated 1.96-fold reduced Tmax, 1.19-fold greater Cmax, & 1.25 times higher relative bioavailability. In short, HFA 134a propellant-based pMDI formulations of anti-migraine medications may be a good substitute for migraine therapy since they act more quickly [73]. Ipratropium Bromide & Fenoterol Hydrobromide pMDI are solutions-based drugs that [71] thoroughly examine the effects of formulation composition (ethanol, water & propellant) on stability & aerodynamic functioning. In a nutshell, the vapor pressure of the cosolvents, the propellant, and the dielectric constant should be within an appropriate range to impart acceptable aerosol characteristics and physical stability[71]. To comprehend the aerodynamic performance, [72] developed montelukast pMDI employing HFA 134a & pre-mixed HFA-134a/HFA-227 propellant.

Nitric Oxide levels in NR-8383 cells incubated with a pre-mixed propellant, however, were considerably greater than in NR8383 cells incubated with a single HFA propellant. Although montelukast pMDI formulations are non-toxic & not anticipated to exacerbate airway cells, more in-vivo research is required before montelukast pMDI formulations can be deemed safe [72].

According to a deposition study, theophylline took 180 minutes to get to its target, the A3 adenosine receptors in smooth muscle cells, where it could start working its effect. Interleukin-8 (IL-8) levels in Calu-3 cells treated with TNF & plain theophylline were found to be 4.5 and 1.81 times lower, respectively, than those in theophylline pMDI during in-vitro inflammatory testing. Encapsulated, theophylline pMDI formulation minimized side effects by lowering the dose needed for local therapy[73].

MDI Devices: Effect of Various Parameters on Aerodynamics and Drug Deposition

An MDI is a small, portable pressurized inhalation device that uses a propellant to administer a specific medicine dose to the patient regularly [74]. The design of inhaler devices has a considerable impact on the results of the drug substance's aerodynamic profile & drug delivery process[75,76]. To effectively treat chronic respiratory disorders, choosing the right inhaler device is essential. The percentage of the radiated dose that is settled in the lung and the volume of medicine deposited in the throat are the major indicators of pMDIs aerodynamic effectiveness (i.e. FPF).

Furthermore, throat deposition is significantly influenced by droplet lifespan (evaporation duration; a discrete two-phase process), and FPF suggests that evaporation kinetics significantly controls pMDI drug delivery. The amount of medicine settled in the lung and throat (i.e., FPF) is significantly influenced by the propellant and co-solvent choices made [77].

Data show that higher sustained plume velocities increase fine particles around the spray's periphery due to better shear, and that fine particles are formed by smaller orifices (0.22mm) and smaller orifices. The drug deposition profile and the formulation's aerodynamic performance are both affected by a little adjustment to the pMDI device[78].

Digital pMDI's Devices

Digital technology may improve patient compliance and adherence to long-term inhalation therapy. E-healthcare and remote technologies are alternatives to conventional laminating. E-healthcare systems have just lately caught the interest of patients, healthcare professionals, and researchers in the biomedical field. For the creation of an absolute digital inhaler, several electrical and mechanical devices, including a nebulizer chronology, mechanical switches, an aerosol actuation counter, a system on a chip, & a Bluetooth Low Energy module, have been investigated and analysed. The use, purpose, and essential clinical applications of the electronic monitoring device are discussed elsewhere[79]. Table I contains a list of the digital pMDIs devices that are currently offered. To quantify the finger muscle power required to actuate pMDI formulation, [80] recently created a modified pMDI pinch gauge.

According to studies, finger muscular strength should be assessed when choosing a pMDI device for senior asthma patients. Patients with lesser finger muscle strength are advised to use a pMDI spacer[80]. This is where the digital pMDIs device comes into play which is fast gaining popularity and holds great promise because it may give patient-centered care along with workable solutions for pharmaceutical companies, patients, and healthcare practitioners to enhance patients' quality of life.

Clinical Potential of pMDIs

The advantages of MDI over other devices have been discussed in great detail in the literature. We think MDI is the easiest, least expensive procedure, making it the clinician's first option. The United States & Europe approved the various metered dose inhalers. However, work is currently ongoing to create electronic and digital pMDI devices that are simple & affordable for patients to use.

CONCLUSION

With the aid of about 100 pertinent & representative pieces of research, this study has highlighted numerous MDI's for efficient drug administration. Dendrimers, polymeric nanocarriers & lipid-based nanocarriers are the most intriguing nanocarriers because of Physicochemical characteristics that are desirable and adjustable.

This review concludes that Liposomes, Polymeric nanoparticles & Dendrimers are all viable options. However, more research is required on the usage of renewable biopolymers.

However, significant future research must be planned, and this study makes the call for that research.

It has been demonstrated that the Pulmonary Route of Administration employing pMDI is efficient in the local and systemic distribution of medications, and biopharmaceuticals to treat a variety of respiratory disorders. MDI has always been affordable, convenient, sturdy, portable, and small. Each gadget, however, has unique benefits and drawbacks. Therefore, additional research is required to find solutions to the problems. But improving patient adherence and digitization are the primary issues that need to be addressed.

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Conflict of Interest

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