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Review Article

Review on a Novel Advancement in Dry Powder Inhaler

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A B S T R A C T

Human health management has always been the focus area of medical practitioners across the world. Health is maintained with the right kind of food intake, regular exercise, and remedial medications whenever and wherever necessary. Medications have been an integral part of human health management and improvement ever since. Along with medications, the right kind of drug delivery mechanism plays a crucial role in the efficacy of the medications. Dry powder inhalers (DPI) are one of the most efficient and advanced targeted drug delivery mechanisms. Currently, a wide range of inhaler devices are available on the market for pulmonary drug delivery with a view to maximising drug delivery with low variability compared to other drug delivery systems. Compared to other oral, topical, and parenteral drug delivery methods, DPI's efficiency is manifold. It has varied benefits, like rapid drug absorption due to the high density of blood vessels and the large surface area of the lungs (high lung deposition); the lungs have low enzymatic activity, so this route has a minimum risk for enzymatic degradation. Faster absorption, maximum efficiency, site target, minimum wastage, user-friendly, etc. Historically, DPIs were used only for respiratory-related ailments. But now, due to their better utility value, DPIs are also used in other maladies treatments.

This research paper focuses on various advancements in the field of dry powder inhalers (DPIs), their advanced manufacturing techniques, challenges, and the evolution of technology that help maintain their versatility, stability, and reliability.

Key Words: Dry Power Inhaler, Lung Deposition, Low Variability, Enzymatic Degradation.

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INTRODUCTION

Dry powder inhalers are pulmonary drug delivery systems that deliver dry powder of active drug for site target and systematic effect via the pulmonary route. The benefits of pulmonary drug delivery systems were reported many years ago. Comparing oral and parenteral routes, the pulmonary route shows a higher local effect within the lung[1]. Nowadays, the pulmonary drug delivery system shows more popularity due to its several advantages over any other drug delivery system, including rapid drug absorption due to the high density of blood vessels and the large surface area of the lungs. The lungs have low enzymatic activity, so this route has a minimum risk for enzymatic degradation. This pulmonary route has been accepted for both local and systematic effects of the [2]. Pulmonary drug delivery by dry powder inhalers (DPI) is more effective due to its propellant-free nature, high patient compliance, high dose carrying capacity, and drug stability. It has been reported that rapid development has occurred in recent years due to the realisation of the full potential of the lungs for local and systematic treatment of [3].

Dry powders have physiochemical properties such as size and shape, surface morphology, charge, hygroscopicity, and moisture content. These properties have a direct effect on the aerosolization process, discharge from treatment devices, and bioavailability of aerosolized[2]. The most common technique used to achieve ideal physicochemical properties of dry powder is mechanical milling; other promising techniques reported are spray drying, freeze drying (lyophilization), and the supercritical fluid-carbon dioxide drying technique.

Recent novel developments were reported that show more effectiveness than conventional dry powder. Dry powder inhalers have more effective than other system contain solid drug suspended or dissolve in non-volatile propellant which result into direct delivery of drug into deep lung [4].

This review paper mainly focuses on DPI design, method of preparation, characterization, limitations andrecent novel innovations in powder formulation.

Considerations in the development of DPIs :

In DPIs, the dose received by patients is dependent on four factors:

1.Physicochemical properties of drug formulation (for example, powder flow, particle size)
2.The performance of the inhaler device, which includes aerosol generation and delivery.
3.Correct use of the inhalation technique for deposition in the lungs.
4.The inspiratory flow rate[5].

Types of Devices:

1.Unit-Dose Devices
2.Multi-Dose Devices

Unit-Dose Devices:

Mainly used for single-dose DPI, in which a powder-containing capsule is placed in a holder inside the DPI. This capsule is opened within the device, and then powder is inhaled. After inhalation of the powder capsule, it must be discarded and a new capsule inserted into the device for the next dose[6].

Multi-Dose Devices:

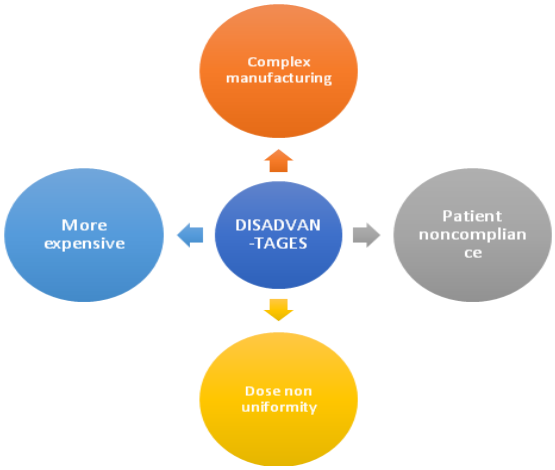
In this device, the drug formulation is inserted into the storage reservoir, and then it is dispensed into the dosing chamber by a simple back-and-forth twisting action on the base of the device. This device has more advantages over unit dose devices, which are capable of working at a moderate flow rate and also deliver carrier-free particles as well as lactose-based[7].

The Ideal Device Should Be:

1.Effective: able to deliver a sufficient fraction of drug .
2.Reproducible: every time, able to produce the same amount of drug fraction.
3.Stable: They should protect drug content.
4.Comfortable and easy to use.
5.Multiple dose: containing several doses of drug for long-term use
6.Versatile: We can administer other drugs from the same device.
7.Toxic-free: should not contain any other chemical contaminants.
8.Affordable: They should have [8].

Advantages:

Disadvantages:



Powder Production Method:

Techniques	Control Parameters
Milling – Conventional ball mill are used for this method. Particle size reduction – 1 mm [9].	1. Moisture content of drug. 2. Milling environment. 3. Quantity of feeding material. 4. Physical and chemical properties of feeding material. 5. Force of inlet air and gas[10].
Spray Drying – Large scale production. Particle size- above 2 µm. Method[11] - 1. Single emulsion technique. 2. Multiple emulsion technique. 3. Co-solvent technique.	1. Viscosity of inlet material. 2. Solute content in inlet material. 3. Temperature. 4. Atomization airflow. 5. Spraying nozzle size. 6. Feed flow rate[12].
Spray Freeze drying – Steps[13] - 1.Spray solution into freezing media. 2.Drying. Particles- light and porous particle.	1. Solute content in inlet material. 2. Freezing time. 3. Drying time. 4. Feeding material[14].
Supercritical Fluid Technology- Causes Solvent extracted and drug solution because Supersaturate. Drug is precipitated as a fine crystal [15].	1. Tank pressure. 2. Atomization airflow and nozzle size. 3. Type of co-solvent. 4. Flow of co-solvent. 5. Solute content in inlet material[16].

1. Characterizations–

Characterizations	Apparatus
Particle size	Malvern mastersizer 2000
Morphology Evaluation	Scanning election microscope
Fourier-Transforminfrared [spectroscopy	Fourier-transforminfrared spectrophotometer
Crystallinity Evaluation	Siemens D5000 Diffractometer
Thermal Analysis	Differential scanning calorimetry
Invitro dissolution test	dialysis bag diffusion technique
Aerosol performance	Anderson Cascade Impactor

2. Challenges –

a) **DPI Design**:

Currently marketed inhalers have only less than 10% to between 20% and 40% efficacy. Still, less than half the dose becomes available at the site of action[17]. So our ultimate goal is to improve efficacy and reduce the cost of devices.

b) Dry Powder Formulations :

After many years of study, we still can't find out the exact mechanism of powder cohesion and dispersion. The physiochemical properties of the drug and excipient directly affect the final formulation. But there is insufficient knowledge of the mixture properties and processes used for mixing that affect the final formulation performance[18].

c) Pulmonary Vaccination:

Nowadays, pulmonary administration of vaccines is trending on a large scale, but it raises special challenges. Vaccination is a once-only administration programme, and if vaccine delivery to the respiratory tract fails, there will be no or insufficient protection[19]. Because of once-only administration, disposable inhalers are preferred for this application. Which may be costly, and failure of dose administration is very high.

d) **Special Patient Groups:**

Patient compliance is most important for the proper administration of drugs. Special inhalers may be needed for special patient groups like small children and the elderly. Most currently marketed DPIs are registered for children aged six years and older due to a lack of clinical data for younger children, especially children below six years. It has never been investigated whether some children under six can use these DPIs too. Due to their low understanding of instructions for use, they need a special device[20].

e) Target Sites For Inhaled Drugs:

After inhalation of DPIs, it shows that one third of the total dose is deposited in the upper airway, one third in the central airways, and one third in the peripheral lung. This combination increases the surface area of drug absorption but also results in drug concentration differences by more than 100 factors[21]. Therefore, one of the greatest challenges for future DPI developments is to increase peripheral deposition.

f) Patient Preference:

It is difficult to measure patient preference for the inhaler devices because of a lack of awareness regarding the new device design among physicians and pharmacists, the locality of the country in which the inhaler is produced, or the manufacture of the inhaler[22].

3. Novel DPIs -

Liposomal Dry Powder:

Microspheres called liposomes are created from phospholipids. They serve as a slow-release reservoir, contain drug particles, and provide sustained drug release. A lipid bilayer surrounds the aqueous compartments in liposomes[23]. In comparison to other drug formulations, liposomal formulations limit the entry of the drug into the systemic circulation, allowing the medicine to be distributed evenly throughout the lungs' airspace. They lead to a reduction in medicine dose frequency. They significantly raise the quality of life and lower medical expenses. In order to create a high-efficiency system for pulmonary drug administration, dry powder inhalers must be carefully constructed. Liposomal aqueous dispersion's instability makes its dry powder form more practical for administration. Numerous studies on liposomal formulation led to the theory that liposomal particles demonstrate controlled and extended medication release at a localised spot, which reduces systemic adverse effects and dosage [24].

Examples –

Author name	Research work	Result
Mahavir Chougule, Bijay Padhi, and Ambikanandan Misra	Development of Spray Dried Liposomal Dry Powder Inhaler of Dapsone.	In this research, they develop aerodynamically light and porous materials by preparing liposomal formulations of dapsone by spray drying, which show high deep lung deposition. This formulation shows prolonged in vitro drug release. Developed formulations show up to 16 hours of drug release, while plain drug spray dried with lactose shows 3 hours of release. Hence, developed formulations play an important role in the management of PCP by providing prolonged release of the drug at the site of action. Also, they reduce dose, dose frequency, and toxicities[25].
Shrenik P. Shah and Ambikanandan Misra	Development of Liposomal Amphotericin B Dry Powder Inhaler Formulation	In this study, they formulate multilamellar Amphotericin B liposomes that are stabilised by lyophilization and have a shelf life of over 1 year in refrigerator storage. They find that this formulation shows better delivery of amphotericin B from the trachea to the terminal bronchioles as compared to marketed DPI formulations. This investigation shows that there is a possibility of localised pulmonary delivery of drugs in an anhydrous state[26].
Mahavir Chougule, BijayPadhi and AmbikanandanMisra	Nano-liposomal dry powder inhaler of tacrolimus: Preparation, characterization, and pulmonary pharmacokinetics	Liposomal formulations of tacrolimus show high deep lung deposition of tacrolimus, and this formulation shows prolonged drug release up to 18 hours in vitro. The data from in vivo studies show 24-hour drug residence within the lungs and systemic dilution of tacrolimus. This prolonged drug release and high residence time of the drug within the lungs after pulmonary administration of the drug are expected to provide prolonged site action, reduce dose frequency, and reduce systemic toxicities. Hence, this study proves that this formulation reduces the risk of acute and chronic rejection[27].

Chitosan Nanoparticle :

Polymer nanoparticulate systems are employed, which is encouraging for both sustained medication activity and drug delivery to the lungs. Large doses of an inhaled nanoparticle can be deposited, particularly in the lower parts of the lungs, by regulating breathing parameters and particle size. Nanoparticles can avoid mucociliary clearance and alveolar macrophage identification. After pulmonary delivery, nanoparticles administered via a DPI demonstrated sustained drug release. The natural biopolymer chitosan, which is widely accessible, has drawn a lot of interest as a matrix for micro- and nanoparticles in controlled-release drug delivery systems. Chtosan's characteristics include low toxicity, biocompatibility, and biodegradability, as well as some other alluring qualities. Chitosan is used in medication delivery because of properties like mucoadhesiveness and enhanced trans-epithelial permeability. It has a positive charge and has been discovered to enhance medication absorption by loosening the lung epithelium's intercellular tight[28].

Examples –

Author Name	Research work	Result
D. J. Singh, A. A. Lohade, J. J. Parmar, Darshana D. Hegde, P. Soni, A. Samad, And Mala D. Menon.	Development of Chitosan-based Dry Powder Inhalation System of Cisplatin for Lung Cancer	Cisplatin mainly shows a cytotoxic effect on hypotriploid alveolar basal epithelial cells, which are affected by cancer, but was unable to attain a half-maximal inhibitory concentration value. Previously, Liang et al. reported this observation and confirmed that human lung adenocarcinoma cells are resistant to cisplatin's cytotoxic effect. This formulation does not change any cisplatin cytotoxic effect in the chitosan matrix, and thus this formulation retains its cell-killing effect as it is. Microspheres showed a higher half-maximum inhibitory concentration value compared to free drug due to the slower release of drug from the chitosan matrix[29].
Hui Wang , Graeme George,Selena Bartlett , ChangyouGao,Nazrul Islam	Nicotine Hydrogen Tartrate Loaded Chitosan Nanoparticles: Formulation, Characterization and in vitro Delivery from Dry Powder Inhaler Formulation	This study suggests that the mechanism of nicotine hydrogen tartrate-loaded chitosan nanoparticles without carriers depends on the zeta potential of particles that show agglomeration or deagglomeration behaviour in dry form. Each particle, agglomerate, and drug carrier show different surface properties, which are complex. This study mainly focuses on understanding the intrinsic surface charges of particles, especially in dry form, to develop efficient DPIs. For this we need to understand the interaction between charged particles and carriers, effect of charged particles or agglomerates on dispersion and deagglomeration process[30].

***Microspheres* :**

Three main types of particles are referred to as "microparticles," including microspheres (uniformly dispersed spheres), microcapsules (a central core encased in a polymeric membrane), and particles of unknown shape[31]. They can be made with a range of natural and synthetic polymers and have particle sizes ranging from 1 to 999 nm. Both hydrophilic and

hydrophobic drug molecules can be included in microspheres, which improves physiochemical stability by protecting the drug from enzymatic degradation and offers continuous drug release of the included molecule. Polylactic acid (PLA), albumin, polyglycolic co-lactic acid (PLGA), and other polymers have all been used to create microspheres. Due to their biocompatibility and biodegradability, albumin microspheres may be a suitable drug delivery system for the lungs[32]. Morphological specifications Through the use of microsphere drug carriers, factors such as shape and size can be easily manipulated and tweaked to meet requirements. Additionally, the drug-incorporated microspheres' particle size makes them less vulnerable to hygroscopic development in the lung. When creating microspheres, some polymers, such as very viscous hydroxypropylcellulose (HPC), have mucoadhesive characteristics that can be used to prolong lung retention duration and decrease mucociliary clearance[33]. When treating illnesses like tuberculosis, microspheres can be crucial in the delivery of therapeutic molecules that target alveolar microphages. Additionally, a study conducted in vitro claimed that microspheres could target alveolar macrophages without possibly inducing an inflammatory response [34].

Examples -

Author name	Research work	Result
Hitendra S. Mahajan, Sadanand A. Gundare	Preparation, characterization and pulmonary pharmacokinetics of xyloglucan microspheres as dry powder inhalation	Montelukast-loaded xyloglucan microspheres were successfully prepared by spray drying technique and optimised by statistical screening design, considering xyloglucan and lactose as independent variables. Optimisation studies revealed that concentrations of xyloglucan and lactose had a prominent effect on entrapment efficiency, flow ability, mucoadhesion, and the release of drugs from microspheres. The results of the present study clearly indicated the promising potential of xyloglucan-containing microspheres for delivering drug to the deep lung and could be viewed as an alternative to conventional dosage forms. In conclusion, formulated polymeric microsphere as DPI are a promising approach for delivering antiasthmatic agents through the pulmonary route[35].
Silvio Farago, Giulia Lucconi, Sara Perteghella, Barbara Vigan	A dry powder formulation from silk fibroin microspheres as a topical auto-gelling device	In this study, it was demonstrated that silk fibroin-based microspheres, blended with selected excipients, could be produced with a cost-effective and industrially scalable technique. According to the technological data collected here, microspheres from formulations C and D could be proposed for direct application to injured tissues. These results represent the starting point for the development of new topical formulations suitable for the treatment of bedsores[36].

***Polymeric Micelles**:*

Polymeric micelles (PMs) have gained more attention recently as potential delivery systems for medications that are poorly soluble. PMs are amphiphilic copolymer-based nanoscopic delivery systems (10–100 nm) with a core–shell architecture that have shown considerable promise in the solubilization and controlled administration of hydrophobic medicines. The unique attributes of PMs, such as their nanoscale size, thermodynamic stability, lengthy circulation, and ease of synthesis, contribute to their tremendous potential as drug carriers. Many efforts have been made to create novel polymeric amphiphiles; however, due to the need for biocompatibility and biodegradability, only a small number of polymer amphiphiles are viable as drug delivery vehicles.

Examples-

Author name	Research work	Result
RémiRosièrea, Matthias Van Woensel , Véronique Mathieu , Ingrid Langer.	Development and evaluation of well-tolerated and tumor-penetrating polymeric micelle-based dry powders for inhaled anti-cancer chemotherapy.	The result of the study shows that the developed powder is able to carry drug micelles deep in the respiratory tract, mainly at lung tumour sites. When they reach the site, dry powder releases drug micelles. These micelles should be in direct contact with lung tumours. Which show prolonged drug release with site target[37].
Hitendra S Mahajan, Prashant R Mahajan	Development of grafted xyloglucan micelles for pulmonary delivery of curcumin: In vitro and in vivo studies	A newly synthesised L-lactide-grafted xyloglucan copolymer can self-assemble to form micelles with 0.0150 wt% CMC. The average particle size was 102.4 nm with 0.275 PDI. The polymeric micelles exhibited higher entrapment efficiency and drug loading for curcumin. In vitro dry powder inhalation performance was observed for developed freeze-dried micelles, suggesting high deep lung deposition of the drug. The data from in vivo studies showed a high and prolonged residence of curcumin within the lungs after pulmonary administration. Novel grafted micelles are expected to provide improved local concentration. The results of the present study clearly indicated the promising potential of novel grafted polymer micelles for delivering curcumin to the deep lungs for effective treatment of lung cancer[38].

***Nanoparticles*:**

The characteristics of nanoparticles are similar to those of microparticles; drug molecules are either uniformly distributed on the matrix surface or loaded into the core of the nano-carrier using biodegradable polymers, either natural or synthetic, enhancing the bioavailability of therapeutic agents through an extended release profile[39]. Drug delivery and diagnostic applications have both exploited nanoparticle-based drug carriers[40]. By extending the retention duration of nanoparticles within the pulmonary mucosa and reducing the impact of the

mucocilliary clearance mechanism, mucoadhesive polymers can be used in the fabrication of nanoparticles to improve bioavailability. However, in vitro and in vivo research has shown that polymeric micro- and nanoparticles have several limitations, such as difficulty in making microspheres smaller than 10 um, evidence of haemorrhage brought on by microsphere clustering in lung tissue, and a large inflammatory response that causes cytotoxicity[41].

Example -

Author name	Research work	Result
Sujit Kumar Debnath, Srinivasan Saisivam, MonalishaDebanth, AbdelwahabOmri.	Development and evaluation of Chitosan nanoparticles based dry powder inhalation formulations of Prothionamide	For the formulation of prothionamide nanoparticles, the ionic gelation technique was used. Prepared formulations were then examined under a scanning electron microscope, which showed a special shape and a 314.37 nm particle size. These nanoparticles were further converted into dry powder. Dry powder shows 1.76 m aerodynamic particle size, which confirms effective delivery of formulation to the respiratory system. In vitro studies show drug release according to Kors Meyer-Peppas kinetic model. Particles change their size during storage[42].
Mohammad D. A. Muhsin, Graeme George, Kenneth Beagley, Vito Ferro, Hui Wang, Nazrul Islam	Effects of chemical conjugation of L-leucine to chitosan on dispersibility and controlled release of drug from a nanoparticulate dry powder inhaler formulation.	This nanoparticle is formulated by using chitosan-N-L-leucine conjugate, which is a water-soluble derivative. The hydrophobic domain of conjugated L-leucine and glutaraldehyde crosslinks enhance dispersibility. Results of this formulation show that leucine-conjugated chitosan nanoparticles are safe for pulmonary drug delivery and improve dispersibility and prolonged release of drugs[43].

Solid Lipid Nanoparticles :

An alternative to traditional colloidal systems like liposomes and polymeric micro- and nanoparticles is provided by solid lipid nanoparticles (SLNs) . In actuality, SLNs offer benefits including high safety and scalability in manufacturing[44]. Drug molecules have been successfully loaded into SLNs, including Prednisolone® and Diazepam®. The physiochemical characteristics of the lipid solid matrix, the polymorphic state of the lipid component inside the SLNs, and the miscibility and solubility of the drug in the SLN lipid all affect the drug loading capacity of SLNs. By adjusting manufacturing settings and employing SLNs as a function of the ratio of lipid/surfactant concentration, controlled release profiles can be created. Drug release can be controlled to provide a sustained release of up to 5–7 weeks . For pulmonary administration, SLNs dispersion can be nebulized or utilised as solid powder in a DPI device.

Examples -

Author name	Research work	Result
Nan Li,Xu Li, Peng Cheng,3 Ping Yang, Pengcheng Shi, Lingyu Kong.	Preparation of Curcumin Solid Lipid Nanoparticles Loaded with Flower-Shaped Lactose for Lung Inhalation and Preliminary Evaluation of Cytotoxicity In Vitro	The study shows that solid lipid nanoparticles are unstable, demulsify, and show uneven particle size distribution. For formulation, they need a higher concentration of surfactant and cosurfactant to improve entrapment efficacy and drug loading. The preparation process was investigated by the emulsion evaporation low-temperature curing method. Use of mixture of surfactant and co surfactant improve encapsulation efficacy, reduce particle size and aggregation of particle, also improve stability and in vitro drug release[45].
Yan-Zhen Li , Xun Sun , Tao Gong , Jie Liu ,Jiao ZuoandZhi-Rong Zhang	Inhalable Microparticles as Carriers for Pulmonary Delivery of Thymopentin-Loaded Solid Lipid Nanoparticles.	In this study, they prepare inhalable microparticles by spray drying with high aerosolization efficiency. This formulation shows higher drug absorption and sustained release. Further, the pharmacodynamic study shows that these thymopentin microparticles show strengthened therapeutic efficacy compared with intravenously administered thymopentin solutions. However, they required further studies to be done for the clinical application of inhalable microparticles, which include dose delivery accuracy and the chronic effects of the carrier on the lungs[46].

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