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A Review on Dry Powder Inhalers of Repurposing Drugs for Covid-19 Treatment

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Abstract **- Dry powder inhalation method has been convincing method for treating respiratory diseases as it directly delivers the drugs to the lungs in the form of fine powder. The novel coronavirus causes respiratory infection mainly targeting the ACE-2 receptors in the lower respiratory tract. Repurposing drugs like Remdesivir, Ivermectin, Favipiravir for treatment of covid-19 can be prepared as powders for inhalation. Covid-19 pandemic has increased the application of dry powder inhalation therapy of antiviral drugs. This review presents account on pulmonary drug delivery of repurposing drugs for treatment of Covid-19.**

Index Terms— Dry powder inhalers, Novel Coronavirus, Repurposing drugs.

1. Introduction

Emergence and resurgence of viral outbreaks pose a global health treat which requires an urgent stationing of advanced therapeutic options because infectious viral diseases can elevate upto undesirable pandemic conditions.COVID-19 primarily a respiratory pathogen targets the alveolar sacs in the human airways and binds with angiotensin converting enzyme-2 (ACE-2) receptors on the alveolar cells to get internalized [1]. New emerging viral infections still lack specific treatment so the efficient strategy is to repurpose the existing drugs. Conventional methods employment leads limited effective delivery of active pharmaceutical ingredient. Dry powder inhalation technique is easy to administer and delivers active pharmaceutical ingredient directly to the primary site of infection and minimizes systemic side effects [2].

2. Dry Powder Inhalers

Dry powder inhalers are free-flowing powdered formulations containing pharmacologically active drug particles (<5 μm) along with suitable carrier which should act locally in the upper respiratory tract or into the deep lung. It contains particles of active drug of respirable range for deposition. Every dry powder inhaler consists of active pharmaceutical ingredient and the carrier either mixed or co-precipitated together into dry powder form. Dry powder inhalers allow active pharmaceutical ingredient to get deep into the lungs and provide effective local therapy in case of respiratory infections like Covid-19 [3].

3. Development Techniques

Dry powder inhalers can be prepared by spray drying, supercritical fluid technologies, spray freeze drying, ultrasound assisted crystallization, flash crystallization, controlled precipitation, co- precipitation of drug and carrier by lyophilization, milling, micronization of a blend consisting of suitable carrier and active pharmaceutical ingredient [4].

4. Evaluation Methods

***Aerodynamic Particle Size Distribution*:** Multistage cascade impactor used to characterize the aerodynamic particle size distribution of dry powder inhalers.

Sieve analysis: Air jet sieving technique works better for finer lactose grades. Nest of standard sieves shaken on a sieve shaker was conventional method used to calculate particle size distribution.

Imaging Techniques: Gamma scintigraphy, single photon emission computed tomography, position emission tomography techniques were used for quantification of drug deposition from dry powder inhalers.

Delivered Dose uniformity: Dosage unit sampling apparatus used to estimate total quantity of drug emitted from the device. In determining the quality, safety, efficacy of dry powder inhaler delivered dose uniformity serves as a critical quality attribute.

Moisture content: Small amounts of moisture present in dry powder inhalation powder effect the solid-state properties and stability of powder particles. Karl Fisher method was used to determine the moisture content of inhalable powders.

Microbial limits: Acceptance criteria for total aerobic count, total yeast count, mould count, freedom from designated pathogens must be satisfied. Formulation must not support the microbial growth and microbial quality should retain throughout the expiration period.

Drug content: Drug content should be determined analytically with a stability indicating method [5].

5. Repurposing Drugs

Drug repurposing is a strategy for recognizing new medical applications of already approved drugs for a different disease from what it was originally developed to treat. Instead of developing entirely new drug for a newly emerged disease, repositioning of approved drugs for other alignments will save the time and cost required for drug development. This method found to be safe because most of the preclinical testing, safety assessment of the repurposed drug was already completed [6]. Different repurposing drugs were listed in Table-1.

Table-1 Repurposing drugs with their indications

Drug	Originally approved	Repurposing indication
Sildenafil	Angina pectoris	erectile dysfunction
Raloxifene	Osteoporosis	invasive breast cancer
Ketoconazole	Fungal infections	Cushing syndrome
Favipiravir	Influenza virus infections	Covid-19
Dapoxetine	Analgesia and depression	Premature ejaculation
Zidovudine	Cancer	HIV- AIDS
Topiramate	Epilepsy	Obesity
Remdesivir	Hepatitis C	Covid-19
Rituximab	Cancer	Rheumatoid arthritis
Minoxidil	Hypertension	Alopecia
Ivermectin	Onchocerciasis	Covid-19
Tamibarotene	Refractory acute promyelocytic leukemia	Covid-19

6. Dry Powder Inhalers of Repurposing drugs

Repurposing drugs like remdesivir, Ivermectin, Tamibarotene, Favipiravir were employed in the treatment of Covid-19, methods and findings mentioned in Table-2. Remdesivir is not suitable for oral delivery since it undergoes first pass metabolism. Parenteral route also faces challenges, since release rates can vary widely. So, delivering remdesivir through dry powder inhalation, potentially making treatment more potent to fight against COVID-19, it could also make the drug more effective [7].

Ivermectin has pharmacokinetic limitations with oral administration and issue of dose limiting toxicity, these limitations can be overcome by targeted delivery to lungs through dry powder inhalers for the potential treatment of COVID-19 [8].

Tamibarotene is an orally active retinoid for the treatment of leukemia, suppress virus-induced lipogenesis within host cells and post-translational protein modifications in the end disrupting propagation of a virus. Dry powder Tamibarotene with broad-spectrum antiviral activity presents a new strategy for COVID-19 management [9].

Favipiravir, a broad-spectrum antiviral drug with potential pharmacological activity against COVID-19, exhibits a low aqueous solubility. A very high oral dose required for significant reduction of viral replication at the infection site. Inhalable dry powder formulation may provide efficient delivery to respiratory tract [10].

Table-2 Methods and Findings

Drug	Method	Findings
Remdesivir	Thin film freezing	High potency remdesivir dry powder formulation was produced with 93% fine particle fraction; 0.82 μm mass median aerodynamic diameter exhibiting desirable performance.
Ivermectin	Spray drying	spray-dried formulation achieved anticipated therapeutic dose with 70% fine particle fraction; median diameter of 4.3 μm.
Tamibarotene	Spray freeze drying	Compared with intraperitoneal injection pulmonary delivery of tamibarotene powder results in rapid absorption and higher bioavailability
Favipiravir	Spray drying	Optimized favipiravir dry powder inhalable formulation exhibited 79.3% fine particle fraction; 2.93 μm mass median aerodynamic diameter suitable for deep lung delivery.

7. Conclusion

Dry powder inhalers provide improved efficacy of active pharmaceutical ingredient than other conventional drug delivery systems as they deliver the drug deep into lungs. By virtue of Covid-19 pandemic dry powder inhalers application extended to antiviral drugs, which shown great potential in combating the pandemic.

Conflicts of Interest

Declared none

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