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Original Article

Development and evaluation of Dry Powder Inhalation Formulation of Remdesivir Nanosuspension by Spray Drying Technique

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ABSTRACT

Introduction: Significant global health issues are caused by respiratory viral infections, such as COVID-19, which call for effective and focused drug delivery methods to improve treatment effectiveness and lessen systemic side effects. The broad-spectrum antiviral Remdesivir has demonstrated potential in treating these infections; however, it has low pulmonary access and poor aqueous solubility when administered by traditional methods. Antivirals can be directly and non-invasively delivered to the lungs, the main site of infection, using Dry Powder Inhaler Pulmonary Drug Delivery System. In order to optimise therapeutic advantages, reduce side effects, and increase local drug concentration, this study attempts to create a DPI formulation of Remdesivir. **Objectives:** The aim is to formulate and assess a spray-dried Remdesivir DPI for better bioavailability and pulmonary delivery. **Materials and Methods:** Remdesivir was formulated as a nanosuspension and then spray-dried into particles that could be inhaled in. The powder was comprehensively characterized using Fourier-Transform Infrared Spectroscopy, Scanning Electron Microscopy, X-ray Powder Diffraction, and Differential Scanning Calorimetry. Solubility enhancement, aerosolisation, and *in vitro* drug release were evaluated. **Results:** The particles had a fine particle percentage of 68.84±4% and a respirable size of 1-5 µm. Aerosolisation was enhanced by the rough, corrugated surfaces that were visible through SEM. Amorphous conversion was verified by DSC and XRPD, increasing solubility by 17-18 times. Within 150 min, more compared to 70% of the drug was released, and cascade impaction confirmed deep lung deposits. **Conclusion:** Remdesivir's modified DPI formulation showed improved solubility, effective lung targeting, and prolonged drug release, indicating a high potential for treating viral respiratory infections.

Keywords: Remdesivir, Dry Powder Inhalation, Pulmonary Delivery, Spray Drying, Solubility Enhancement.

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INTRODUCTION

The urgent need for effective antiviral therapies was highlighted by the COVID-19 pandemic. Among the various drugs that were studied, Remdesivir, which was earlier developed to combat Ebola, showed promising results in treating severe instances of COVID-19.[1] Remdesivir, However, has problems with solubility and bioavailability that limit its clinical use despite its effectiveness.[2] Nanosuspension formulations have gained popularity as a remedy to these problems because they increase solubility and dissolution rates, which in turn improve bioavailability and treatment outcomes.[3]

For the administration of antiviral drugs, inhalation drug delivery systems offer a promising method, particularly for respiratory conditions like COVID-19, where the medicine's tailored distribution to the lungs is beneficial. Dry powder inhalers, or DPIs, have been popularised because of their non-invasive features, ease of use, and potential for rapid drug absorption.[4] However, there are significant formulation issues in developing a stable and efficient dry powder formulation of Remdesivir suitable for use in DPIs.

A popular technique for converting liquid suspensions into dry powders is spray drying, which offers advantages like good scalability, efficient particle size management, and drug stability preservation.[5] This study uses the spray drying process to produce a dry powder inhalation form of Remdesivir nanosuspension, aiming to enhance solubility, increase pulmonary bioavailability, and ensure formulation stability as the second sentence sounds more concise and scientific. Our aim is to develop an inhalable Remdesivir formulation that can overcome the drawbacks

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of existing delivery modalities, particularly intravenous administration, by optimizing the spray drying process.

Respiratory viruses, such as influenza, rhinovirus, coronaviruses, and human Respiratory Syncytial Virus, have a major impact on global health, particularly in susceptible groups including children and people with weakened immune systems.[6] Effective antiviral treatments are urgently needed, as evidenced by the rise of new respiratory illnesses including the Severe Acute Respiratory Syndrome coronavirus and the avian influenza H5N1.[7] Despite advancements in antiviral research, effective treatments for respiratory viral infections remain elusive, contributing to the worldwide burden of disease.

By acting as an adenosine analogue and blocking the activity of viral RNA polymerases, Remdesivir has demonstrated antiviral qualities against a variety of viruses, including SARS-CoV, MERS-CoV, and RSV.[8] However, issues with administration strategies and bioavailability restrict its use in clinical practice. Although intravenous injection is effective, it is less feasible for long-term use, requires hospitalisation, and may have adverse consequences.[9] Oral Drug delivery is difficult due to significant first-pass metabolism which leads to insufficient systemic absorption as it sounds better and is easy to understand.[10]

By eliminating first-pass metabolism and allowing direct deposition in the lungs, inhalation-based drug delivery is a viable substitute that enhances local therapeutic efficacy and lessens systemic side effects.[11] Metered-dose inhalers and other inhalation devices are progressively being replaced by dry powder inhalers because of their improved drug stability, mobility, and lack of propellant.[12] For drugs with poor solubility, like Remdesivir, spray drying is comparatively beneficial as it sounds better and give a comparison also among the several techniques for formulating inhalable formulations because it offers precise control over particle size, shape, and crystallinity all of which are essential for efficient Pulmonary drug delivery.[13]

The goal of this study is to use spray drying to formulate a dry powder inhalation formulation of remdesivir nanosuspension. Our goal is to enhance the lungs' aerodynamic properties, drug stability, and bioavailability by optimising formulation parameters and processing parameters. By addressing key limitations in existing approaches for treatment of respiratory virus infections, this technique presents a viable substitute for intravenous remdesivir treatment.

MATERIALS AND METHODS

Materials

The Mylan R&D Center, located at Bandenalleshandra Link Road, Bandenalleshandra, Bangalore, India, kindly supplied the Remdesivir used in this investigation as a sample. Sigma Life Sciences in Sanjali, Gujarat, provided the Pluronic F68, while Fine Chem Industries Research Laboratory in Mumbai provided the Pluronic F407. We purchased D-Mannitol from Loba Chemie Ltd., in Mumbai. High-Performance Liquid Chromatography in this work used methanol and acetonitrile, while all experimental techniques used distilled water. Every other chemical and reagent that was employed was of analytical purity and didn't require any additional cleaning.

Design of Experiments

A three-factor, two-level factorial design (2-2-2-2) has been used to create and refine Remdesivir's formulation for inhalation in dry powder. The independent variables that were selected were the number of high-pressure homogenization cycles, the pressure of the homogeniser, and the concentration of the stabiliser. There were two degrees of evaluation for each factor high and low. The concentrations of the drug and solvent, among other compositional and processing factors, were kept constant. Design Expert Software (version 8.0.7.1; M&S Stat-Ease Inc., Minneapolis, USA) was used to create the factorial design. The ideal goal size range for the finished batch was between 600 and 800 nm, and the average particle size was chosen as the response variable.[14]

Method of Preparation of Remdesivir Dry Powder for Inhalation

Spray drying was used to generate Remdesivir's DPI formulation. A number of DPI forms have been made in triplicate using the 2-factorial design as a basis. The best batch was selected based on the DOE results, and it was sprayed using a standard 0.7 mm nozzle on a spray dryer (LU222, VCX-750, Labultima, India). The spray drying process was set with an input temperature of 140°C and an output temperature of 110°C. Compressed air was used to atomise the dispersible feed, which was then dried in a spray drying chamber after being fed to the nozzle at a rate of 1 mL per minute by a peristaltic pump. The dry powder that resulted was gathered from the device's cyclone chambers and kept in the drier until it could be examined further.[15,16]

Characterization of Formulated Remdesivir Dry Powder for Inhalation

Percentage Yield

By directly measuring the powder that was gathered from the units for spraying (cyclones 1 and 2), the practical yield of the developed DPI was ascertained. Based on the total weight of the feeding stuff solution used for spraying, the theoretical yield has been computed.[17,18]

The percentage yield has been calculated by the following equation:

$$\text{Percentage yield} = \text{Practical yield}/\ \text{Theoretical yield} \times 100$$

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Scanning Electron Microscopy

The surface morphology and particle shape of the DPI formulations have been assessed using Scanning Electron Microscopy. A small portion of the powder composition was applied to a carbon strip using a smoke burner, and a layer of gold was applied on top. The images were obtained with the assistance of the FEI Nova Nano SEM 450, a field emission scanning electron microscope. The SEM apparatus was provided by the Central Instrumentation Centre of the SPPU in Pune.[19]

Differential Scanning Calorimetry

Differential Scanning Calorimetry was used to assess the thermal characteristics of Remdesivir, Pluronic F68, D-mannitol, and the enhanced DPI formulation (Mettler Toledo, USA). As nitrogen was purged at a rate of 50 to 60 mL per minute, three to 8 mg of sample was placed in aluminium pans, sealed firmly, and heated at a rate of 10°C per minute between 30°C and 350°C. The temperature transitions were recorded and analysed to look for any changes in the crystalline or amorphous characteristics of the drug and excipients.[20, 21]

X-ray Powder Diffraction

Using X-ray powder diffraction, the prepared DPI's and each excipient's crystallinity was evaluated. An X-ray diffractometer equipped with a K-beta filter and a primary monochromatic radiation source was used for this study. The device ran at 40 mA of current and 40 kV of accelerating voltage. To detect any changes in the drug's crystalline state, samples were continually scanned at a rate of 10°/min between 5° and 80°.[22]

Solubility Study

At a pH of 7.4, the solubility of the DPI formulation and ordinary Remdesivir was assessed in phosphate buffer. The buffer was supplemented with excess powder until precipitation was clearly visible. Further, the mixtures were agitated for 24 hr at 250 rpm using an orbital shaker at 25°C. The samples were centrifuged for 15 min at 15,000 rpm after this equilibration period, and the supernatant was separated. An ultraviolet-visible spectrophotometer set to 246 nm was used to measure the drug's concentration in the supernatant.[23]

In vitro Diffusion Study

Franz diffusion cells with a dialysis membrane were used to evaluate the Remdesivir DPI formulation's *in vitro* drug release properties. The phosphate buffer (pH 7.4) was in the receptor compartment, whereas the dry powder was in the donor compartment. This setup's temperature was set at 37±1°C using a running water bath. Samples were taken and replaced with an equivalent volume of fresh buffer at prearranged intervals of 15, 30, 60, 90, 120, and 150 min. The level of Remdesivir in the collected samples was ascertained using UV-visible spectrophotometry at a wavelength of 246 nm. [24]

Aerosolisation Performance of DPI Formulation

A Next Generation Impactor (N-V 8-stage system) was used to assess the aerosolization efficiency of the developed DPI. An Aeroliser inhaler was filled with gelatin capsules containing a predetermined amount of DPI (500 mg). The powder spread out via the impactor when it was ignited. The fine particle fraction, which represents the proportion of drug particles smaller than 5 µm that can enter the deeper regions of the lungs, was computed by measuring the drug's deposition at each impactor stage. In order to evaluate the DPI formulation's aerodynamic performance, the Mass Median Aerodynamic Diameter (MMAD) was also calculated. The five-stage setup is optimized to accurately measure the Fine Particle Fraction, which is the percentage of the drug mass that falls within the 0.5-5 µm size range. The MMAD was calculated from NGI deposition data using CITDAS software (Copley Scientific, UK).[25-27]

RESULTS

Percentage Yield

Cyclones 1 and 2 of the spray dryers were used to calculate the optimized batch's yield %. It was determined that the formulated batch had a yield percentage of 58.22%.

Scanning Electron Microscopy

The enhanced DPI formulation was shown to have an uneven shape and a rough surface by SEM imaging (Figure 1). The particle size was ideal for inhalation drug delivery because they ranged from 1 to 5 µm. A good pulmonary delivery depends on these DPIs' ability to effectively reach the lungs while minimizing inertial and gravitational deposition in the oropharyngeal region. The particle's rough surface may be due to the quick evaporation of water in the spray drying chamber. This characteristic of a corrugated surface increases the dynamic shape factor coefficient, improving the aerodynamic performance of the particles. This enhancement thereby decreases cohesiveness and encourages powder dispersion into an aerosol.

Fourier-Transform Infrared Spectroscopy

An FTIR spectrophotometer (8400 IR Affinity 1-CE, Shimadzu, Japan) was used to obtain the FTIR spectra of Remdesivir, Pluronic F-68, D-mannitol. The DPI formulation's component compatibility was confirmed by these findings. Through the detection of distinctive functional groups and bond vibrations, FTIR analysis aids in the identification of potential molecular interactions. Pluronic F-68's FTIR spectrum (Figure 2) showed a strong band at 2856.58 cm^{-1} that was ascribed to C-CH_3 stretching and a sharp band at 3477.66 cm^{-1} that was associated with -OH stretching vibrations. Ether group C-O stretching was attributed to symmetric and asymmetric peaks at 962.48 and 1060.85 cm^{-1}.[28]

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There were no chemical interactions visible in the improved DPI formulation (Figure 2), which showed distinctive peaks like those of Remdesivir and its excipients. At 1066.64 cm^{-1}, a C-O stretching peak was seen, which is in line with D-mannitol, Pluronic F-68, and Remdesivir. While O-H and N-H stretching were seen at around 3400 cm^{-1} and 3441.01 cm^{-1}, respectively-matching those of the pure drug-C-N stretching was seen at 1039.63 cm^{-1}.[30] The DPI formulation's component compatibility is confirmed by these findings.

Differential Scanning Calorimetry

The thermal properties and crystallinity of the individual components as well as the optimized DPI formulation were examined using DSC analysis. Pluronic F-68's crystalline shape was indicated by a prominent endothermic peak at 56.13°C in its DSC thermogram (Figure 3).[31] The crystalline structure of D-mannitol was confirmed by its prominent melting peak at 172.13°C (Figure 3).

Two endothermic peaks were detected for the improved DPI formulation (Figure 3) at 165.64°C and 53.12°C, which corresponded to D-mannitol and Pluronic F-68, respectively. Compared to the constituent parts, these peaks were less distinct and had lower intensities, indicating some amorphization during formulation.

Pluronic F-68's overlay thermogram (Figure 3) revealed a reduced peak, signifying its shift to an amorphous state. The Remdesivir peak was hardly perceptible and the D-mannitol peak moved to a lower temperature, indicating that the spray-drying technique had converted it to an amorphous state.

X-ray Powder Diffraction

The Pluronic F68 diffractogram (Figure 4) showed five distinct peaks, the greatest of which was located at two theta degrees of 23.52, signifying an intensity of 14,564. At two theta degrees of 19.36, 26.44, 21.30, and 27.18, respectively, other peaks were observed with intensities of 12,844, 2,220, 2,157, and 1,978. Based on these prominent peaks, DSC analysis verified that Pluronic F68 was crystalline in nature. The D-Mannitol diffractogram showed five distinct peaks (Figure 4). Intensities of 108,278 were recorded for the tallest peak, which was situated at two theta degrees of 23.38, and 57,762, 25,249, 20,936, and 19,094 for the remaining summits, which were situated at two theta degrees of 18.74, 44.08, 38.68, and 28.[30]

In the diffractogram of the optimized DPI batch, Remdesivir was shown to be responsible for two small peaks at two theta degrees of 16.10 and 22.26 (intensities 1,906 and 2,424) (Figure 4). The strength of these peaks sharply decreased in comparison to the peaks of plain Remdesivir, suggesting a transition from crystalline to amorphous form. Additionally, peaks at 23.34 and 18.80 (intensities 2,406 and 6,476) were discovered, indicating that the Pluronic F68 in the formulation had become amorphous after the spray-drying process. The diminishing intensity of peaks at two theta degrees of 28.20 and 43.96 (intensities 3,782 and 3,364) further confirmed the shift from crystalline to amorphous forms. These conclusions were corroborated by the DSC data, which demonstrated that the spray-drying process effectively converted the excipients into an amorphous state.[31]

Solubility

Both the plain Remdesivir and its DPI forms underwent solubility tests in phosphate buffer (pH 7.4); the outcomes are displayed in

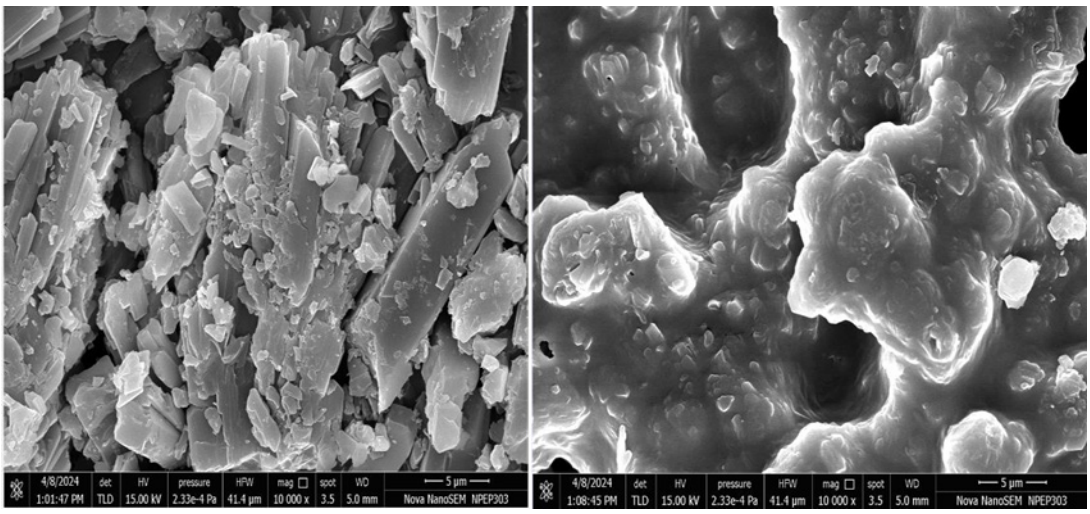

Figure 1: SEM images of Optimized DPI formulation.

Table 1. Remdesivir was shown to be 17-18 times more soluble in DPI formulations compared to in plain Remdesivir. According to XRPD and DSC investigations, the decrease in particle size and the transition from a crystalline to an amorphous state account for this improvement in solubility.

In vitro Diffusion Study

Using Franz diffusion cells fitted with a dialysis membrane, the release of Remdesivir from DPI was examined *in vitro*. The outcomes were evaluated using UV spectroscopy. In DPI formulations, more than 70% of Remdesivir was dissolved in 150 min, according to the drug release characteristics (Table 2), whereas approximately 50% was released in 120 min in a phosphate buffer with a pH of 7.4.DPI formulations were found to have a lower initial release rate, although exhibiting a greater overall drug release at the 90-min mark. The time it took for the drug to permeate the membrane might be the reason for the increase in the release rate after 90 min. According to earlier research, the spray drying procedure affects the release profile, morphology, and particle size.

Table 1: Solubility of Remdesivir and remdesivir in DPI formulations.

Sample Name	Solubility (mg/mL)
Remdesivir	0.0294
DPI Formulation	0.5284

Aerosolisation Performance of DPI Formulation

The spray-dried DPI formulation was propelled into a cascade impactor, with the deposition results outlined in Table 3. The findings reveal that a considerable amount of the DPI formulation settled in the lower stages of the cascade impactor, indicating effective Pulmonary drug delivery. The Fine Particle Fraction (FPF) was measured at 68.84±4%. The optimized DPI formulation showed an MMAD of 6.8±0.3 µm, confirming efficient Pulmonary deposition.

DISCUSSION

Effective drug delivery methods that may directly target the lungs are necessary for respiratory viral infections, especially those brought on by SARS-CoV-2. Despite being authorized for intravenous administration, Remdesivir frequently accumulates in pulmonary tissues in inadequate amounts, which limits its therapeutic effect. Formulations for dry powder inhalation offer a focused, non-invasive method that can improve local drug delivery, lessen systemic adverse effects, and increase patient compliance.

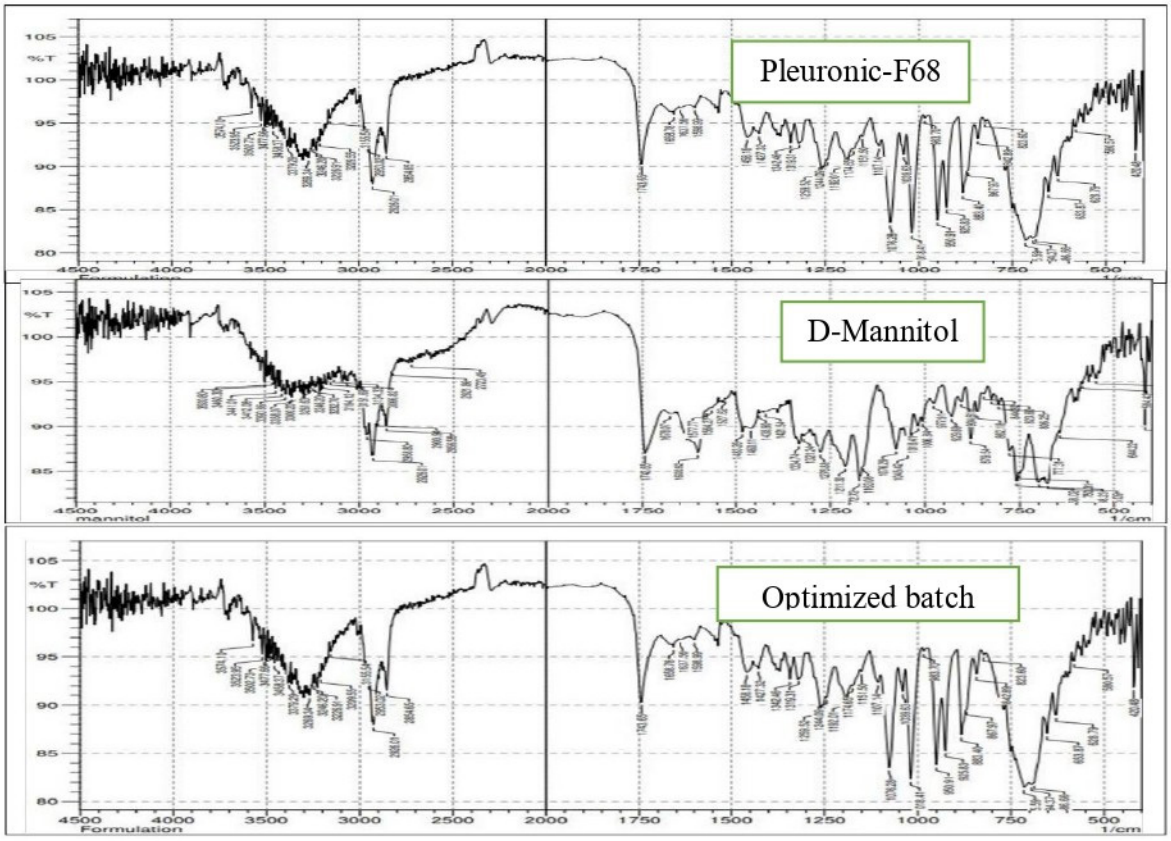

Figure 2: FTIR overlay spectra of Pluronic F-68's, D-mannitol and optimized batch.

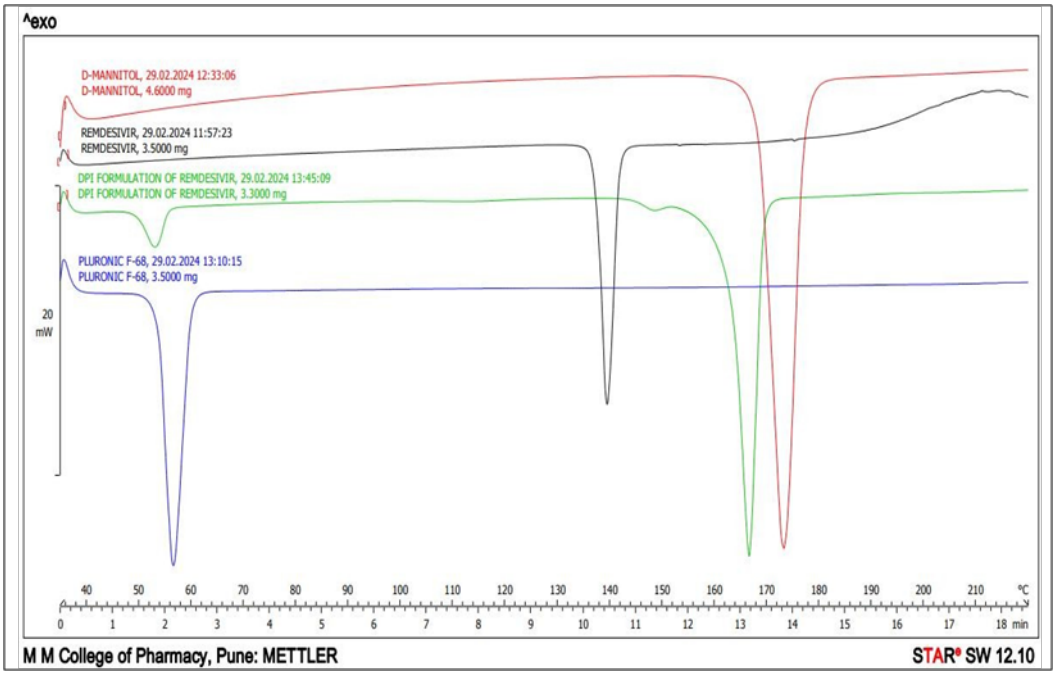

Figure 3: DSC thermogram of Remdesivir, D-Mannitol, Pluronic F-68 and DPI formulation.

Table 2: ***In vitro*** **% drug diffusion from Remdesivir DPI formulations.**

Time (min)	% Cumulative Drug Release
15	3.73±0.45
30	9.84±1.23
60	19.82±1.66
90	33.08±1.5
120	49.91±2.2
150	70.01±3.5

Remdesivir's DPI formulation was effectively created in this study by employing the spray drying technology, and its physicochemical and performance properties were assessed. With a yield of 58.22%, the improved batch was in line with previous spray-dried formulations of hydrophobic drugs. Nevertheless, yield losses brought on by cyclone inefficiencies and wall deposition suggest that more spray-drying parameter improvement is required for improved scalability.

Scanning Electron Microscopy (SEM) morphological characterization showed that the DPI particles had a particle size distribution of 1 to 5 µm and an uneven, corrugated surface. These characteristics are thought to be ideal for pulmonary administration as they minimize oropharyngeal loss while permitting deposition in the lower respiratory tract. Aerosol dispersion is enhanced and particle cohesiveness is decreased by the textured surface, which is probably the result of fast solvent evaporation during spray drying.

Remdesivir, Pluronic F-68, and mannitol all retained their distinctive functional group peaks, according to FTIR analysis (Figures 2 and 3), which showed no discernible chemical interactions. This points to strong physicochemical compatibility, which is necessary for stable drug release and formulation stability.

Particularly for Pluronic F-68 and mannitol, the XRPD patterns showed a notable decrease in or disappearance of strong crystalline peaks, suggesting that both the drug and the excipients experienced a crystalline-to-amorphous transition after spray drying. This change is known to improve solubility and dissolution rate, particularly in drugs that are poorly soluble in water, such as Remdesivir. It is further corroborated by DSC data.

Remdesivir's solubility in the DPI formulation was 17-18 times higher compared to conventional dosage form, according to solubility experiments (Table 1). This improvement is ascribed to the formulation's amorphous structure and smaller particle size, both of which boost drug wettability and dissolution. These enhancements are especially important for pulmonary applications, where absorption depends on rapidly dissolving in lung fluid.

According to *in vitro* diffusion tests (Table 2) over 70% of Remdesivir was released in 150 min but the initial release was delayed, mostly because of saturation lag across the dialysis membrane. This sustained release characteristic can lower the frequency of dosing and helps in sustaining therapeutic drug levels over time.

The Fine Particle Percentage (FPF) of the aerosolization performance, as assessed by cascade impaction, was 68.84±4% (Table 1). This shows that a significant amount of the formulation

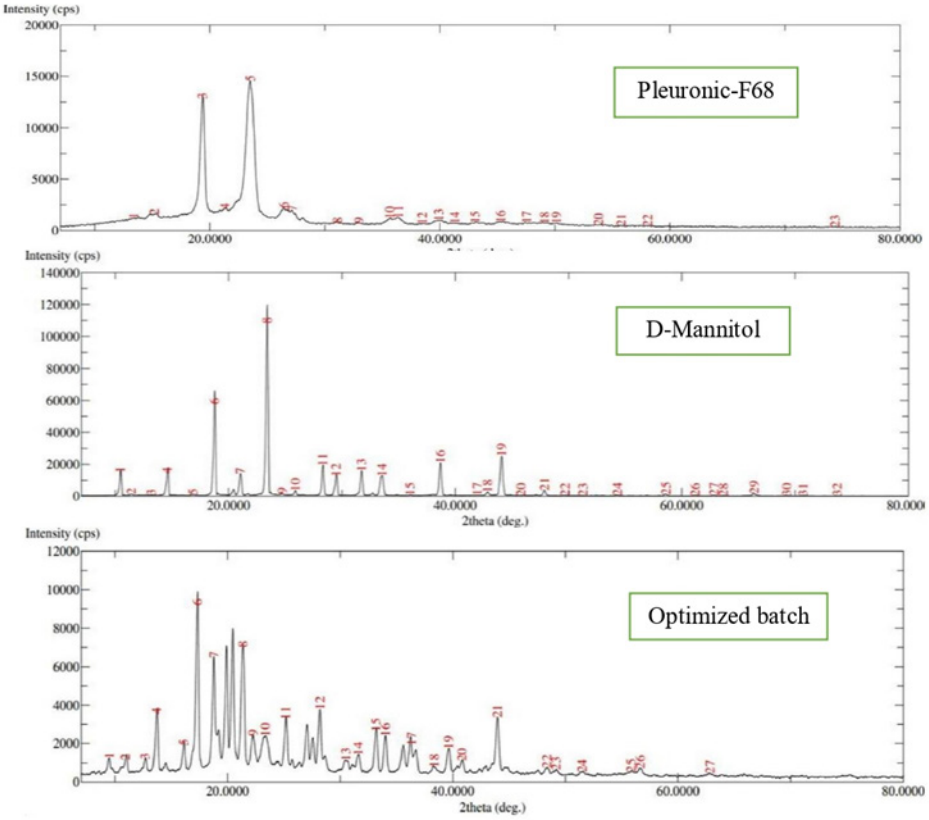

Figure 4: X-ray Powder Diffraction (XRPD) diffractograms of Pluronic F-68's, D-mannitol and optimized batch.

Table 3: Amount of DPI at various stages of cascade impactor.

Sl. No.	Stage of cascade impactor	Amount (mg)
1.	0	203.5±1.25
2.	1	157.2±2.15
3.	2	46.4±1.21
4.	3	35.3±2.15
5.	4	23.9±1.56
6.	5	29.8±1.28

is made up of respirable particles, indicating that it is appropriate for deep lung administration.

To confirm treatment results, *in vivo* pharmacokinetic and pharmacodynamic analyses should be a part of future research. To evaluate shelf-life, long-term stability testing should be carried out under ICH-recommended conditions. Additionally, studying different excipients can enhance drug dispersion and mucosal absorption even more, and researching the impact of storage parameters like temperature and humidity will assist guarantee formulation robustness. To sum up, the spray-dried Remdesivir DPI formulation showed a number of advantageous characteristics, such as appropriate particle size, improved solubility, effective aerosol performance, and prolonged release. These features make the formulation a viable option for antiviral drugs to be delivered specifically to the lungs, which could enhance the effectiveness of treatment for respiratory viral infections.

CONCLUSION

The Remdesivir nanosuspension was effectively transformed into a dry powder inhalation formulation using the spray drying method. It was demonstrated that the particle size of the DPI formulation was suitable for delivering the drug to the upper and middle respiratory tracts. A considerable portion of the DPI formulation comprised particles in the 1-5 µm range, which is perfect for drug delivery in the lungs, according to the formulation's fine particle fraction, which was 68.84±4%.

Images from Scanning Electron Microscopy showed that the DPI formulation had a non-uniform shape and textured surface, which is known to decrease particle cohesiveness and promote powder dispersion into aerosol form.

Studies employing Differential Scanning Calorimetry and X-ray powder diffraction revealed that the enhanced batch of Remdesivir DPI converted from having a crystalline structure to an amorphous one. This conversion implies that the spray drying procedure affected the crystallinity of the drug and the

excipients, which may have increased the drug's solubility. It was discovered that the DPI formulation of Remdesivir was 17-18 times less soluble compared to plain Remdesivir in a phosphate buffer with a pH of 7.4. The drug's transformation from a crystalline to an amorphous state by the use of spray drying is linked to this increase in solubility.

Each of these studies verified that the spray-dried particles were suitable for Pulmonary delivery. Remdesivir DPI's greater persistence in the lungs after pulmonary delivery is expected to produce a prolonged local impact, reducing the dosage which is favourable.

The results of the trials indicated that the Remdesivir DPI formulation would be an effective method to deliver drug through the lungs. Antiviral drugs like Remdesivir, which are designed to specifically target respiratory viral infections, may be delivered into the lungs using this formulation, which provides a feasible substitute for traditional dosing forms.

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ABBREVIATIONS

REM: Remdesivir; **DPI:** Dry Powder Inhaler; **SD:** Spray Drying; **MMAD:** Mass Median Aerodynamic Diameter; **FPF:** Fine Particle Fraction; **SEM:** Scanning Electron Microscopy; **PXRD:** Powder X-ray Diffraction; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared Spectroscopy; **UV:** Ultraviolet; **API:** Active Pharmaceutical Ingredient; **PDI:** Polydispersity Index; **GSD:** Geometric Standard Deviation; **ZP:** Zeta Potential; **%RH:** Percent Relative Humidity; **USP:** United States Pharmacopeia; **ANOVA:** Analysis of Variance; **SD:** Standard Deviation; **RPM:** Revolutions Per Minute; **mm:** Micrometre; **mg:** Milligram; **mL:** Millilitre; **°C:** Degree Celsius.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The idea, design, data collection, analysis, and interpretation were all greatly influenced by the writers. The final version of the paper has been approved for submission by all authors who participated in its drafting or critical revision for intellectual content. According to the International Committee of Medical Journal Editors' (ICMJE) authorship guidelines, each author satisfies the requirements for authorship and pledges to take responsibility for every facet of the work.

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