RESEARCH ARTICLE

Formulation and Evaluation of Moxifloxacin Dry Powder Inhaler Combined with Mucolytic Agent for Pulmonary Diseases

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Received: 10th December, 2022; Revised: 20th March, 2023; Accepted: 08th July, 2023; Available Online: 25th September, 2023

ABSTRACT

The DPI is the device that administers the drug through the dry powder to the lungs. People with Multi-drug resistant tuberculosis or other lung diseases frequently use such devices to take their prescribed medicines. Numerous approaches have been used to formulate dry powder inhalation formulation and enhance the delivery performance of dry powder inhaler preparation. In the case of multi-drug resistance tuberculosis, a high dose of combination therapy was delivered, resulting in resistance to the anti-TB medications in the majority of patients. Moxifloxacin and levofloxacin are being used to minimize the need for a high-dose treatment regimen. This study aimed to achieve local lung administration of tumor-targeting Moxifloxacin, by administering microspheres that can be inhaled as a dry powder inhaler for targeting Phagocytes of alveoli via pulmonary passage. Spray drying had been used to formulate MXN-DPI formulations, afterward optimized with the 2^3-factorial design model. Two different amounts of lactose, leucine, and medication were used to make the eight batches. The developed formulation was studied for physicochemical properties like morphology and particle size. The particle dimensions of the MXN-DPI compositions have been confirmed to be in the range of 1.4 to 4.1 µm. The prepared formulations effectively showed drug release up to 93% in 5 hours, which was observed through *in-vitro* diffusion studies.

Keywords: Dry powder inhaler, Multi-drug resistance tuberculosis, Moxifloxacin, Spray drying.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.3.07

How to cite this article: Ratnaparkhi MP, Kamble OV, Salvankar SS, Shinde SR, Kulkarni GM, Shewale AB, Kadam DD, Shaikh AJ. Formulation and Evaluation of Moxifloxacin Dry Powder Inhaler Combined with Mucolytic Agent for Pulmonary Diseases. International Journal of Drug Delivery Technology. 2023;13(3):818-824.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Tuberculosis is an infectious bacterial infection brought about by the bacterium *Mycobacterium tuberculosis*. It is the second prominent cause of death and constitutes the primary infectious agent-related cause of mortality.[1] TB infection causing damage to the lungs is known as pulmonary tuberculosis. but when the other regions of the body are affected due to *M. tuberculosis*, then it can be called extra-pulmonary TB. The WHO described that about 1.45 million TB-related deaths occurred worldwide in 2019.[2] The current first-line therapy for TB is more curative, but the major disadvantage of this therapy is several side effects on the body and patients become resistant to the particular drug or therapy.[3,4] As a result, developing reliable and effective treatment regimens that improve the rate of recovery and decrease mortality while reducing medication resistance is critical. Moxifloxacin is most potent against *M. tuberculosis* and has broad-range action against bacterial species that are gram-positive as well as gram-negative[5,6] and approved for the treatment of multiple-drug resistant tuberculosis.[7] It is administered to patients who are unable to tolerate first-line medicament treatment of TB.[8] Several recent studies have highlighted the effectiveness of moxifloxacin as a treatment, whether used in combination with other types of distinctive treatment-reducing therapies for the treatment of TB that is susceptible to drug therapy with bedaquiline, levofloxacin, or rifapentine or as an element of a multi-drug regimen against TB that is resistant to multiple medications.[9,10]

Pulmonary medicine delivery is becoming increasingly popular as a non-intrusive yet effective method of treating various disorders, particularly those affecting the lungs.[11,12] The possible application of the pulmonary as an intermediary for pharmaceutical delivery, including peptides and proteins, has encouraged a fascination with this approach. The human lungs have a broad surface area, connected with its abundant blood supply, establishing optimum scenarios enabling fast absorption of medication throughout the systemic circulation and pharmacological activity to begin.[13,14] Furthermore, targeted administration of drugs to the lungs increases the therapeutic activity by lowering serious consequences that are systemic while increasing pharmacological effectiveness.[15,16]

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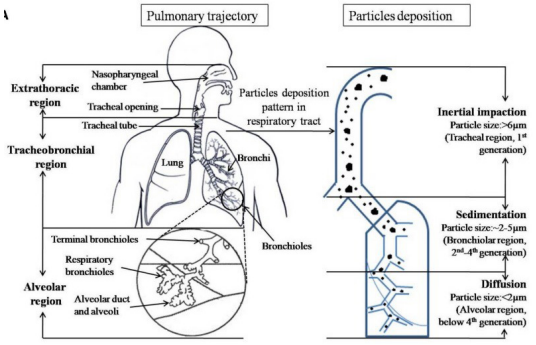

Figure 1: Mechanism of particle deposition in the respiratory system

Similarly, the lungs have low regional metabolic activity and, as a result, not much or no first-pass metabolism.[17] Lastly, alveolar macrophages can be targeted to treat tuberculosis in the lungs.[18] Powder-based inhalers have been gaining popularity as an effective technique for delivering drugs to the respiratory tract.[19,20] Dry powder inhalers are instruments that administer a dry powder-based formulation of the pharmaceutical active chemical to the lungs for localized as well as systemic action. They are more effective for adherence among patients and pulmonary administration than nebulizers or metered dose inhalers since they are more ecologically conscious, lightweight, and transportable.[21] For systemically its impact, the particle size associated with these powdered formulations ought to stay between 2 and 5 m to achieve a regional effect.[22] Inhalable powders exhibit considerable inter-particulate adhesion at this size range, resulting in poor powder flow. As a result, numerous techniques have been developed to increase powder aerosolization, loading the drug into innocuous particulate matter structures, such as microparticles, or modifying particle shape, porosity, or powder density. The patient's biological circumstances, such as breathing patterns and overall lung health, and physical and chemical characteristics, like form, dimension, hygroscopicity, and humidity, determine the amount and nature of particulate accumulation inside airways.[23,24] Following particle consumption, the three fundamental mechanisms for particle deposition are Brownian diffusion, gravitational deposition, and impaction caused by inertial forces, which are shown in figure 1.[25,26] Spray drying is a one-step technology that allows particles to be engineered and produced directly from liquids using a regulated technique. Spray drying had been chosen as the optimum technique for generating DPI formulations as an outcome. The dry powder yield is between 45 and 50%. Approximately 40% of the sample may be lost during the spray-drying. As a result, our yield correlated with the regular sample production behavior.[27]

MATERIALS AND METHODS

Materials

MXN-HCl was provided by Sanket Pharma Pvt. Ltd, Sambhajinagar, as a free gift. N-acetylcysteine, lactose monohydrate, and other chemicals were kindly supplied by Loba Chemicals.

Table 1: MXN-DPI formulation table with factors

Sr No.	*Lactose (gm)*	*L-leucine (gm)*	*Mucolytic Agent (%)*
1	5	0.2	5
2	4	0.4	5
3	4	0.2	5
4	5	0.4	10
5	5	0.4	5
6	4	0.2	10
7	4	0.4	10
8	5	0.2	10

Methods

Preparation of MXN-DPI

A spray drying technique was used for manufacturing MXN-DPI combined with mucolytic agent formulations.[28] The factorial approach was utilized comprehensively to investigate the impact of formulation elements affecting the physiochemical properties of MXN-DPI formulations by considering the total number of variables and their level. The effect of three independent variables (Concentration of Lactose, L-leucine, and N-acetylcysteine) on the dependent variables (particle size, polydispersity index, drug content, %drug release) was investigated using the program Design Expert. The software generated eight experimentation batches. Due to quick evaporation during spray drying, 10% ethanol in a water-based solution is known to reduce particle size.[29] In 400 mg of MXN and various additives, each at various amounts, were dissolved in a water-based mixture containing 10% ethanol to produce the solution used for feeding. The most effective ingredient concentration is obtained, as shown in Table 1, which represents the independent variables and their values.

Characterization

Flow properties of prepared batches

- *Determination of bulk density*

The bulk density of the prepared MXN-DPI formulations were estimated employing 10 mL labeled cylindrical vessel that contained a drug-containing formulation. It was determined after direct volume and mass measurements by equation as shown below:

$$Bulk\ Density = \frac{Mass}{volume}$$

The flow properties were assessed utilizing Hausner's ratio and the compressibility index. The formula for the calculation of these parameters was shown as follows.

$$Hausner's\ ratio = \frac{\delta t}{\delta b}$$

$$Carr's\ index = \delta t - \left(\frac{\delta b}{\delta t}\right)$$

Where δt and δb are the tapped density and bulk density, respectively.

To determine the repose angle, processed dry powder formulation was released via a funnel onto a horizontal surface. The diameter and height of the powder cone was measured when the formulation passed across the funnel.[27,28]

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left[\frac{\text{powder cone height (h)}}{\text{powder cone radius (r)}}\right]$$

- *Particle size analysis*

Ethyl alcohol was used to disperse MXN-DPI formulation. The obtained suspension of the formulation was sonicated for 30 seconds before being analyzed with Zeta Sizer (Malvern Zeta Sizer, UK), which calculates the particle size through laser diffraction. The particle size of each formulation was assessed three times (n=3) at 90°C scattering angles and 25°C conditions.

- *Scanning electron microscopy*

The surface profile of the unprocessed drug and the optimized formulation were examined using field emission SEM (FEI Nova NanoSEM 450) at 20 kV and magnifications ranging from 5000 to 30,000.

- *Fourier transform-infrared spectroscopy*

The spectrum of untreated moxifloxacin, NAC, physical combinations of excipients, and MXN-DPI formulations were examined between 500 to 4500 cm^{-1} by FTIR (Shimadzu, Japan) to determine whether pharmaceutical active ingredients and additives interact.

- *Differential scanning calorimetry*

Each product's thermal performance was assessed using differential scanning calorimetry. The MXN, NAC, and DPI formulations' thermal properties were investigated using the DSC (Mettler Toledo) method. Each specimen (3–10 mg) was placed in aluminum pans, followed by sealing with lead and being subjected to heating at temp. of 10°C/min alongside purging with nitrogen at the following temperature range: 40 to 300°C. The STARe programme was used for analyzing the data.

- *X-ray powder diffraction*

The pure drug (MXN-HCl), excipients, and spray-dried powder (MXN-DPI formulation) were all identified for their crystalline nature using an X-ray diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) at 40 kV voltage and 10°/min scan rate across a 2 theta range of 5 to 60°.

Drug Content Determination

Standard preparation

The standard drug (MXN) was precisely weighted in order to obtain dilutions of 2, 4, 6, 8, and 10 µg/mL. Their absorbance was assessed at a wavelength of 288 nm. The calibration curve was constructed by taking absorbance versus concentration.

Sample preparation and analysis

The 40 mg of the formulation was solubilized in PBS (pH 7.4) using a sonication (10 minutes). The absorbance is recorded at 288 nm wavelength on UV. If the formulation's absorbance was beyond the calibration curve's range, then it was diluted 10 times.

In-vitro Diffusion Study

Buffer preparation: (pH-7.4)

Weighed accurately, 240 mg of Na_2HPO_4, 20 mg of KH_2PO_4, and 700 mg of NaCl were dissolved in distilled water.

Sample preparation

The 40 mg of the DPI formulation was dispersed in 5 mL of PBS (pH 7.4).

Cell preparation

The Franz diffusion cell was utilized while conducting the diffusion study. In this investigation, the acceptor cell was filled with PBS solution, and the dialysis membrane was inserted between the donor and acceptor cells in order to close the air gap produced by the acceptor cell.

Sample loading

The prepared sample was loaded inside the donor membrane exactly above the dialysis membrane.

Withdrawal of elutes

Elutes were withdrawn at different periods of half-hour intervals, i.e., 0, 30, 60,……..300 minutes. At each withdrawal, an equal volume of buffer was added in the acceptor membrane to maintain the *in-vitro* conditions.

Analysis of elute

Elutes were analyzed by using a UV-spectrophotometer and recorded the absorbance at a wavelength of 288 nm to determine the release pattern of the formulation.

Stability Studies

A stability study of the optimized MXN-DPI formulation was conducted for one month at various temperatures and relative humidity. In brief, a prepared sample was put up in a vial and kept in a stability chamber at the sequential temperatures and humidity levels: 5 ± 2°C and 40 ± 5% RH, 25 ± 2°C and 75 ± 5% RH. As per the International Conference on Harmonization recommendations,[39,40] a durability study suggested that criteria like visual appearance, particle size, and drug content (%) were used to evaluate after one month.[39,40]

RESULTS AND DISCUSSION

Flow Properties

DPI must have adequate flow properties in order to be handled conveniently. Also, it can guarantee the distribution of a precise dose, permit the process of fluidization, and make it simple to dispense the powdered drug through the device that delivers it.[34] The average bulk density of the optimized MXN-DPI formulation, which is given in Table 2, was 0.95 ± 0.11 g/cm^3, showing that the formulation can be effectively spread after the formation of an aerosol. Meanwhile, the flow characteristics of the optimized formulation suggested that the formulated powder exhibited better flow ability than the plain drug. These results lead to the hypothesis that prepared formulation may improve the flow ability of tiny medication particles, making it easier to insert smaller drugs into capsules and respiratory gadgets consistently.

Table 2: Flow properties of the Pure MXN and optimized MXN-DPI

Parameter	*Pure MXN*	*MXN-DPI Formulation*
Bulk Density (g/mL)	0.25 ± 0.04	0.95 ± 0.12
Tapped Density (g/mL)	0.339 ± 0.05	1.11
Carr's Index	32.34	12.8
Hausner's ratio	1.48	1.16
Angle of Repose(ɵ)	41°	28 ± 3°

Particle Size Analysis

The engulfment of micron-scale particles throughout pulmonary administration greatly relies on the particle size of formulations. In contrast to the most minor elements, polystyrene formulations with a diameter of 1 to 6 µm were more likely taken in by rat alveolar phagocytes, which was demonstrated by Makino *et al*.[29] In a similar manner, Champion *et al*. observed that smaller rifampicin-loaded PLGA parts were more readily taken up by alveolar macrophage cells than those that were larger.[30] Generally, larger or too-small particles are not recognized by lung monocytes. The optimized MXN-DPI formulation utilized in the present investigation has a median size of the particles of 2.8 µm (Figure 2), which meets the requirements for delivering MXN-DPI to phagocytes in the alveolar cavity for addressing TB.

Particle Morphology

Along with their size, particle shape and morphological traits have a big impact on how effectively particles that are inhaled function. Multiple investigations have discovered that the physical characteristics of particles may impact the initial contact between microglia and particles as well as the following scavenging process.[31,32] Particles with a round-shaped form tend to be engulfed more often compared to those with a protracted or rod shape.[33] Figure 3 exhibits the surface characteristics and shape of MXN-DPI formulations observed through scanning electron microscopy. It was observed that the formulated DPI has an irregular shape with a flawless nature, which was intended for formulated particles as it will help in the attachment to the mucosal membrane of the bronchi or alveoli and gives rise to an activity for a prolonged period.

Fourier Transform Infrared Spectroscopy

FTIR spectral examination has been carried out to learn more about potential interactions among MXN and excipients, and

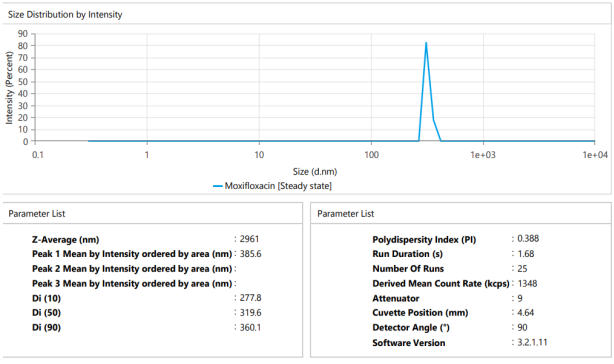

Figure 2: Particle size and PDI of optimized batch by zeta sizer

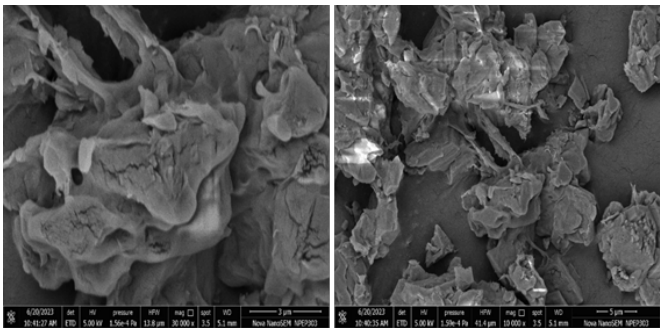

Figure 3: Particle morphology by SEM analysis

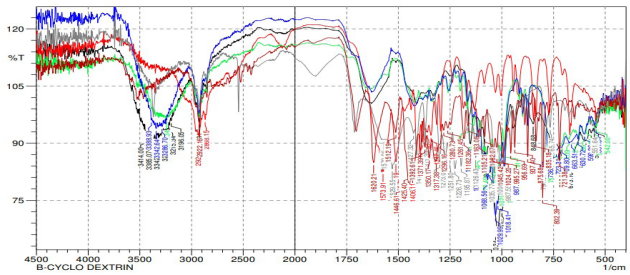

Figure 4: FT-IR overlay of MXN, N-Acetylcysteine, Lactose, L-leucine, Drug+Excipient and Optimized Formulation

the obtained spectra are shown in Figure 4. The distinctive peaks in spectra of MXN were seen at 1280.73 cm^{-1} for C=O (stretching), 1620.21 cm^{-1} for N-H (Bending), 1392.61 cm^{-1} for O-H (Bending), 1371.39 cm^{-1} for C-F and 995.27 cm^{-1} for C=C (stretch aromatic), 2922.16 cm^{-1} for C-H (Stretching). There were no new or missing peaks from the original spectra of the unprocessed MXN or the other excipients in the physical blend (MXN + Other Excipients) and MXN-DPI formulation.

Differential Scanning Calorimetry

DSC analysis assessed the melting range along with the crystallization characteristics of the unprocessed MXN, N-acetylcysteine, and MXN-DPI formulation (Figure 5). According to the DSC assessments, moxifloxacin displayed peak at 246.17°C, which matches the melting range of unprocessed MXN. At 112.45°C, N-acetylcysteine exhibited an endothermic peak. The optimized MXN-DPI formulation's thermogram showed the typical energy consuming peaks at 146, and 218°C, which were attributed to lactose and N-acetylcysteine. It's important to highlight that the MXN peak disappeared in the optimized MXN-DPI thermogram, indicating that there is a change in the nature of MXF from crystalline to amorphous form.

X-ray Diffraction

For determining the crystal nature of an entity as well as any potential alters in crystallinity brought on by drug-polymer interaction, XRD analysis has been a frequently employed analytical approach. Figure 6 showcases the XRD patterns for unprocessed MXN, N-acetyl cysteine, and the MXN-DPI formulation. Sharp peaks were seen in the XRD Peak of MXN, suggesting that it was crystalline in nature. In comparison to the XRD diffractogram of the unprocessed

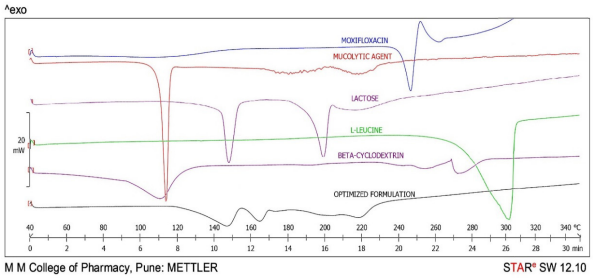

Figure 5: Overlay of DSC analysis

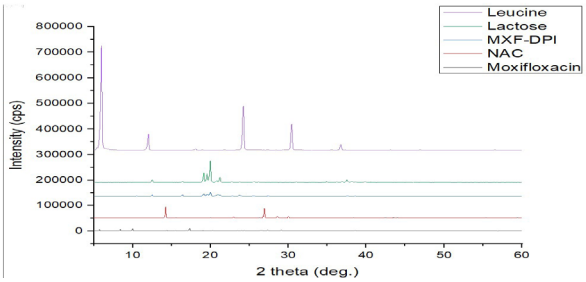

Figure 6: XRD of Moxifloxacin, NAC, Leucine, Lactose, and MXN-DPI

drug, no notable differences in the count or strength of peaks were seen within the physical combination of MXN-DPI formulation. These findings imply that the MXN and excipients are compatible with one another.

Optimization

2^3 factorial design have generated 8 experimental runs for the Preparation of formulations. Responses observed for these runs have been presented in Table 3. The values of 3 independent variables are Y1: particle size (µm), Y2: Drug Release (%), Y3: Drug Content (%). The sequence of the primary effects procedure was appropriate. Table 4 displays the R2, SD, and %coefficient of variation values for each of the three responses. The influence of independent variables such as drug lactose, L-leucine, and mucolytic agent concentration is presented on a 3D surface and contour plots. Additionally, a figure may be used to analyze the quantitative relationship between the obtained values of the responses and those of the projected ones.

In-vitro Diffusion Study

Table 5 shows the release profiles of MXN-DPI formulations. More than 80% of MXN in F2, F3, F4, F5, F6, and F8 has been released up to 5 hours. However, 60 to 78% MXN in F1 and F7 was released in 5 hours. These obtained values suggested that the excipients have a role in retaining MXN release in a pH medium of 7.4. The optimized MXN-DPI formulation effectively showed drug release upto 93.76% in 300 minutes, which is shown in Table 6 and Figure 7.

Table 3: Formulation variables and responses for MXN-DPI

Sr No.	*Lactose (gm)*	*L-leucine (gm)*	*Mucolytic agent (%)*	*Particle size (µm)*	*PDI*	*% Drug content*	*% Drug release*
1	5	0.2	5	1.411	0.369	77.7	62.24
2	4	0.4	5	4.663	0.198	82.5	82.88
3	4	0.2	5	3.037	0.465	81.4	81.88
4	5	0.4	10	2.906	0.388	95.1	93.94
5	5	0.4	5	4.162	0.401	87.6	85.9
6	4	0.2	10	2.356	0.449	79.4	88.93
7	4	0.4	10	2.391	0.203	75.4	78.44
8	5	0.2	10	1.808	0.355	89.6	80.57

Table 4: Values of R^2, SD, and %coefficient of variation

Responses	R^2	*Adjusted* R^2	*Predicted* R^2	*SD*	*% CV*
Y1: Particle Size	0.9999	0.9996	0.9964	0.0219	0.7714
Y2: PDI	0.9993	0.9951	0.9556	0.0071	2.00
Y3: Drug Content (%)	0.9998	0.9986	0.9874	0.2475	0.2961
Y4: Drug Release (%)	0.9997	0.9979	0.9812	0.4243	0.5184

Table 5: *In-vitro* drug release study of DPI formulations (F1-F8)

Sr. No.	*MXN-DPI formulations*	*Drug Release (%)*
1	F1	62.24
2	F2	82.88
3	F3	81.88
4	F4	93.94
5	F5	85.9
6	F6	88.93
7	F7	78.44
8	F8	80.57

Table 6: *In-vitro* drug release of optimized batch

Time (min)	*Drug release (%)*
30	16.33392
60	22.68121
120	36.37216
180	53.88759
240	72.03373
300	93.7695

Stability Study

The durability of the MXN-DPI formulation during storage has a key influence on physical and chemical attributes of the formulation designed for inhalation, including physical nature, particle size, and drug content. The findings of stability examination after storage of optimized MXN-DPI formulation were outlined in Table 7. None of the tested parameters demonstrated any noticeable modifications within the one-

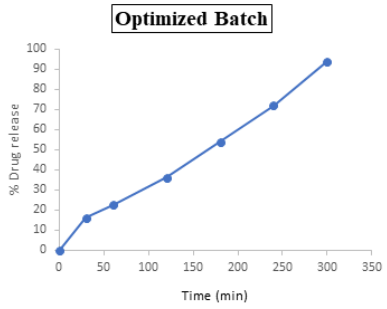

Figure 7: *In-vitro* %Cumulative drug release of Optimized MXN-DPI formulation

Table 7: Stability study of optimized batch

Formulation	*Test Condition*	*Temperature (°C)*	*Drug Content (%)*	*Physical Appearance*
Optimized Batch	Initial	5	95.1	Pale yellowish in color
	After one Month	2	93.3	Pale yellowish in color

month storage. These findings point to the longer time stability of MXN-DPI formulation under various storage circumstances.

CONCLUSION

Moxifloxacin dry powder inhalation formulation with a mucolytic agent was effectively produced using a spray drying approach. The spray-dried particles obtained showed essential characteristics for lung delivery as DPI. Furthermore, the formulation was optimized by a statistical screening strategy. Evaluation after optimization illustrated that the amount of lactose and mucolytic agent profoundly affected the flow pattern, particle size, and drug release from MXN-DPI formulation. The outcomes of *in-vitro* drug release examination confirmed drug release up to 5 hours, on the basis of which it was anticipated to offer extended local activity against pulmonary diseases within the lungs after the pulmonary administration of MXN-DPI formulation. Overall, the developed MXN formulation as DPI is an appealing option for administering anti-TB drugs for combination as well as specified therapy through the pulmonary route.

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