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Formulation, Development and Evaluation of Inhalable Nanoparticles for the Treatment of Respiratory Diseases

Md. Nasar Mallick[1], Sidhartha Sankar Hota[2], Akhil Sharma[3], Usha D S[4], Tahajul SK[5], Sateesh Kumar Mishra[6*]

[1]School of Medical and Allied Sciences, Galgotias University, Yamuna Expressway, Gautam Buddha Nagar, India
[2]Faculty of Pharmacy, C V Raman Global University, Bhubaneswar, India
[3]R.J. College of Pharmacy, Raipur, Gharbara, Tappal, Khair, India
[4]Department of Pharmacy Practice, KLE College of Pharmacy
[5]Brainware University, 398, Ramkrishnapur Road, Indiia
[6]Gulabkali Memorial College of Pharmacy, Gaura Road Chakghat, India
Email: drskmishra1008@gmail.com

Inhalable nanoparticles present a promising approach for targeted pulmonary drug delivery in respiratory disease management. This study focuses on the formulation and evaluation of Quercetin-loaded PLGA nanoparticles for dry powder inhalers (DPI). Nine formulations (A1–A9) were prepared and characterized for their physicochemical and aerodynamic properties. Among these, formulation A8 exhibited the highest yield (84.88%), with entrapment efficiencies ranging from 62.82% to 82.67%. The particle size ranged between 265–514 nm, and the zeta potential values were between -5.89 to -14.70 mV. Morphological analysis revealed spherical nanoparticles with rough surfaces. The in-vitro drug release study demonstrated a maximum release of 93.55% for A8 over 720 minutes, indicating sustained release potential. Lyophilized nanoparticles showed an 85% yield and 78.22% drug content. The nanoparticles were blended with lactose to prepare DPI formulations, which exhibited favorable flow properties, including bulk density (0.225±0.032 g/cm³), tapped density (0.224±0.028 g/cm³), Hausner's ratio (1.12±0.024), Carr's index (8.18±0.015%), and angle of repose (25.96±0.011°). Aerodynamic assessment indicated efficient lung deposition, with a fine particle fraction (FPF) of 31.25±0.9% and a mean median aerodynamic diameter (MMAD) of 3.34±0.03 µm, suitable for lower lung targeting. Stability studies revealed minor

degradation over time, confirming acceptable stability. Overall, formulation A8 showed superior characteristics, making it a strong candidate for targeted pulmonary drug delivery.

Keywords: Inhalable nanoparticles, respiratory disease, quercetin, PLGA, dry powder.

1. Introduction

Respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), and pulmonary infections, pose significant global health challenges, leading to considerable morbidity and mortality. The increasing incidence of these conditions has underscored the need for innovative therapeutic approaches that offer effective management with fewer side effects. In recent years, the focus has shifted toward using advanced drug delivery systems that can enhance drug efficacy, reduce systemic toxicity, and provide targeted treatment to affected areas. A promising approach is the development of inhalable nanoparticles for localized delivery, particularly quercetin-loaded PLGA (poly(lactic-co-glycolic acid)) nanoparticles (NPs) [1-3].

Quercetin, a naturally occurring flavonoid found in various fruits and vegetables, has attracted significant attention due to its potent antioxidant, anti-inflammatory, and anti-viral properties. Its ability to modulate oxidative stress and inflammation makes it a promising candidate for treating respiratory diseases where inflammation and oxidative damage play key roles in disease progression. However, the clinical use of quercetin has been limited by its poor water solubility, low stability, and rapid degradation when administered orally. These drawbacks have highlighted the need for a delivery system that can enhance the bioavailability and stability of quercetin while providing targeted action [4-6].

To address these challenges, PLGA nanoparticles have emerged as a leading choice for drug delivery in respiratory diseases. PLGA is a biodegradable and biocompatible polymer approved by the U.S. Food and Drug Administration (FDA) for various medical applications. Its ability to encapsulate hydrophobic compounds like quercetin and provide sustained release has made it a popular choice for nano-formulations. By loading quercetin into PLGA nanoparticles, researchers aim to enhance the therapeutic potential of quercetin, making it a viable treatment option for chronic and acute respiratory conditions [7, 8].

The inhalable delivery of drug-loaded PLGA nanoparticles offers distinct advantages over traditional administration routes. Inhalation ensures direct delivery of the drug to the lungs, allowing for higher local concentrations, faster onset of action, and minimized systemic exposure. This targeted approach not only increases drug efficacy but also reduces the likelihood of systemic side effects, which is a common issue with oral or intravenous drug delivery. The nanoparticles are engineered to reach the deeper regions of the lungs, such as the alveoli, where they can exert their therapeutic effects, particularly in diseases like COPD and asthma, which involve deep lung inflammation and oxidative stress [9-11].

Moreover, the encapsulation of quercetin in PLGA nanoparticles provides controlled and sustained drug release, maintaining therapeutic levels over an extended period. This sustained release is particularly beneficial in chronic respiratory diseases that require long-term

management, as it reduces the frequency of dosing and enhances patient adherence to treatment. In addition to improving the bioavailability and stability of quercetin, the nano-formulation may also enhance its uptake by lung cells, leading to more effective disease control [12, 13].

Inhalable quercetin-loaded PLGA nanoparticles represent a cutting-edge approach in the treatment of respiratory diseases, combining the therapeutic benefits of quercetin with the advanced delivery capabilities of nanotechnology. This innovative strategy holds the potential to revolutionize the management of respiratory diseases, offering a more effective and patient-friendly solution that aligns with the growing emphasis on targeted, localized, and sustained therapeutic interventions.

2. MATERIALS AND METHODS

2.1 Materials

Drug sample and chemical reagents used in the formulation of inhalable nanoparticles were procured from different reputed companies.

2.2 Method

2.2.1 Compatibility Study

2.2.1.1 Fourier Transforms Infrared Spectroscopy (FT-IR)

A common method for identifying medicinal substances is infrared spectroscopy. By comparing the spectrums of the polymer and drug separately with the spectra of the polymer-drug complex, FT-IR spectroscopy assists in verifying the development of the complex between the two. FT-IR analysis was used to assess if the chosen medicine and the chosen excipients were compatible. FT-IR analysis was performed using KBr pellet to examine the medicine both alone and in combination with certain excipients [14].

2.2.2 Formulation of Quercetin Loaded PLGA Nanoparticles

In current research ionic gelation probe sonication method is used for the preparation of PLGA nanoparticles which is the mild and simplest form of preparation. In this method, PLGA is cross-linked with a cross-linking agent to form a nanoparticulate matrix. The weighed quantity of drug (Quercetin) was added to PLGA solution in acetic acid with continuous stirring for about 1 hr. Sodium tripolyphosphate (TPP) solution was added drop wise into the PLGA solution. This solution was further allowed to stir for 2 hrs on a magnetic stirrer. The final suspension was probe sonicated to form the NPs.

2.2.3 Optimization of Nanoparticles by 3^2 Full Factorial Designs

To study all the possible combinations of all factors at all levels, a two-factor, three-level full factorial design was constructed and conducted in a fully randomized order. The dependent variables measured were particle size (Y1), % entrapment efficiency (Y2) and in vitro drug release (Y3) in phosphate buffer saline (pH 7.4). Two independent variables, the concentration of PLGA (X1) and the concentration of tripolyphosphate (X2) were set at three different levels [15].

Table 1. Composition of factorial batches of nanoparticles.

Batch	PLGA (mg)	TPP (mg)	Quercetin (Drug) (mg)
A1	100	40	20
A2	200	40	20
A3	300	40	20
A4	100	40	30
A5	200	40	30
A6	300	40	30
A7	100	40	40
A8	200	40	40
A9	300	40	40

2.2.4 Evaluation Parameters of Nanoparticles

2.2.4.1 Percentage Yield

The percentage yield is the actual yield divided by the theoretical yield. The formula used to calculate the prepared nanoparticles' percentage yield was as follows.

$$\text{Percentage Yield} = \frac{\text{Actual Yield}}{\text{Theoretical Yield}} \text{X100}$$

2.2.4.2 Encapsulation Efficiency (EE)

Using the ultracentrifugation process, the unentrapped medication was separated from the nanolipid formulation. Nanoparticles were centrifuged for 90 minutes at 13,000 rpm. After appropriately diluting the clear supernatant from the resultant solution with pH 7.4 phosphate buffer, it was measured at 369 nm using a U.V. visible spectrophotometer. The following formula was used to determine the entrapment efficiency [16].

$$\text{EE} = \frac{\text{Total quantity of drug} - \text{Quantity in supernatent}}{\text{Total quantity of drug}} \text{ X } 100$$

2.2.4.3 Particle Size

Particle size of prepared nanoparticles was measured by Malvern zetasizer (Malvern P analytical Ltd).

2.2.4.4 Zeta Potential

Quercetin loaded PLGA nanoparticles were subjected to zeta potential (ζ) measurements using a Zetasizer 4 (Malvern Instruments Ltd., Malvern, UK). An automated aqueous dip cell was used to test the zeta potential. Samples were placed in a capillary measuring cell with the cell location changed after being diluted with ultra-purified water.

2.2.4.5 Scanning Electron Microscope (SEM)

A scanning electron microscopic method was utilized to determine the size and shape of the prepared nanoparticles.

2.2.4.6 In-vitro Drug Release

All nine batches of PLGA nanoparticles loaded with quercetin (A1-A9) were analyzed using the dialysis bag technique. In a USP dissolving test apparatus with a basket-style stirring element, the nanoparticles equal to a dosage of quercetin (6.5 mg) were added. The basket was filled with the dialysis bag. The dissolving media, a phosphate buffer solution (pH 7.4), was maintained at 37°C. The rotational speed of the basket was 50 RPM. At intervals of 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes, 5.0 mL of medium was extracted using a 5.0 mL syringe and replaced with 5.0 mL of brand-new phosphate buffer solution (pH 7.4). The amount of medication was measured at 369 nm using a UV visible spectrophotometer [17].

2.2.5 Lyophilisation of the Optimized Nanoparticles

For around 48 hours, the optimized batches of the NP prefrozen suspension were lyophilized. Following lyophilization, the dry NP powder was sieved 100 times to create a homogeneous powder before being placed in a dry, clean glass vial. Studies on dry powder characteristics, including yield and drug content percentages, have been conducted.

2.2.6 Formulation of Dry Powder

To obtain a respirable powder, A8 NPs were further adsorbed onto the coarse and fine inhalable lactose pre-blend to prepare a dry powder inhaler (DPI) formulation.

2.2.7 Dry Powder Capsule Formulation

After the preparation of dry powder of nanoparticles, it was filled in a capsule with lactose carriers.

3. RESULT AND DISCUSSION

3.1 FTIR

The FTIR spectra of the pure drug Quercetin was obtained and shown in figure 1.

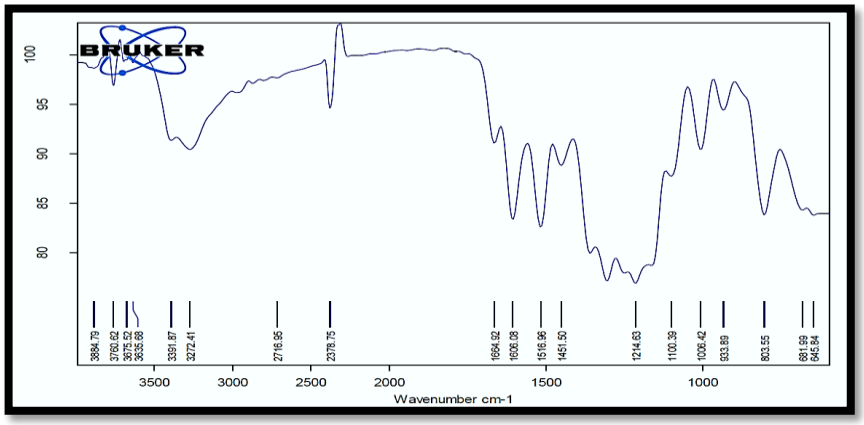

Figure 1. FT-IR spectra of Quercetin

3.2 Evaluation of Nanoparticles

The Quercetin loaded PLGA nanoparticles were prepared and evaluated for following parameters.

3.2.1 Percentage Yield

The amount of Quercetin in each formulation was determined. The percentage yield of formulations A1-A9 was found respectively. The formulation A8 showed the maximum % yield. The percentage yield for all batches of quercetin loaded PLGA nanoparticles was depicted in table 2 and figure 2.

Table 2: Percentage yield of Quercetin Loaded PLGA nanoparticles (Formulation batches A1-A9).

Nanoparticles Batches	Percentage yield (%)
A1	63.28
A2	74.08
A3	77.63
A4	62.81
A5	58.32
A6	74.54
A7	72.65
A8	84.88
A9	69.77

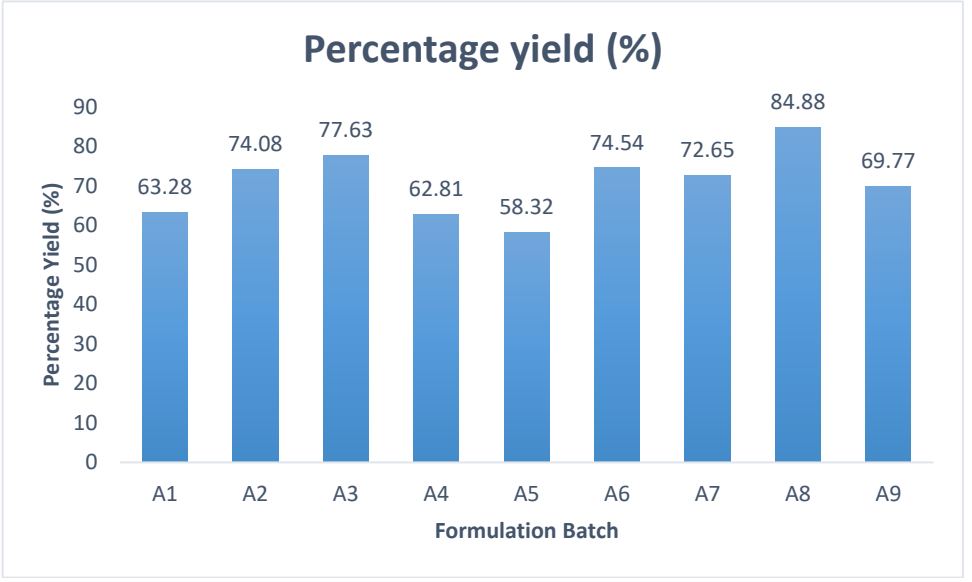

Figure 2. Percentage yield of Quercetin loaded PLGA nanoparticles (Formulation batches A1-A9)

3.2.2 Encapsulation Efficiency (EE)

The amount of active constituent in the supernatant was determined using UV spectrophotometer at 369 nm and the absorbance readings were used to calculate the amount of free drug which further determined the %EE. The %EE of all the batches was calculated & mentioned in table 3 & figure 3. The %EE ranged between 62.82% to 82.67%.

Table 3. EE% of Quercetin Loaded PLGA nanoparticles (Formulation batches A1-A9).

Nanoparticles Batches	EE (%)
A1	78.57
A2	74.63
A3	72.45
A4	62.82
A5	68.58
A6	65.25
A7	67.65
A8	82.67
A9	78.09

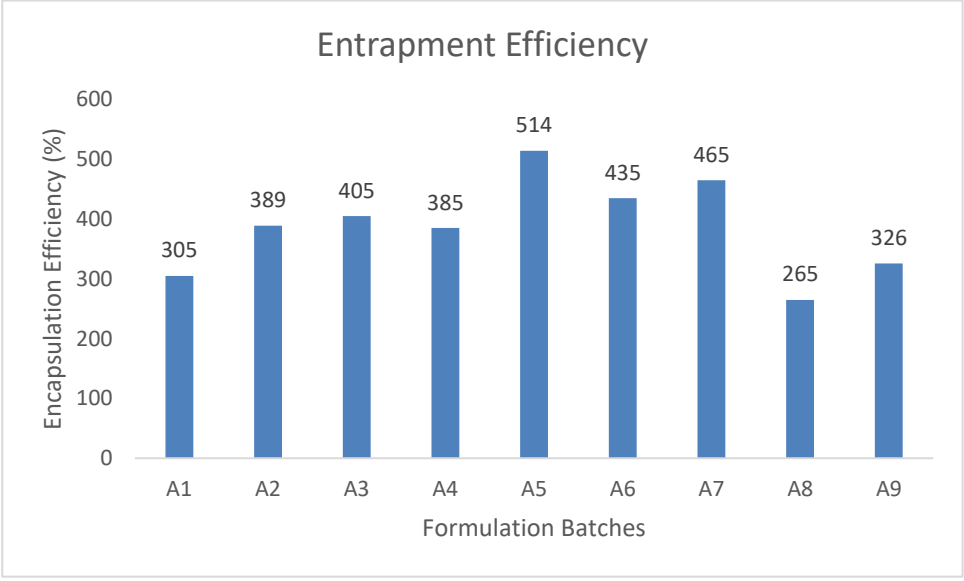

Figure 3. EE% of Quercetin loaded PLGA nanoparticles (Formulation batches A1-A9)

3.2.3 Particle Size

The particle size of the Nanoparticles was determined by using a Zetasizer 4 (Malvern Instruments Ltd., Malvern, UK). The particle size and size distribution are the most important characteristics of Nanoparticles system. The particle size of formulations A1-A9 was found in the range of 265-514nm respectively. The particles size of nanoparticles was shown in table 4 and figure 4.

Table 4. Particle size of Quercetin Loaded PLGA nanoparticles (Formulation batches A1-A9).

Nanoparticles Batches	Particle Size (nm)
A1	305
A2	389
A3	405
A4	385
A5	514
A6	435
A7	465
A8	265
A9	326

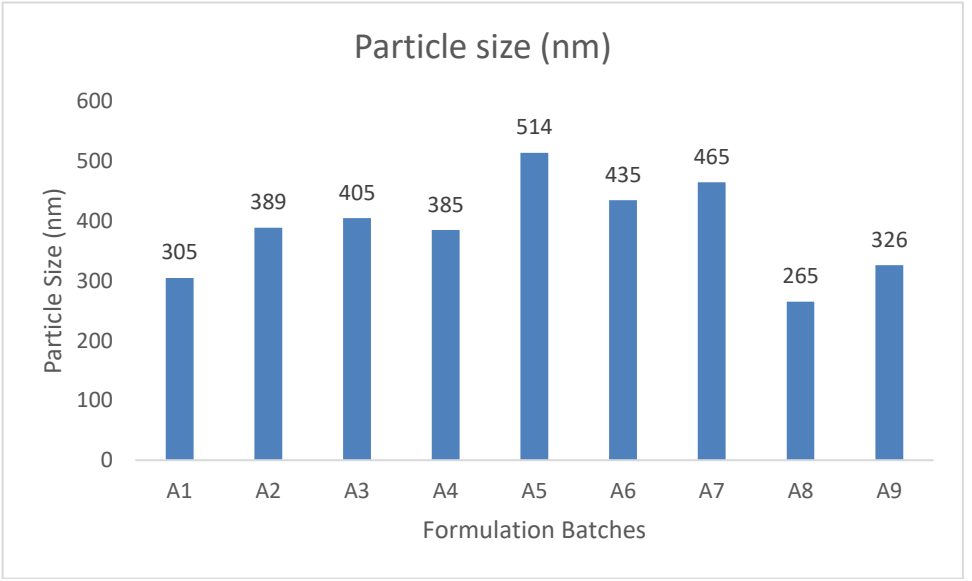

Figure 4. Particle size of Quercetin loaded PLGA nanoparticles (Formulation batches A1-A9)

3.2.4 Zeta Potential

Zeta potential of Quercetin loaded PLGA nanoparticles was determined and found to be in the range of -5.89 to -14.70mV. Results were shown in table 5.

Table 5: Zeta potential of Quercetin loaded PLGA nanoparticles (Formulation batches A1-A9)

Nanoparticles Batches	Zeta potential (mV)
A1	-13.80
A2	-12.52

A3	-10.54
A4	-9.47
A5	-5.89
A6	-10.85
A7	-12.65
A8	-14.70
A9	-11.67

3.2.5 Scanning Electron Microscope (SEM)

The surface morphology study of prepared batches of Quercetin loaded PLGA nanoparticles was conducted and it was found that nanoparticles were spherical in shape with rough surface.

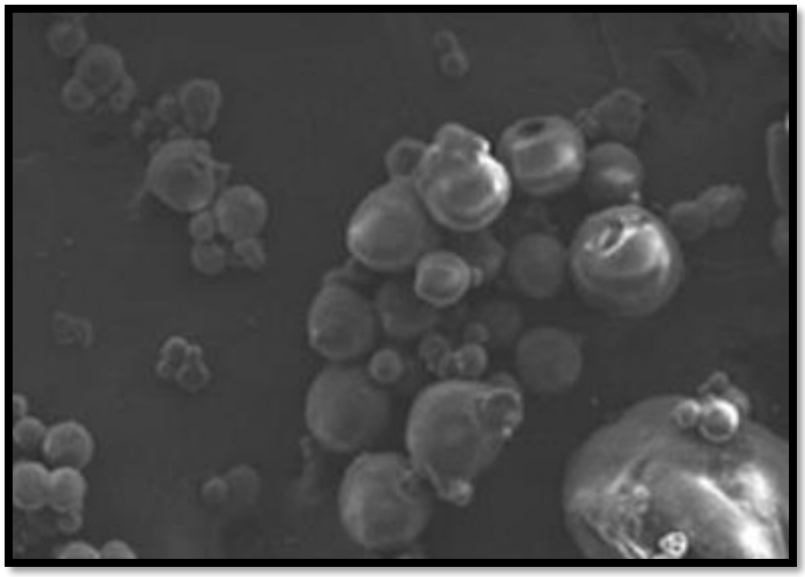

Figure 5. SEM image of Quercetin loaded PLGA nanoparticles

3.2.6 In-vitro Drug Release

The dissolution profile of all the batches of Quercetin loaded PLGA nanoparticles was obtained in phosphate buffer pH 7.4. The in-vitro dissolution testing was performed for 12 hr. (720 minutes). The in-vitro drug release from Quercetin loaded PLGA nanoparticles ranged from 72.98% to 93.55%. The maximum in-vitro drug release was found to be 93.55% from F8 at the end of 720 minutes as shown in the table 5 and figure 6.

Table 5. In-vitro drug release profile of Quercetin loaded PLGA nanoparticles

Time (Min.)	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	0
60	5.63	6.78	6.55	5.89	8.5	6.34	6.84	8.13	5.76

120	13..97	12.89	16.45	15.89	13.12	13.22	12.45	17.11	11.47
180	22.42	26.13	21.51	18.45	20.33	19.27	17.95	26.85	16.50
240	28.56	33.46	28.1	24.13	24.48	27.65	23.38	36.13	21.92
300	33.99	36.16	32.45	28.89	30.61	37.48	28.97	41.6	31.12
360	39.21	40.89	38.29	34.31	32.97	46.37	34.67	48.61	35.51
420	41.62	45.27	46.78	39.12	38.22	52.75	40.16	55.72	41.33
480	52.33	53.69	52.16	43.55	41.66	59.46	48.13	62.75	45.22
540	58.22	60.13	61.74	50.23	49.65	67.32	53.92	69.81	50.30
600	63.72	68.33	70.23	55.29	55.12	70.85	59.12	74.32	55.33
660	68.88	80.12	73.12	63.88	61.84	80.56	69.5	85.21	63.22
720	74.46	82.12	85.13	75.47	72.98	88.33	78.30	93.55	80.12

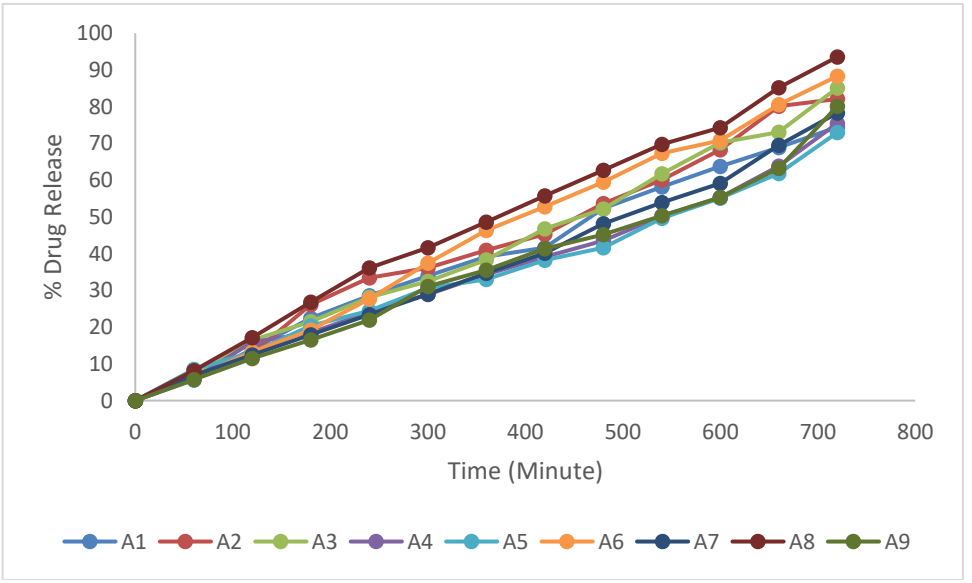

Figure 6. Percentage drug release of Quercetin loaded PLGA nanoparticles

Based on the result obtained from evaluation study, it was observed that the batch A8 showed better results when compared with other batches.

Form the study it was observed that the A8 is considered as optimized batch as compare to other batches.

3.3 Evaluation of Lyophilized Dry Powder

3.3.1 % yield of Lyophilized Batch

The % yield calculation of the lyophilized batches of NP has been carried out where total material used i.e. drug (Quercetin), polymer (PLGA) and cryoprotectant (Mannitol) used and actual yield of the dry powder has been calculated as shown in table 6.

Table 6. Results of % yield of Lyophilized Batch

Name of Nanoparticles	Nanoparticles = Drug +Polymer (1:2) (g)	Nanoparticles: Cryoprotectant (Ratio 1:3)	Theoretical Yield	Practical Yield (g)	% Yield
A8 NP	1.5	4.5	6.0	5.1	85

3.3.2 % Drug Content of Lyophilized Powder

The assay testing had been carried out to find the % drug content in the lyophilized powder of NP. The results show the % drug content of NP respectively shown in table 7.

Table 7. Results of % Drug Content

Lyophilized Batch	% Drug Content
A8 NP	78.22

3.4 Formulation Dry Powder Inhaler

To obtain a respirable powder, the prepared NPs were further absorbed onto the coarse and fine inhalable lactose pre-blend to prepare a dry powder inhaler (DPI) formulation. As per the literature for dry powder inhalers, the angle of repose gives more desirable flow property. The flow property of Inhalac®206 and Lactohal®230 was found excellent and their ratio as 9:1 showed excellent flow characteristic, this combination was selected for preparation of dry powder inhaler.

3.4 Results of Solid-State Characterization for Dry Powder Inhaler

As per the drug content found in lyophilized powder of NP, the amount of dry powder taken and mixed with the lactose carrier. The results of solid-state characterization of the final dry powder inhaler are as described in table 8.

Table 8. Results of Solid-State Characterization of DPI

Bulk Density (g/cm^3) ± SD	Tapped Density (g/cm^3) ± SD	Hausner 's ratio ± SD	Carr's Index ± SD	Angle of Repose ± SD
0.225±0.032	0.224±0.028	1.12±0.024	8.18±0.015%	25.96±0.011˚

3.5 Dry Powder Capsule Formulation

Depending on the drug content, the nanoparticles powders were filled in a capsule with lactose carriers (nano: lactose - 1:1) where Inhalac® 206: Lactohal® 230 have been taken in a ratio of 9:1. Around 32 mg of dry powder is filled in the capsule.

3.5.1 In-vitro Lung Deposition Study

Aerodynamic property of DPI was investigated by Anderson Cascade. The deposition of total amount of inhalable dry powder remaining in capsule, device, throat, pre-separator, stages 0-7 and filter was calculated by collecting sample from impactor part using distilled water and from the drug content of the fine particle fraction (FPF) and fine particle dose (FPD) was calculated. Fine particle dose was calculated from ratio of the total mass of powder (R) having particle size below 5 μm, found on the stages of apparatus and filter to the nominal dose (n).

Fine particle fraction was calculated from the ratio of R to the total emitted dose (ΣA) of powder delivered from the mouth piece of the inhaler into the apparatus i.e.

Fine Particle Fraction = (R / ΣA) × 100

Geometric standard deviation was a measure of the spread of an aerodynamic particle size distribution. Typically calculated as follows, GSD = ½ (d84/d16)

Where, d84 and d16 represent the diameter at which 84% and 16% of the aerosol mass are contained, respectively in diameters less than these diameters.

The Mass median Aerodynamic Diameter (MMAD) was determined by the following formula,

$$D_{aer}\,(MMAD) = ½\ \rho\ x\ d\ (MAD)$$

Where, ρ is tapped density in units of g/cm3 and d is mean arithmetic diameter in micron.

For the study of cascade impaction, 10 capsules which contain individually around 32 mg of dry powder have been taken and tested under Anderson cascade impactor. The distribution and results of in-vitro lung deposition of the dry powder collected and the results calculated by using Copley Inhaler Testing Data Analysis Software i.e. (CITDAS,Version 3.1) shown in table 9.

Table 9. Different stages of cascade impactor with their cutoff diameter

Stages	Cutoff diameter at 28.3L/min (μm)
0	9.2
1	6.1
2	4.9
3	3.5
4	2.3
5	0.7
6	0.5

The dry powder reaches up to stage 7 plate of cascade impactor. The powder collected and measure the content of the drug at each stage. And values have been added to the software as mentioned above. The FPF value of the NP DPI formulation was found to be 31.25±0.9% which represented good lung deposition and better local targeting into the lungs. The Mean Median Aerodynamic Diameter (MMAD) was found to be 3.34±0.03 μm confirming the good in-vitro deposition and as it is less than 5 μm suggested that the powder may retain in the lower region of the lung for a long duration.

3.6 Stability Study

The optimized batch was kept on accelerated conditions to check the stability. The physical appearance, in-vitro drug release was observed for stability determination. The result was summarized in table 10, 11 and shown in figure 7.

Table 10. Effect of stability conditions on various parameters of batch A8 formulation of lyophilized powder

S. No.	Parameters	Results			
		Day 0	Day 30	Day 60	Day 90
1.	Appearance	No aggregation, Free flowing	No aggregation, Free flowing	No aggregation, Free flowing	No aggregation, Free flowing
2.	In-vitro Drug Release at 12 hr	93.55%	90.60%	88.67%	87.98%

Table 11. Effect of stability conditions on release of drug from batch A8 formulation of lyophilized powder

Time (Minute)	Day 0 (Drug Release in %)	Day 30 (Drug Release in %)	Day 60 (Drug Release in %)	Day 90 (Drug Release in %)
0	0	0	0	0
60	8.13	7.95	7.56	6.52
120	17.11	16.88	14.19	12.94
180	26.85	26.77	25.51	24.63
240	36.13	35.37	33.63	31.25
300	41.6	40.84	39.15	38.58
360	48.61	47.71	46.78	44.96
420	55.72	54.65	53.48	51.51
480	62.75	60.84	59.55	57.32
540	69.81	68.48	67.15	65.54
600	74.32	72.65	71.34	70.97
660	85.21	83.69	82.59	80.15
720	93.55	90.60	88.67	87.98

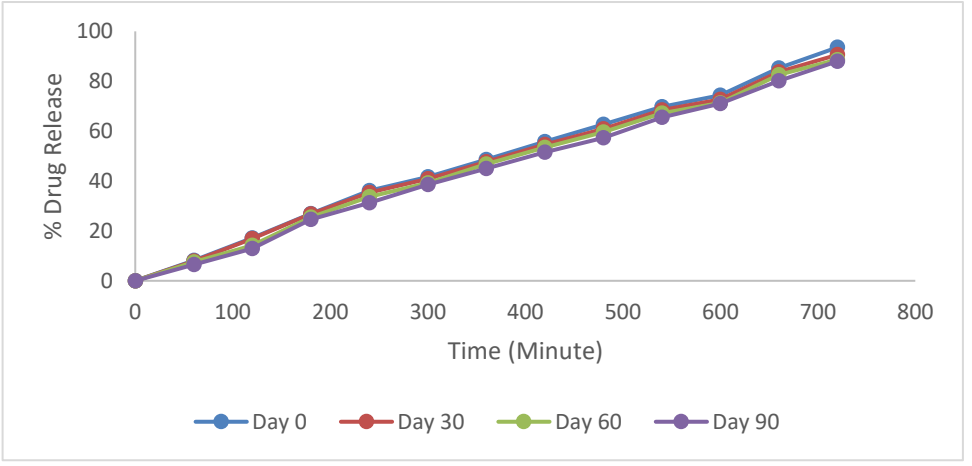

Figure 7. Effect of stability condition on drug release from batch A8 formulation of lyophilized powder

Stability is of prime importance to affirm the final performance of formulation. The stability studies were performed for appearance and in vitro drug release at different time intervals. The results of the stability studies suggested the stability went little down with the increase in days number.

4. CONCLUSION

The formulation, development, and evaluation of inhalable nanoparticles for the treatment of respiratory diseases demonstrated promising results, with formulation A8 emerging as the most effective. The maximum yield of 84.88% and high entrapment efficiency (82.67%) highlighted the efficiency of A8. Particle sizes ranged from 265-514 nm, with zeta potential values between -5.89 to -14.70 mV, ensuring adequate stability. Surface morphology analysis revealed spherical nanoparticles with a rough surface. The in-vitro drug release was maximum for A8, achieving 93.55% over 720 minutes. The lyophilized nanoparticles showed an impressive yield of 85% and drug content of 78.22%. To enhance respiratory delivery, the nanoparticles were formulated into a dry powder inhaler (DPI) using lactose carriers. The DPI exhibited favorable flow properties, including a bulk density of 0.225 g/cm³, a Hausner's ratio of 1.12, and an angle of repose of 25.96˚. Cascade impactor studies confirmed excellent lung deposition, with an FPF of 31.25% and MMAD of 3.34 μm, indicating effective targeting to the lower lungs. Stability studies suggested minor declines in performance over time, but overall stability was satisfactory. These findings highlight the potential of nanoparticle-based DPI formulations for efficient and targeted respiratory disease treatment.

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