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Original Article

Pulmonary Drug Delivery of Budesonide in the Form of Inhalable Microspheres

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ABSTRACT

Objectives: Chronic Obstructive Pulmonary Disease (COPD) is a major healthcare issue that is rising and expected to increase in day-to-day life. Our research work focused on developing Dry Powder Inhaler (DPI) microspheres that deliver medication in the form of dry powder into the lungs. Budesonide was used as a drug along with Polycaprolactone which is a biodegradable and biocompatible polymer used in the formulation of microspheres. Due to its non-toxicity with many drugs, it is suitable for controlled release. **Materials and Methods:** The microspheres were formulated using solvent evaporation technique and evaluation parameters such as size, shape, drug loading, and entrapment efficiency for better patient compliance and treatment were performed. **Results:** The microsphere had particle size ranging from 1 µm-5 µm, within the inhalable range. The morphological study showed a smooth surface area with spherical-shaped particles. The particles were monodispersed with PDI less than 0.5. The % drug release was found to be 95.3% after 48 hr showing sustained drug release from Polycaprolactone microspheres. The *in vivo* study suggested that the given formulation effectively inhibited the LPS-induced toxicity in a dose-dependent fashion and proved to be anti-inflammatory. **Conclusion:** Budesonide inhalable microsphere of Polycaprolactone was proven to be beneficial without any toxicity for the treatment of coronary obstructive pulmonary technique.

Keywords: Microspheres, Biodegradable, Inhalation, Polycaprolactone, COPD, Kinetics.

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INTRODUCTION

Lungs are the central organs of the respiratory system with the basic function of facilitating air exchange from the environment into the bloodstream. Respiratory diseases are among the leading causes of mortality.[1,2] Air pollution, smoking and continuous climate change are increasing causes of respiratory diseases.[3] Inflammation is the first response by the body to show infection.[4] A Dry Powder Inhaler (DPI) has been designed to enable the direct administration of dry powder directly to the lungs. These pharmacological agents are commonly used to cure various pulmonary conditions.[5] DPIs work by using the patient's inhalation to draw the dry powder medication into their lungs. The device typically contains a capsule or blister pack of medication, which is inserted into the inhaler.[6] COPD, a prevalent serious respiratory ailment, impacts numerous individuals worldwide.[7] It is marked by airflow restriction resulting from chronic bronchitis or emphysema, leading to breathing difficulties.[8] COPD can be triggered by smoking, although other elements like air pollution exposure, genetic predisposition, and environmental hazards can also contribute.[9] Budesonide is a corticosteroid commonly prescribed for treating COPD and asthma. It is categorized as class II medication under Biopharmaceutical Classification, distinguished by low solubility and high permeability.[10] Budesonide exhibits low solubility in water, which may result in limited absorption in the gastrointestinal tract due to its potential to dissolve slowly.[11] However, Budesonide is known to have high permeability, allowing it to easily pass through biological membranes, such as the intestinal lining or the lung tissue, which may enhance its effectiveness in treating COPD.[12] Polycaprolactone (PCL) is a biodegradable, biocompatible polymer.[13] It is a potential material for inhaled drug delivery systems, especially as a carrier for the creation of nanoparticles and microspheres for pulmonary drug administration. PCL microspheres enable controlled and prolonged medication delivery as carriers for dry powder inhalers. The current paper focused on preparing inhalable microspheres of budesonide to target the drug to the lungs and give sustained drug release.[14,15]

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MATERIALS AND METHODS

Materials

Polycaprolactone (MW 80000), Budesonide and Polyvinyl Alcohol (PVA) were procured from Yarrow Chem Products Mumbai, Maharashtra, India. Methanol was purchased from Himedia Chemicals Mumbai, Maharashtra, India.

Methods

UV-visible spectrophotometer scans

Ultraviolet (UV)-visible scan was conducted in water to ascertain the λ_{max} of the drug. A drug solution of 10 µg/mL was made in water and examined within the 200-400 nm range to ascertain the maximum absorption wavelength.

Standard calibration curve of the drug in Methanol

10 mg drug was diluted with 100 mL of methanol to prepare a standard stock solution of 100 µg/mL. 1 mL of stock solution was diluted in 10 mL of purified water resulting solution of 10 µg/mL of concentration. Similarly, more dilutions of 10 µg/mL, 15 µg/mL, 20 µg/mL, 25 µg/mL and 30 µg/mL were made using a stock solution. The absorbance of all solutions was recorded, and the standard graph was plotted between concentration and absorbance as shown in Figure 2.

Solubility studies of drug

An excess Budesonide was added to beakers holding 25 mL of distilled water to make a saturated solution. The beakers were shaken for 24 hr at 25°C by using the shake flask apparatus. The resulting saturated solutions were filtered. The filtrate was diluted and monitored using UV-visible spectroscopy (Shimadzu).[16,17]

Melting point

Budesonide was placed into a glass capillary tube from one end and the other end of the tube was closed by sealing in flame. To measure the melting point, the capillary tube was inserted melting point apparatus that was connected to a thermometer. The melting point was recorded.[18,19]

Formulation of Microsphere by Solvent Evaporation Method

This method involves the Oil-in-Water (o/w) emulsion solvent evaporation technique. The varying weight ratio of the medication (budesonide) and polymer (Polycaprolactone) was dispersed in 10 mL of organic solvent (methanol) to create a homogeneous solution. The aqueous phase was made by dissolving Polyvinyl Alcohol (PVA) in water at several concentrations (1%, 1:5, 2% w/v). The organic medium was incrementally added by a syringe dropwise into the aqueous phase. The dispersion was agitated at 2500 revolutions per minute at 25°C. The resultant emulsion was further homogenized for 2 hr using a mechanical stirrer at 2500 revolutions per minute. Microspheres were harvested at 3000 rpm via centrifugation for 15 min, thereafter, filtered through Whattman filter paper.

Evaluation of Budesonide-Loaded PCL Microspheres

FTIR (Fourier Transform Infrared Spectroscopy)

FTIR is used for the identification of the drug and the compatibility between the drug and polymer. FTIR of pure drug (budesonide), polymer (Polycaprolactone), and physical mixture of polymer-drug and Budesonide-PCL-Microspheres were done using an FTIR spectrophotometer.[20] The samples were blended with potassium bromide and compressed into a pellet. The FTIR spectrum gives information about various functional groups present in the sample. These peaks demonstrate important details about the chemical composition and molecular structure. Furthermore, any changes in the peak direct the possibility of a chemical reaction between the drug and polymer. KBr is used as a carrier for a sample in FTIR because it does not show any absorption spectrum in the IR region and ensures that the sample does not block the path of the light.[21-23]

XRD Scan

XRD to analyse if the sample is amorphous or crystalline in nature. Sharp peaks were obtained for crystalline and broad peaks for amorphous samples. It also gives information about the arrangement of atoms within the lattice. On the 2θ scale, samples were measured between 10° and 40° at a voltage of 40 kV and a current of 40 mA.

Particle Morphology

To examine the surface properties, and shape of the particle, Scanning Electron Morphology (SEM) was used.[24] This analysis involves the exposure of the sample to an electron beam of 5KV voltage which results in the emission of secondary electrons. Secondary electron emission was measured, and these emitted electrons supplied visual data (pictures) that revealed the surface characteristics and particle size of inhalable microspheres. The samples were adhered to stubs made of aluminium using double-sided adhesive tape with a thin coating of gold. Photomicrographs were captured at different magnifications.

Particle Size Analysis

To assess the Poly Dispersibility Index (PDI), particle size and zeta potential of microspheres, the Dynamic Light Scattering (DLS) method was used utilizing the MalvernZetasizer instrument. The samples were mixed in a ratio of 1:1 using High-Performance Liquid Chromatography (HPLC) grade water and allowed to fill into the cuvette for monitoring. This analysis is essential for understanding the size range, uniformity and performance of microspheres.

Flow property

Flow property is a critical parameter for ensuring dose uniformity. It is assessed by measuring the Carr's Index, angle of repose, and Hausner's ratio. Fixed funnel technique was used to determine the angle of repose of powder. The powder was accurately weighed and introduced through a funnel, which was adjusted so that its tip just contacted the apex of the powder pile. The powder was allowed to free flow on the surface through the funnel. The diameter and height of the resulting cone were measured, and the following equations were employed.

Hausner ratio=Tapped density/Bulk density;

Carr's index (%)=(Tapped density-Bulk density)/Tapped density×100.

The cone's height and diameter of the powder were measured, and the following equation was used to determine the angle of repose.

$$\text{Tan } \theta = h/r$$

Where, h=height of the pile, r=radius of the pile base, θ=angle of repose.

Drug Loading (DL) and Encapsulation Efficiency (EE)

Budesonide-loaded PCL inhalable microspheres containing budesonide equivalent to 10mg of the drug were taken, crushed, and mixed in 10 mL methanol. The mixture was then sonicated for 15 min, filtered using Whattman filter paper and analysed to determine the absorbance in a UV spectrophotometer at 243 nm.[25-27] DL and EE can be calculated by the formula mentioned below:

$$\%\text{Drug Loading} = \frac{\text{weight of drug presnt in microspheres}}{\text{weight of microspheres taken}} \times 100$$

$$\%\text{ Encapsulation efficiency} = \frac{\text{weight of drug present in microspheres}}{\textit{weight of drug taken}} \times 100$$

In vitro Drug Release Studies

In vitro drug release investigations were conducted utilizing USP apparatus II at 37±0.5°C and 100 rpm in 900 cc of Simulated Lung Fluid (SLF) at pH 7.4. Microspheres corresponding to 10 mg of the medication were positioned in the dialysis bag and filled with 5 mL of Simulated Lung Fluid (SLF). This bag was sealed at the ends and attached to the paddle of the dissolution apparatus. At a predetermined period, the 5 mL samples were withdrawn, filtered and analyzed in a UV spectrophotometer. During each sampling, 5 mL of new dissolution phases was introduced into the dissolution apparatus to sustain sink conditions.

In vitro Drug Release Data Kinetics Model Fitting

DD Solver was implemented to analyze the kinetics of drug release utilizing first-order, zero-order, Hixson-Crowell cube root, Korsmeyer-Peppas and Higuchi models were employed to evaluate *in vitro* release data and drug release kinetics for inhalable formulation. The model exhibiting the highest R^2 value, lowest Sum of Squares (SS), and highest sample selection criteria (MSC) values was selected to clarify the drug release mechanisms.

In vitro Lung Deposition Study

The *in vitro* lung deposition studies of the drug and budesonide-loaded PCL microspheres were carried out by using an Anderson Cascade Impactor (ACI). ACI is a multistage (6-8) device with nozzles and a pump, which is used for the evaluation of the size distribution of aerosol particles in the air.[28,29] Air is drawn into the impactor using a pump. Microspheres equivalent to 10 mg drug were encapsulated in size 3 capsule and kept inside a Rotahaler, a device in which the ca rotates under the influence of the patient's breath. ACI with an airflow rate of 28.3 L/min for 60 sec was used to quantify the aerodynamic properties like Fine Particle Fraction (FPF), Emitted Dose (ED), Fine Particle Dose (FPD) and MMADT. A throat piece is positioned at the top of ACI to replicate the human throat. The formulas for calculating the aerodynamic properties are mentioned below:

FPD= Mass of the particle on stages 2 through 7.

FPF = fine particle dose/initial particle mass × 100.

Emitted Dose (ED) = Total particle mass on all stages/initial particle mass ×100

$$\text{MMADT} = \sqrt{\boldsymbol{d}\frac{\rho}{\rho 0 X}}$$

d -Geometric mean diameter of particle size analysis, ρ- tapped density.

ρ_0- reference density 1 gm/cm^{3,} X- shape factor (1 for sphere).

In vivo Study

To determine the cytotoxicity study on Raw 264.7 cell lines (Murine macrophage cell lines (NCCS, Pune), budesonide microspheres sample (Sample name PDA) in 5 concentrations (6.25, 12.5, 25, 50,100 ug/mL) was studied. MTT assay is a calorimetric assay used for the determination of cell proliferation and cytotoxicity based on the reduction of yellow-coloured water-soluble tetrazolium dye MTT to formazan crystals. Mitochondrial lactate dehydrogenase produced by live cells reduces MTT to insoluble formazan crystals, which upon dissolution into an appropriate solvent exhibit a purple colour, the intensity of which is proportional to the number of viable cells and can be measured spectrometrically at 570 nm.[30,31]

The experiments used 4 assay controls (i) Medium control (medium without cells) (ii) Negative control (medium with cells but without the experimental drug/compound) (iii) Disease control (medium with cells treated with 1 ug/mL of LPS) (iv) Std control (LPS induced cells followed by 1 mM of Diclofenac sodium).

The cell lines, Raw 264.7 (Murine macrophage cell line) purchased from NCCS, Pune, India were maintained in DMEM high glucose media supplemented with 10% FBS along with the 1% antibiotic-antimycotic solution in the atmosphere of 5% CO_2, 18-20% O_2 at 37°C temperature in the CO_2 incubator and sub-cultured for every 2 days. Passage number 34 was used for the current study.

200 µL cell suspension was seeded in a 96-well plate at the required cell density (20,000 cells per well), without the test agent. The cells were allowed to grow for about 24 hr.

The inflammation was induced in the cells by stimulating with 1 µg/mL of LPS (from *E. coli*) for 2 hr and adding appropriate concentrations of the given test agents. One well was left untreated (without LPS treatment) and considered a control. The plate was incubated for 24 hr at 37°C in a 5% CO_2 atmosphere. After the incubation period, the plates were removed from the incubator, spent media was removed and MTT reagent was added to a final concentration of 0.5 mg/mL of total volume. The plates were wrapped with aluminium foil to avoid exposure to light. The plates were returned to the incubator and incubated for 3 hr. The MTT reagent was removed and then 100 µL of Solubilisation solution (DMSO) was added. Gentle stirring in a gyratory shaker will enhance dissolution. Occasionally, pipetting up and down may be required to completely dissolve the MTT formazan crystals especially in dense cultures. The absorbance was determined on a spectrophotometer or an ELISA reader at 570 nm wavelength Cell viability was calculated using the below formula:[32]

$$\% \text{ cell viability} = [\text{Mean abs of treated cells} / \text{Mean abs of Untreated cells}] \times 100$$

Given test compound was evaluated to analyze the cytotoxicity effect on LPS-induced Raw 264.7 cells. The concentrations of the test compound used to treat the cells are given in Table 1.

RESULTS AND DISCUSSION

UV-visible scan

The UV-visible scan was used to determine λ_{max} at which drug shows maximum absorption. The λ_{max} of budesonide was 290 nm in distilled water using the UV-visible spectroscopy technique.

Standard Calibration Curve of Drug

The standard calibration curve of budesonide in purified water shows a linear relationship between absorbance and concentration with an R^2 value equal to 0.9973.

Solubility studies

Solubility of budesonide in distilled water was found as 24 µg/mL with concentration.

Melting point

Melting point of budesonide was found to be 226°C, near the original melting point value.

Formulation of Microsphere by Solvent Evaporation Method

Microspheres of budesonide were effectively formulated using solvent evaporation technique. Total 9 formulations were prepared using different drug-polymer ratios in varied concentrations of PVA shown in Table 2.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectrum of budesonide, PCL with different formulations is shown in Figure 1. The Figure shows that there is no incompatibility between polymer and drug. Spectra of pure budesonide, Polycaprolactone and a physical mixture of drug and polymer (1:1) were analyzed using an FTIR spectrophotometer. The samples were compressed into discs and 200-400 mg of KBr was used as a carrier for 400-400 cm^{-1}. The FTIR Spectra for budesonide microspheres showed characteristics band at 1724 cm^{-1} and similarly. Polycaprolactone showed peak at 1728 cm^{-1}, which promised good resulting incompatibility is shown in this Figure between drug and polymer.

X-ray diffraction (XRD)

The structural characteristics of Budesonide and polycaprolactone microspheres were identified by XRD diffractometer as shown in Figure 1. The specimens were examined at 40 kV and 40 mA using a 2Θ scale. During the process, the diffractometer emitted X-rays and interacted with the specimen. When X-rays struck atoms within the sample, they scattered, leading to constructive interference. The sample undergoes scattering as the X-rays

Table 1: Different Concentration of test compound used to treat the cells.

Sl. No.	Culture Condition	Cell Lines	Concentration treated to cells
1	Untreated	Raw 264.7	No treatment
2	Blank	-	Only media without cells
3	LPS alone	Raw 264.7	1 ug/mL
4	PDA (Budesonide microspheres)	LPS induced Raw 264.7	LPS+5 (6.25, 12.5, 25, 50,100 ug/mL)
5	LPS+Std	264.7	LPS+1 mM/mL

Table 2: Formulation, Entrapment Efficiency and Drug loading of Budesonide Microspheres.

Formulation	Polyvinyl alcohol	Drug: Polymer	Entrapment Efficiency	Drug loading
F1	1%	1:3	90.545	67
F2	1%	2:5	91.869	87
F3	1%	3:2	90.195	86
F4	1.5%	1:3	93.576	91
F5	1.5%	2:5	92.29	90
F6	1.5%	3:2	92.41	90.11
F7	0.5%	1:3	94.07	92
F8	0.5%	2:5	91.2	86
F9	0.5%	3:2	93.15	91.1

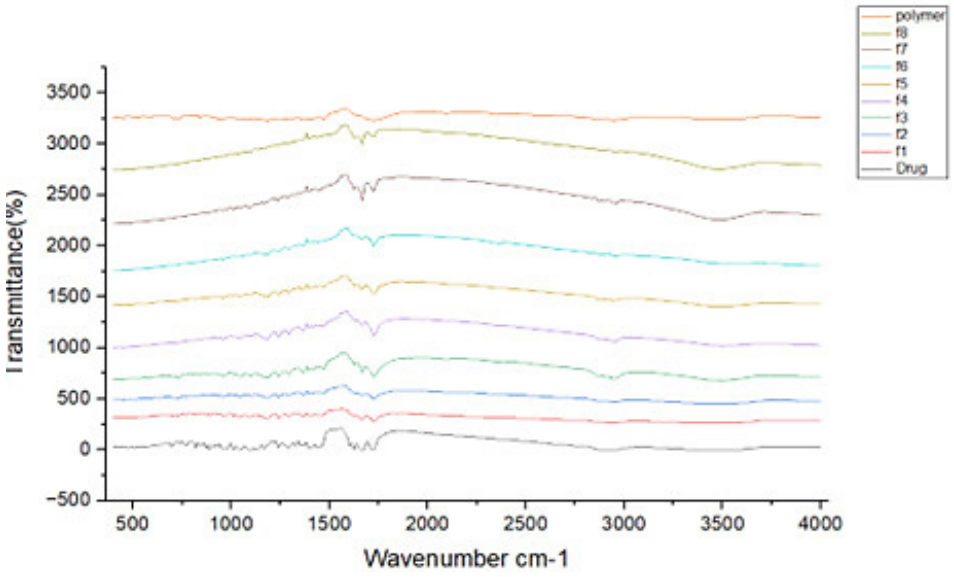

Figure 1: FTIR and XRD Scan of drug, polymer and different formulations.

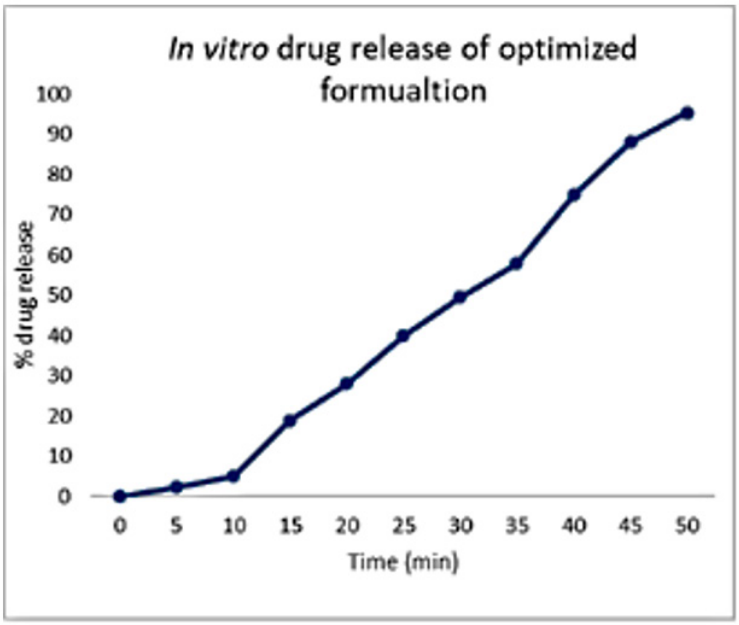

Figure 2: *In vitro* drug release Kinetic of drug release.

strike the sample resulting in constructive interference. The diffraction pattern is recorded during constructive interference which elucidates the crystal structure of the sample and specific arrangement of atoms within its lattice. The formulations have less intense peaks that suggest than the drug.

Particle Size and Morphology

The morphology of optimized budesonide microspheres for inhalation, the particle size must be 1-1000 µg m in size. The SEM images showed that the optimized formulation (F7) particles were micrometre in size and their shape was spherical with a smooth surface.

Particle size Analysis and Zeta Potential

The particle size of the F7 formulation was found to be 1713 nm (1.71 µm) and the Poly Dispersibility Index (PDI) was 0.4894 by measuring the angular variation in the intensity of light scattered. The results showed that the particles are within the desired size range of 1-5 µm. The formulation was monodispersed with a PDI value of less than 0.5. The zeta potential of the F7 formulation was found to be -7.213 mV. A negative charge depicts the prominent repulsive forces, elevating the flight of the budesonide dry powder inhaler which results in enhancing the deposition of the drug in the airway region of the lungs thus yielding good results.

Table 3: Kinetics of drug release.

Fitting release	R^2	R^2 adjusted	SS	MSC
Zero Order	0.9500	0.9500	492.7464	2.7957
First Order	0.8166	0.8166	1807.7324	1.4959
Higuchi	0.6875	0.6875	3079.9004	0.9630
Korsmeyer-peppas	0.9928	0.9919	70.7799	4.5361
Hixon-cornwell	0.8618	0.8618	1361.9500	1.7790

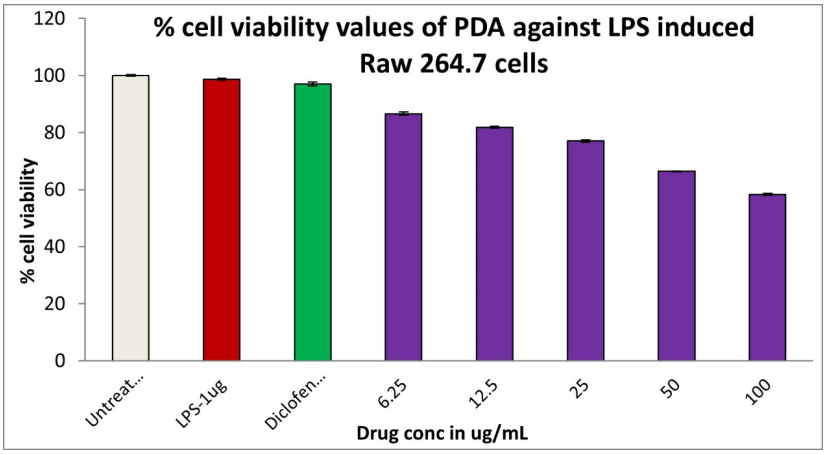

Figure 3: The % cell viability values of PD against LPS-induced Raw 264.7 cells after the incubation period of 24 hr.

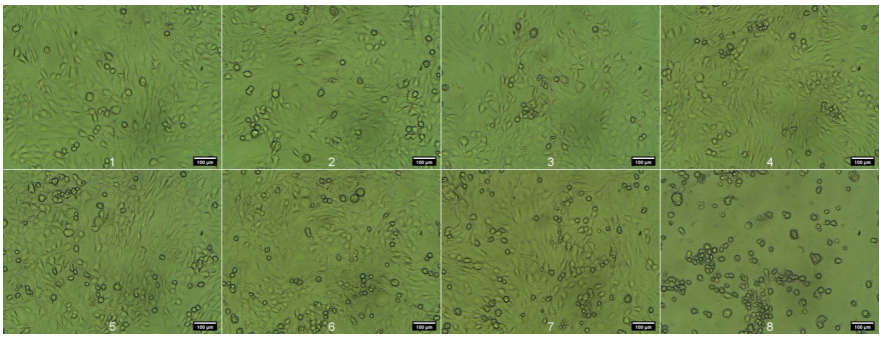

Figure 4: Overlaid montage photo represented the morphology of LPS-induced Raw 264.7 cells treated by different concentrations of PDA after the incubation period of 24 hr. All the images were acquired under the inverted biological microscope at 20x magnification and recorded with the help of a Digital camera equipped with the MICAM software. Scale bar: 100 µm.Photo Legend:1-Untreated; 2-LPS-1 µg; 3-LPS+Diclofeanc-1 mM; 4-LPS+PDA-6.25 µg; 5-LPS+PDA-12.5 µg; 6-LPS+PDA-25 µg; 7-LPS+PDA-50 µg; 8-LPS+PDA-100 µg.

Table 4: Aerodynamic characteristics.

Parameters	Budesonide	Budesonide-loaded microspheres
Emitted dose (%)	61	79
Fine Particle Fraction (FPF) %	56	72
$MMAD_T$ (μm)	-	3.11

Table 5: % cell viability values of a given sample, PDA against LPS induced Raw 264.7 cells after the treatment period of 24 hr.

Culture Condition	%Cell Viability	Max non-toxic dose
Untreated	100	25 ug/mL with >75% cell viability
LPS-lug	98.68	
LPS+Diclofenac-1 mM	96.99	
LPS+PDA 6.25 μg/mL	86.62	
LPS+PDA 12.5 μg/mL	81.83	
LPS+PDA 25 μg/mL	77.07	
LPS+PDA 50 μg/mL	66.42	
LPS+PDA 100 μg/mL	58.31	

Flow Properties

All formulations (F1-F9) showed good flow characteristics with the angle of repose < 20, Carr's index < 10 and Hausner's ratio < 1.12.

Entrapment Efficiency

Drug loading and entrapment efficiency of microspheres were 92% and 94.07% respectively as shown in Table 2 for optimized formulation F7.

In vitro drug release

An *in vitro* drug release study of optimized formulation (F7) was performed in pH buffer for 50 hr and given in Figure 2. The % drug release was found to be 95.3% after 48 hr showing sustained drug release from Polycaprolactone microspheres.

Kinetics of drug release

As mentioned in Table 3, the kinetic drug release for various models has been listed. From the outcome, it was concluded that the drug release kinetics obey the Korsmeyer-peppas model with R2 value of 0.9928 adjusted R2 value of 0.9919 and MSC of 4.5361. The Korsmeyer-Peppas model indicates controlled drug release through diffusion and erosion processes from a polymeric system.

In vitro Lung Deposition Studies

Aerodynamic characteristics of Formulation (F7) were evaluated by ACI and given in Table 4. The Budesonide-loaded inhalable microspheres showed better results than plain budesonide shown in Figure 2.

In vivo Study

The MTT assay results suggested that the given test compound effectively inhibited the LPS-induced toxicity in adose-dependent fashion and proved anti-inflammatory. Diclofenac disodium with 1 mM was used as a std control for the study. The % cell viability values of the given sample (PDA) against LPS-induced Raw 264.7 cells after the treatment period of 24 hr are given in Table 5 and represented in Figure 3 as an Overlaid bar graph. Figure 4 represents the morphology of LPS-induced Raw 264.7 cells treated with different concentrations of PDA after 24 hr of incubation.

CONCLUSION

In the current study, a significant attempt has been made for the development and evaluation of sustained-release Budesonide microspheres for inhalation. The hepatic metabolism of budesonide is rather extensive. As a result, microspheres were created to improve bioavailability and prepare slow-releasing microspheres for the respiratory tract.

ABBREVIATIONS

COPD: Chronic Obstructive Pulmonary Disease; **DPI:** Dry Powder Inhaler; **PCL:** Polycaprolactone; **PVA:** Polyvinyl alcohol: **UV:** Ultraviolet; **FTIR:** Fourier Transform Infrared Spectroscopy; **SEM:** Scanning electron morphology; **PDI:** Poly dispersibility index; **DLS:** Dynamic light scattering; **HPLC:** High performance liquid chromatography; **DL:** Drug Loading; **EE:** Encapsulation Efficiency; **SLF:** Simulated lung fluid; **SS:** Sum of squares; **MSC:** Model selection criteria; **ACI:** Anderson cascade impactor; **FPF:** Fine particle fraction; **ED:** Emitted dose; **FPD:** Fine particle dose; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **DMSO:** Dimethyl sulfoxide; **ELISA:** Enzyme-linked immunoassay; **LPS:** Lipopolysaccharide.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Budesonide is a steroid used to treat asthma and COPD. However, the extensive first-pass metabolism of budesonide makes oral bioavailability very poor. Therefore, in this research paper, inhalable microspheres of budesonide were prepared using polycaprolactone as a biodegradable sustained-release polymer. Dry powder inhalers provide direct delivery of the drug to the lung. Microspheres of budesonide were prepared using the solvent evaporation method. A total of 9 formulations (F1-F9) were prepared using PCL and PVA in different ratios. The formulations were evaluated for particle size, PDI, zeta

potential, particle morphology, entrapment efficiency, drug loading and % drug release. The flow properties of microspheres were evaluated by measuring the angle of repose, Carr's index and Hausner's ratio. The aerodynamic properties of the formulation were evaluated using the Anderson cascade impactor. The compatibility studies using FTIR showed no interaction between the drug and excipients. The SEM image of the optimized formulation showed spherical smooth particles of micron size. The size of optimized formulations was 1.71 µm in the inhalable range of 1-5 µm. The PDI value of 0.4 showed particles were monodispersed. The inhalable microspheres showed good flow properties. F7 showed the best encapsulation efficiency and drug loading. The *in vitro* lung deposition studies showed the microspheres had good aerodynamic properties. The kinetic of drug release obeys the Korsmeyer Peppas model. The *in vivo* study suggested that the given test compound effectively inhibited the LPS-induced toxicity in a dose-dependent fashion and proved to be anti-inflammatory.

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