



**FORMULATION AND EVALUATION OF LEVODOPA LOADED INTRANASAL MUCOADHESIVE NANOPARTICLES FOR TREATMENT OF PARKINSONISM**

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**ABSTRACT**

The objective of this study was to formulate and evaluate Levodopa-loaded intranasal mucoadhesive nanoparticles for the treatment of Parkinsonism. Levodopa is a commonly used drug for the treatment of Parkinson's disease, but its oral administration often leads to irregular absorption and side effects. By utilizing the mucoadhesive nanoparticle system, the aim was to enhance the drug's bioavailability, ensure sustained release, and improve its therapeutic efficacy. Chitosan nanoparticles were prepared using the ionotropic gelation method, and the formulations (F1-F6) were optimized based on parameters such as drug entrapment efficiency, particle size, and zeta potential. The cumulative drug release study revealed a sustained release of Levodopa over 12 hours, with formulation F2 showing the best release profile (96.32%). The mean particle size for the optimized formulation (F2) was 88.23 nm, and the zeta potential was -37.45 mV, indicating good stability. Regression analysis indicated that the drug release followed first-order kinetics ( $R^2 = 0.9508$ ). These findings suggest that the Levodopa-loaded mucoadhesive nanoparticle formulation has significant potential for improving the treatment of Parkinson's disease by enhancing drug absorption through the nasal route, offering controlled release, and reducing side effects associated with oral dosage forms.

**Keywords:** Levodopa, Mucoadhesive nanoparticles, Intranasal delivery, Parkinsonism, Nanoparticle formulation, Drug release, Chitosan nanoparticles, Sustained release, Zeta potential, Bioavailability, Ionotropic gelation.

**INTRODUCTION**

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects millions of people worldwide. It is characterized by motor dysfunctions such as tremors, rigidity, bradykinesia, and postural instability, primarily caused by the degeneration of dopaminergic neurons in the substantia nigra of the brain. The hallmark of PD is the depletion of dopamine, a neurotransmitter that plays a critical role in controlling movement. Levodopa (L-DOPA),

a precursor of dopamine, has long been the cornerstone of PD therapy. However, its oral administration is associated with several limitations, including poor bioavailability, rapid metabolism, and the need for frequent dosing. These challenges often lead to fluctuating therapeutic effects and side effects such as dyskinesia (Kish, 2007).

In recent years, there has been growing interest in developing alternative drug delivery systems to overcome these limitations and enhance the therapeutic

efficacy of Levodopa. Nanoparticles, particularly those with mucoadhesive properties, have gained attention as potential carriers for drug delivery, offering controlled release, increased bioavailability, and targeted delivery to specific sites of action. Mucoadhesive nanoparticles can adhere to the mucosal surface of the nasal cavity, providing a direct pathway to the brain through the olfactory and trigeminal nerves, bypassing the blood-brain barrier (BBB). This offers a promising approach for improving the delivery of Levodopa to the central nervous system (CNS), potentially reducing the frequency of dosing and minimizing side effects (Patel *et al.*, 2013).

Nanoparticles can be prepared using various biocompatible polymers such as chitosan, a polysaccharide derived from chitin. Chitosan possesses excellent mucoadhesive properties, biodegradability, and non-toxicity, making it an ideal material for drug delivery applications (Bhatt *et al.*, 2010). In this study, Levodopa-loaded mucoadhesive nanoparticles were formulated using the ionotropic gelation method, where chitosan was crosslinked with sodium tripolyphosphate (STPP). The nanoparticles were characterized for their size, surface charge (zeta potential), drug entrapment efficiency, and in vitro drug release profiles. The formulation's stability and its potential for intranasal delivery were also evaluated.

The primary objective of this research was to formulate and evaluate Levodopa-loaded mucoadhesive nanoparticles for intranasal administration to improve drug delivery and therapeutic outcomes in patients with Parkinson's disease. By targeting Levodopa directly to the brain via the nasal route, this

approach aims to provide a more effective and patient-friendly alternative to traditional oral drug delivery methods.

### Materials

The preparation and evaluation of mucoadhesive nanoparticles involved several instruments. A UV-Visible Spectrophotometer (Labindta) was used for drug concentration, and Fourier Transform Infrared Spectroscopy (Bruker) analyzed chemical interactions. A Micro Centrifuge (Remi) and pH Meter (EI) assisted in sample preparation and pH measurement. The formulations were weighed using an Electronic Balance (Bensor) and their melting point was determined with a Melting Point Apparatus (Chemline). A Hot Air Oven (EI) and Vortex Apparatus (EI) aided in drying and mixing. Particle size was measured using a Malvern Analyzer, and surface morphology was examined with a Scanning Electron Microscope (Jeol). Moisture content was determined by an IR Moisture Balance (Scope Enterprise), and a Sonicator (EI) was used for dispersion. These instruments ensured the accuracy and quality of the nanoparticles.

### Methods

#### Preparation of mucoadhesive nanoparticles of Levodopa

Chitosan nanoparticles were prepared using the ionotropic gelation method, as described by Lazaridou (2020). First, a 1% (w/v) chitosan stock solution was prepared by dissolving chitosan in 1% (v/v) acetic acid at room temperature. For the drug-loaded nanoparticles, 5 mg of Levodopa was dissolved in the chitosan solution. A 1% sodium tripolyphosphate (STPP) solution was then prepared in water. The STPP solution was added dropwise to the chitosan solution

using a syringe while stirring continuously. The mixture was magnetically stirred for 30 minutes, followed by filtration and rinsing with distilled water. Gel-like beads were formed and air-dried for 24 hours, then oven-dried at 40°C for 6 hours to complete the preparation.

### Evaluation of nanoparticles

#### Percentage Yield

The prepared nanoparticles with a size range of 100-150nm were collected and weighed from different formulations (Joysa, 2015). The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the nanoparticles.

% Yield

$$= \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$

#### % Drug Entrapment efficiency

The various formulations of mucoadhesive nanoparticles were subjected for entrapment efficiency. 10 mg of mucoadhesive nanoparticles from all batches were accurately weighed and crushed. The powder of nanoparticles were dissolved in 10 ml 6.8 pH phosphate buffer and centrifuge at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 6.8 pH phosphate buffer. The percentage drug entrapment was calculated using calibration curve method by UV Vis. Spectroscopy at 282 nm (Saha, 2010).

#### Measurement of mean particle size

The mean size of the nanoparticles was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Malvern particle size analyser) at a scattering

angle of 90°. A sample (0.5mg) of the nanoparticles suspended in 5 ml of distilled water was used for the measurement (Zhang *et al.*, 2013).

#### Determination of zeta potential

The zeta potential of the drug-loaded nanoparticles was measured on a zeta sizer (Malvern particle size analyser) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate (Kouchak and Azarpanah, 2015).

#### Scanning electron microscopy (SEM) of Nanoparticles

From the formulated batches of nanoparticles, formulations (F2) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology (Sadiq and Rassol, 2014).

#### In vitro drug release in gastrointestinal fluids of different pH

The prepared nanoparticles were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C (Mishra *et al.*, 2017).

A weighed quantity of formulation (equivalent to 10mg) was filled in capsule and kept basket of dissolution apparatus, dissolution media (900 ml, pH 6.4) at

37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The samples withdrawn were assayed spectrophotometrically at 282.0 nm for Levodopa and using UV visible spectrophotometer. The release of Levodopa was calculated with the help of Standard curve of Levodopa.

#### Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

#### RESULTS AND DISCUSSION

In the formulation and evaluation of Levodopa-loaded mucoadhesive nanoparticles, the percentage yield for different formulations (F1 to F6) varied. The highest yield was observed in formulation F2 (84.45 ± 0.31%), followed by F1 (78.85 ± 0.88%), while F6 showed the lowest yield at 69.98 ± 0.36%. These results indicate that formulation F2 produced the most favorable yield.

The drug entrapment efficiency, which reflects the percentage of Levodopa successfully incorporated into the nanoparticles, was also analyzed. Formulation F2 exhibited the highest drug entrapment at

72.65 ± 0.32%, while the lowest entrapment was seen in F6 (68.85 ± 0.41%). These findings suggest that F2 showed optimal drug encapsulation.

The mean particle size of the nanoparticles was measured using photo correlation spectroscopy (PCS). The optimized formulation F2 showed a mean particle size of 88.23 nm, which is in the desirable range for mucoadhesive nanoparticle formulations. This small size is crucial for efficient nasal delivery and enhanced absorption.

Zeta potential, an important parameter for assessing the stability of the nanoparticles, was measured for the optimized formulation F2 using a zeta sizer. The zeta potential of F2 was found to be -37.45 mV, indicating good stability due to the electrostatic repulsion between particles.

The cumulative drug release of Levodopa from the nanoparticles was studied in a dissolution medium at pH 6.4. The release profile showed that the drug release was gradual, with 11.25% released at 1 hour, increasing to 95.56% at 10 hours, and reaching 96.32% at 12 hours. This demonstrates a sustained release pattern suitable for extended therapeutic action.

Regression analysis of the release data from formulation F2 was performed to determine the release kinetics. The results showed that the release followed a first-order model ( $R^2 = 0.9508$ ), with the Pappas plot showing the best fit ( $R^2 = 0.9695$ ), indicating that the drug release was governed by diffusion and matrix erosion. The zero-order model had a lower  $R^2$  value (0.9359), further supporting the conclusion that the drug release is not zero-order but influenced by other factors like diffusion.

**Table 1: Formulations of the mucoadhasive nanoparticles of Levodopa**

Sr. No	Formulation Code	Levodopa (mg)	Chitosan (mg)	STPP (mg)
1.	F1	5	250	500
2.	F2	5	250	750
3.	F3	5	250	1000
4.	F4	5	500	500
5.	F5	5	500	750
6.	F6	5	500	1000

**Table 2: Percentage yield for different formulation**

S. No.	Formulation	Percentage Yield*
1.	F1	78.85±0.88
2.	F2	84.45±0.31
3.	F3	72.25±0.45
4.	F4	71.15±0.33
5.	F5	70.36±0.74
6.	F6	69.98±0.36

\*Average of three determinations (n=3)

**Table 3: Drug entrapment for different formulation**

S. No.	Formulation	Drug entrapment (% w/w) of prepared microsphere
1.	F1	66.32±0.45
2.	F2	72.65±0.32
3.	F3	68.78±0.15
4.	F4	69.98±0.74
5.	F5	67.74±0.32
6.	F6	68.85±0.41

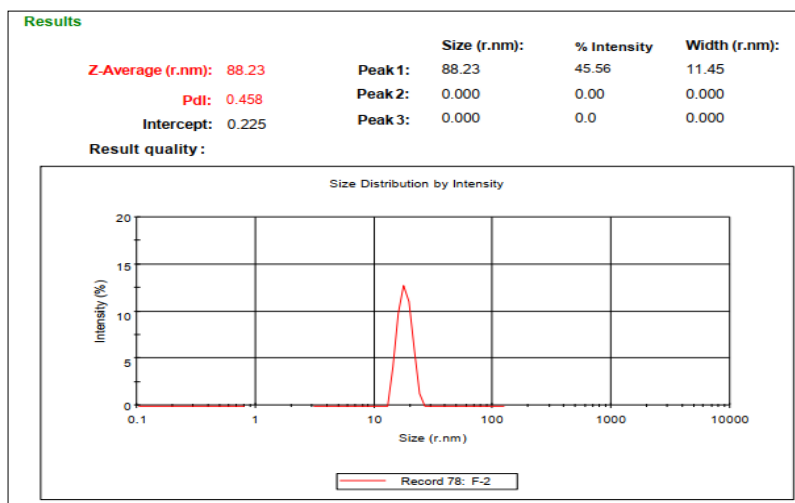


Figure 1: Particle size data of chitosan nanoparticle

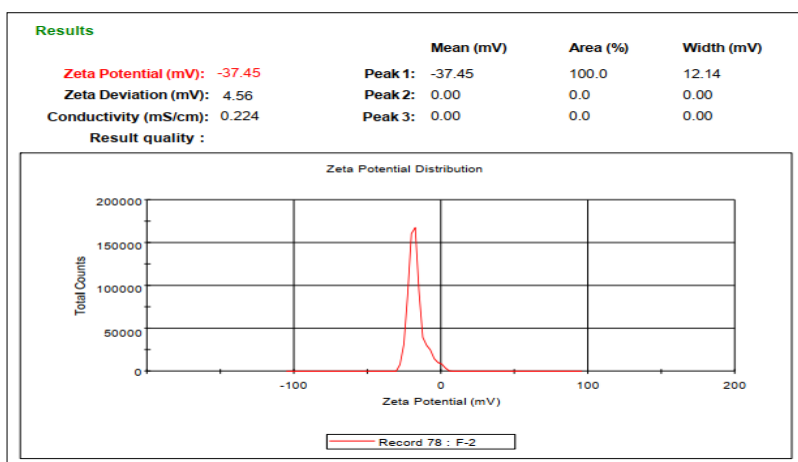


Figure 2: Zeta potential data of chitosan nanoparticle

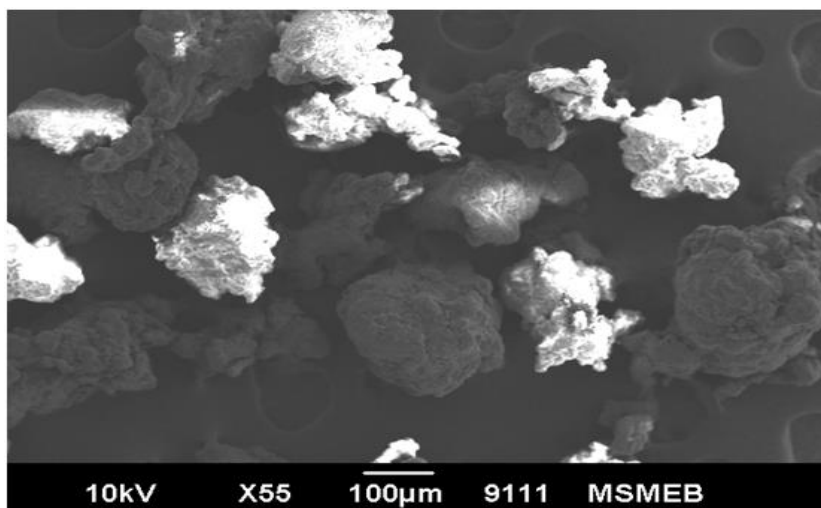


Figure 3: Scanning electronic microscopy image of optimized formulation F2

**Table 4: Cumulative % drug release of Levodopa nanoparticles**

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release
			Nanoparticle
1	pH 6.4	1	11.25
2		2	28.89
3		3	35.65
4		4	49.98
5		5	62.23
6		6	69.98
7		7	74.45
8		8	83.32
9		9	92.23
10		10	95.56
11		12	96.32

**Table 5: Regression Analysis Data of nanoparticle Formulation**

Formulation	Zero order	First order	Pappas plot
F2	$R^2 = 0.9359$	$R^2 = 0.9508$	$R^2 = 0.9695$

## CONCLUSION

In conclusion, formulation F2 exhibited the best performance in terms of yield, drug entrapment, particle size, zeta potential, and sustained drug release, making it the most promising formulation for Levodopa-loaded intranasal mucoadhesive nanoparticles aimed at the treatment of Parkinson's disease. Further stability studies and in vivo evaluations would be beneficial to assess the clinical potential of this formulation.

## DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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