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Original Article

Nasal Administration of Dolutegravir Loaded Nanoparticles Based Mucoadhesive *in situ* Gel: Design and *in vivo* Assessment

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ABSTRACT

Background: To assess the potential for targeting the brain through intranasal delivery, this study focuses on optimizing and developing a mucoadhesive *in situ* gel formulation containing Dolutegravir nanoparticles. **Materials and Methods:** Employing a central composite design, the study optimized the concentration of variables of Hydroxypropyl methylcellulose (HPMC, X_1) and Poloxamer 407 (X_2) on the gelation temperature (Y_1) and drug release (Y_2). The optimized drug loaded nanoformulations were assessed for various pharmaceutical features, *in vitro* release and evaluated *in vivo*. **Results:** Both variables significantly impacted the responses ($p<0.05$). The selected formulation displayed beneficial rheological characteristics and prolonged drug release. *In vivo* pharmacokinetic analysis in rats post-intranasal administration of the optimized *in situ* gel demonstrated markedly higher ($p<0.0001$) C_{max} (2-fold) and AUC_{0-t} (3-fold) values in the targeted brain tissue as compared to intravenous administration. Reduced Dolutegravir exposure in the central compartment validates limited absorption with nasal therapy. **Conclusion:** The study affirms the potential of the *in situ* mucoadhesive nasal gel in delivering Dolutegravir to the brain. Thus, the optimized nasal gel emerges as a promising therapeutic alternative for Neuro AIDS by efficiently delivering Dolutegravir to the brain.

Keywords: Dolutegravir, *in situ* gel, Nasal route, Brain, *in vivo*.

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INTRODUCTION

Nasal medicine delivery is one of the most difficult problems that current pharmaceutical scientists must deal with. In comparison to oral drug administration, nasal delivery is significantly more effective and has limited side effects.[1] From a pharmacokinetic standpoint, intranasal administration overcomes the poor absorption in the digestive system, bypasses the blood brain barrier and evades first-pass metabolism, which in turn results in improved bioavailability.[2,3] The nasal route provides direct delivery of actives to the brain via the intranasal pathway and the endothelium membrane is highly permeable with a rich blood supply.[4] In this context, the potential of nanocarriers for brain targeted delivery has been extensively studied in the recent past.[5-8] On the other hand, drug delivery techniques that produce *in situ* gel by forming a solid or semi-solid depot from a liquid formulation have received attention in the last two decades.[9-12] When subjected to physiological circumstances, *in situ* activated gel-forming systems change from a liquid phase to a gel phase.[13] *In situ*-gelling liquids have been widely investigated in direct brain delivery of therapeutic actives by applying them in the nasal cavity.[10] Liquids applied inside the nasal cavity are capable of changing from liquids to gels due to a chemical or physical change brought on by the physiological settings.

The use of poloxamer 407 in developing *in situ* gel has been explored in various studies.[14] Typically, this polymer is a non-ionic triblock synthetic copolymer that is capable of phase transition when applied to the mucous membrane. Indeed, it possesses some distinctive characteristics like mucoadhesion, low toxicity/tissue sensitivity, controlled drug release and is compatible with various pharmaceutical actives and excipients.[15] The combination of poloxamer with Hydroxypropyl Methylcellulose (HPMC) has demonstrated its potential as an *in situ* gel in delivering several drug molecules in various investigations.[14,16,17]

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Dolutegravir sodium, identified as a second-generation integrase strand transfer inhibitor, plays a crucial role in impeding the integration of HIV viral DNA into the host DNA, a pivotal stage in viral replication.[18] The proposed mechanism of action for Dolutegravir involves its capacity to precipitate enzyme-linked cations, thereby hindering the insertion of viral DNA into the host gene.[19] Because of its significantly lower cellular resistance, Dolutegravir is recommended over other integrase inhibitors.[20] The bioavailability of Dolutegravir is 34%, while has a 14 hr half-life.[21,22] Dolutegravir is categorized as Biopharmaceutical Classification System II suggesting this molecule has high membrane permeability and low water solubility.[22] The feasibility of direct brain delivery of different BCS class II drugs was demonstrated by developing mucoadhesive *in situ* gel formulations by different research groups.[23-25] In this context, this study sought to develop an *in situ* gel formulation of Dolutegravir-loaded polymeric nanoparticles and evaluate its viability for nose-to-brain delivery.

MATERIALS AND METHODS

Materials

The Dolutegravir sodium drug was a gift from Yarrow Chem Products in Mumbai, India. All other chemicals used in this investigation were bought from S.D. Fine Chem, Mumbai, India, and utilized as received. All the solvents used are of analytical grade.

Preparation of Nanoparticles

In this study, the emulsification solvent evaporation technique with sonication was used to develop nanoparticles with minor modifications reported in the literature.[26] Weighed amount of polymer (Eudragit E100-400 mg) and medication (Dolutegravir sodium-100 mg) was dissolved in 10 mL of acetone to make an organic phase. An O/W type emulsion was produced by mixing this organic phase with an aqueous phase that already contains an emulsifying agent (Polyvinyl alcohol, 0.5%, 90 mL).[26] Phases of organic solvent and water have a volume ratio of 1 to 9. By using outside energy through a sonicator, nano droplets were created from this emulsion. When the extremely volatile organic solvent is evaporated, these nanodroplets turn into nanoparticles. Ambient-temperature magnetic stirring for 2 hr at 300 rpm leads to evaporation of the organic solvent.

Characterization of Nanoparticles

Fourier Transform Infrared Spectroscopy (FTIR)

The weighed amount of the drug (100 mg) or the physical mixture of the drug, poloxamer 407 and HPMC was scanned by IR spectrophotometer as described earlier.[27] The potassium bromide disk method was used and the spectra were acquired between 4000 to 500 cm^{-1}.

Drug Content

Methanol (10 mL) was mixed with 1 mL of drug-loaded nanoparticles in a centrifuge tube over the course of a day.[28] The following morning, the mixture was vortexed for 15 min. The supernatant was then extracted from the solution after centrifuging it at 5000 rpm for 30 min. A UV-spectrophotometer was used to check the Dolutegravir sodium at 259 nm in the supernatant. The following equation, which is usually used to calculate the drug content was used. % Drug content=(Amount of drug obtained in particles)/(Theoretical amount of drug)×100.

Entrapment Efficiency

The nanoparticle dispersion (10 mL) was taken and the nanoparticles were initially separated by centrifugation in order to ascertain how much drug was contained inside them. Centrifugation (20 min at 4500 rpm) was used to separate the free medicines from the ones that were trapped in the nanoparticle dispersion.[29] Separated and diluted supernatant liquid was used to determine the amount of free drug in the mixture with the help of UV spectrophotometer analysis. The amount quantified was later subtracted from the total quantity of medicine that was first added. The % entrapment efficiency (EE) was calculated as follows:

$$EE = W_{initial\ drug} - W_{free\ drug})/(W_{initial\ drug}) \times 100$$

Zeta Potential and Particle Size Analysis

Nanoparticles were diluted with distilled water, taken in a clear disposable zeta cell and analysed at 25°C to detect the Zeta potential and particle size (Zetasizer, Anton Paar litesizer 500, Graz, Austria). Three zeta runs were performed on the sample to establish its size and potential.[29]

Scanning Electron Microscopic (SEM) Study

SEM was used to check the morphology of prepared Dolutegravir loaded Eudragit containing nanoparticles. The sample micrographs were captured after mounting them on aluminum stubs. The samples were further sputter-coated with a thin layer of gold/palladium. The samples were viewed under an SEM device (Philips XL30, Almelo, Netherlands).[30]

Optimization of *in situ* Gel

Response Surface Methodology (RSM), a method that uses fewer tests to evaluate the interactions between important variables and answers, uncover relevant variables, and ideal process conditions was statistically optimized for the *in situ* gel formation procedure.[14] Poloxamer 407 (X_1) and HPMC concentrations (X_2) were two independent variables that were optimized for gelation temperature (GT-Y_1) and drug release (DR-Y_2) as described in a publication before.[31] The optimization was done at five

distinct levels and the centre point employing Design-Expert 12 software (Stat Ease Inc., Minneapolis, MN, USA). A total of 13 experimental runs were produced for this investigation employing central composite design (CCD). Table 1 shows the complete experimental plans. The response (Y_1) in each trial was determined using a 2FI model and a quadratic model for GT and DR.

$$Y_{1\,(2FI)}=b_0+b_1X_1+b_2X_2+b_3X_1X_2$$

$$Y_{1\,(Quadratic)}=b_0+b_1X_1+b_2X_2+b_3X_1X_2+b_4\,X^2_1+b_5\,X^2_2$$

Y_1 is the dependent variable, while b_0 is the average trial-to-trial response. The significant impacts and average values of the various factors, X_1 and X_2, are represented by the estimated coefficients b_i for these variables. The polynomial terms X^2_1 and X^2_2 are represented by the letters X_1 and X_2, respectively.

Preparation of Dolutegravir *in situ* Gel

The cold technique reported before[32] was used to prepare *in situ* gel with minor modifications. Poloxamer was first dispersed separately in a very small amount of water at a 20% w/v concentration under cold circumstances. Then, HPMC was dissolved and methylparaben, PEG 400, and Dolutegravir (0.5% w/v) were added afterward and mixed to produce a clear solution. Finally, using distilled water the volume was adjusted to 100 mL and then freezed at 4 to 10°C overnight.[32] Figure 1 shows typical images of the developed *in situ* formulations in the gel and solution states.

Characterization of *in situ* Gel

pH

A digital pH metre (Digital pH metre 335, Techno Scientific Products, Bangalore, India) was used to measure the pH of the selected *in situ* gel. After preparation, the pH readings were immediately recorded.[33]

Appearance

The clarity of the optimised formulation's appearance was evaluated by eye inspection in well-light conditions, and it was then visualised against a black/whiteboard to examine the mobility of the fibres and particulate particles. Additionally, the formulations were examined for the development of turbidity and the presence of any particle debris.[34]

Drug Content

The developed gels containing nanoparticles (1 g) were mixed with methanol (10 mL) in a 15 mL centrifuge tube and vortexed to dissolve the drug inside the polymeric particles. The solution was further diluted with methanol, centrifuged, and filtered. The filtrate was measured using a UV spectrophotometer at the predetermined wavelength.[33]

Gelation Temperature

Gel (2 mL) before were applied to a test tube that was submerged in water. Over the period of 2 min, the water bath's temperature was raised at 1°C increments until gel was developed. The sample was next tested for gelation, which was determined to have happened when the meniscus stopped moving while the test tube was 90°C inclined.[35]

Viscosity Studies

Viscosity was measured using a Brookfield viscometer (DV-1 prime and Pro pair, Middleboro MA, USA) with an S-94 spindle. The spindle was lowered at an angle into the *in situ* sol and gel formulations in a beaker while maintaining a 37°C temperature.[36] The viscosity of each recipe was evaluated at a speed of 100 rpm.

Spreadability

An excess quantity of optimal *in situ* gel formulation was placed between two glass slides, which were then compressed to a uniform thickness for 5 min. A specific weight of 100 g was placed on the top of the glass. The upper glass was connected to a pan in which 50 g weight was added. The time taken by the upper glass plate to move over the lower plate was considered as

Figure 1: Representative images of the solution and gel states of nasal *in situ* formulation developed.

Table 1: Both actual and coded values of formulation parameters for the Central Composite Design.

Factors/ independent variables	Levels			Responses/ dependent variables	Constraints
	-1	0	+ 1		
Poloxamer 407- X_1	20	21	22	Gelation temperature (GT-Y_1)	Minimum
HPMC-X_2	1.2	1.55	1.9	Drug release (DR-Y_2)	Maximum

the spreadability and the values were calculated by the formulae described in literature.[37]

In vitro Diffusion Studies

Franz diffusion cells with a 2.0 cm diameter and 10 mL capacity were used for *in vitro* drug diffusion experiments. The diffusion membrane used was a dialysis membrane produced by Himedia, which has a molecular weight range of 12000-14000 kDa. Dialysis membrane fragments were submerged in Phosphate Buffer (PB), pH 6.4, before the experiment. The diffusion cell received PB after a dialysis membrane was affixed. The temperature of 37ºC was maintained. After a 20-minute preincubation period, 1 g of formulation was added to the donor chamber. Gelation was aided by temperature. Samples of 1 mL were taken from the acceptor compartment after 30 min and continued until 12 hr. After each predetermined sampling interval, the same quantity of PB was replaced.[38] Various mathematical models[39] were used to select the best-fit release kinetics from the release data.

In vivo Study

The methodology for animal studies was reviewed and approved by the Institutional Animal Ethical Review Board under the reference SACCP-IAEC/2022-02/72. Albino Wistar rats, weighing between 200-300 g, were employed to assess different pharmacokinetic characteristics. For each time point, six rats were randomly assigned to Group 1 and Group 2. The animals were individually housed in cages in an animal room which was kept clean and vermin-free. The room temperature was controlled and had a 12 hr light/dark cycle. Rats were provided with standard feed and water throughout the acclimation period. Rats were administered formulations after a minimum 12 hr fasting period. The dosage was calculated based on the 50 mg daily human dose using an equation found in scientific literature.[40] In first group, the rats received an intranasal dose of a selected formulation containing 0.5% w/v drug as shown in Figure 2a. Animals in the second group had the same dose of drug which was administered by intravenous route through the tail vein. At pre-arranged intervals, 200 µL of samples were taken from the retro-orbital plexus of all rats after they had been sedated with thiopental sodium (30 mg/kg). The same volume of acetate buffer (pH 4.5) was added to the plasma to precipitate the proteins, and the samples were then subjected to an HPLC method developed in the lab, which had a brief retention period of 3.7 min (Figure 3). Furthermore, the homogenized brains (Figure 2b) of the slain animals were extracted using acetonitrile for 5 min at 4ºC. The pharmacokinetic parameters of interest were determined using noncompartmental analysis.

RESULTS AND DISCUSSION

FTIR

Pure drug Dolutegravir sodium, as well as the physical mixture of drug, Poloxamer 407 and HPMC were investigated using the FTIR. Present are the FTIR spectra (Figure 4a) of pure Dolutegravir used in the formulation. The characteristic peak of Dolutegravir sodium at the single bond stretch (C-H stretch) was 2874 cm^{-1} and in double bond (C=O, C=C,) at 1588, 1644 cm^{-1}, respectively. as reported in the literature.[22] The characteristic peaks of Poloxamer 407 and HPMC single bond stretching of (C-H) 2919, (C-H, C-O) 1421 cm^{-1} were present in the physical mixture (Figure 4b). The spectra of the physical mixture indicate all the major drug peaks with non-significant variation in peak intensity or shift, probably due to the association or interaction of the components used in the physical mixture.[41]

Preparation and Characterization of Nanoparticles

The particle size of the system has a major impact on the stability of the nanoparticles and their distribution throughout the body.[42] The prepared nanoparticles that have been characterized for the formulation were discovered to be 380 nm and 23.7 mV, respectively. The higher drug content (~98%) and EE (~71%) signify the selection of the polymer and the method used here is ideal for Dolutegravir. Similar observations were also reported when Eudragit 100 was used to develop nanoparticles of other drugs.[43,44] Particle size distribution also demonstrates narrow size of prepared carriers. The SEM image of the prepared nanoparticles clearly indicates a well-defined and spherical morphology (Figure 5). The uniformity in size noticed here is

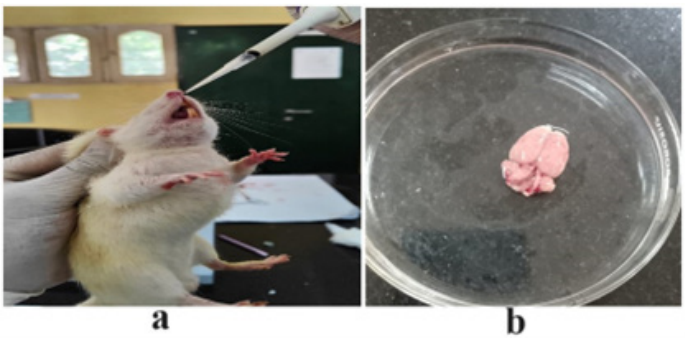

Figure 2: Intranasal administration of developed gel in a) rats and b) isolated brain tissue.

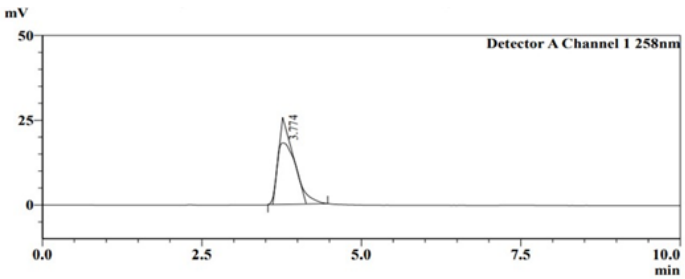

Figure 3: Representative HPLC chromatogram of Dolutegravir.

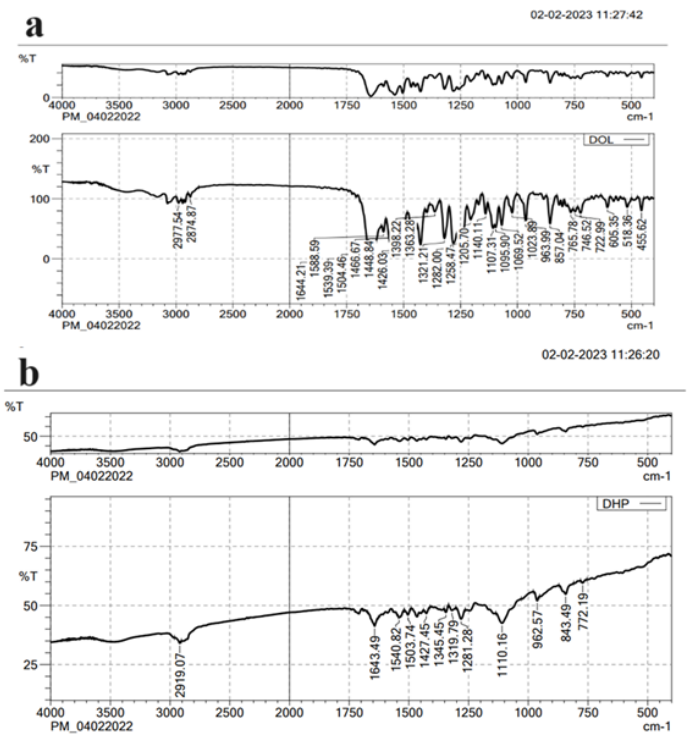

Figure 4: FTIR spectra of a) Dolutegravir and b) physical mixture of Dolutegravir, poloxamer 407 and HPMC.

a critical aspect of nanoparticle design, as it can significantly influence their biological interactions and performance in various applications, particularly in drug delivery and biomedical fields.[45] In addition, the combination of the round shape and uniform size distribution is crucial for enhancing the colloidal stability and systemic circulation of the nanoparticles. Indeed, the interesting morphology observed here is ideal for nasal delivery.

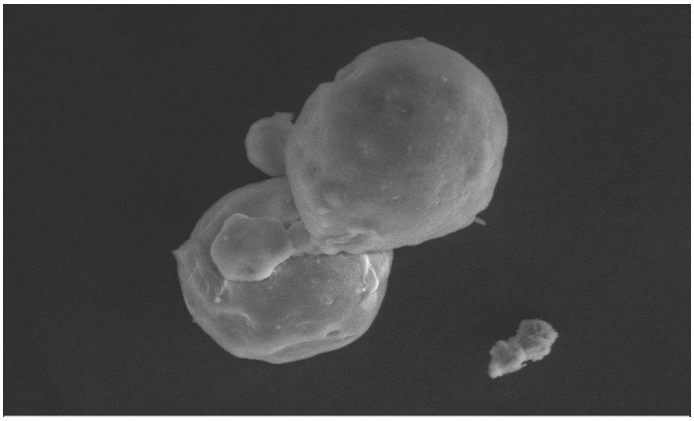

Figure 5: SEM image of Dolutegravir loaded nanoparticles.

Preparation of Dolutegravir *in situ* Gel

In order to determine the best amounts of the chosen variables and how they interact to produce the least GT and maximum DR, the response surface approach's CCD was utilised. The design expert predicted 13 runs in all, and Table 2 contains the results of the observations. The measured gelation temperature was determined to be between 36.8°C and 47°C, and the predicted DR was between 18.65% to 72.03%.

Utilizing Type I sequential sum of squares, R^2 values, and model summary statistics, quadratic models were formed for each response. The robustness of these models is supported by elevated modified R^2 values. The precision assessment involved expressing studentized residuals in terms of standard deviation. Figure 6 depicts the normal probability of studentized residuals and explores the impact of test orders on the CCD. ANOVA discerned quantitative effects, and polynomial equations were derived through multiple regression.

Table 2: The results of predicted experimental runs observed.

Std	Run	Factor 1	Factor 2	Response 1	Response 2
		Poloxamer	HPMC	GT (°C)	DR (%)
9	1	22	1.90	36.8	48.48
13	2	21	1.55	44.2	49.80
8	3	21	1.90	40.5	34.98
11	4	21	1.55	44.2	34.98
6	5	22	1.55	38.0	49.80
14	6	21	1.55	44.5	49.80
12	7	21	1.55	44.2	49.80
5	8	21	1.55	44.2	49.80
7	9	20	1.90	41.5	46.80
3	10	22	1.20	37.0	18.65
4	11	20	1.55	46.0	72.03
1	12	20	1.20	47.0	41.94
2	13	21	1.20	45.0	21.97
10	14	21	1.55	44.2	49.80

Table 3: Estimated impact for several parameters involved in creating *in situ* gels.

	Response 1		Response 2	
Source	***F*-value**	***p*-value**	***F*-value**	***p*-value**
Model	217.77	<0.0001*	17.01	0.0004*
A-Poloxamer	655.10	<0.0001*	15.69	0.0042*
B-HPMC	132.27	<0.0001*	20.33	0.0020*
AB	53.57	<0.0001*	9.93	0.0136*
A^2	103.49	<0.0001*	9.41	0.0154*
B^2	44.71	0.0002*	38.82	0.0003*
Lack of Fit	4.86	0.0803	0.5762	0.6553

* Significant factors.

Table 3 shows the determined F values, *p* values, and estimated impacts for the GT and DR. These numbers were used to gauge how significant the model's coefficients were. The impact of independent variables on responses was further examined using the Response Surface Methodology (RSM). Response surface graphs in three dimensions make it possible to comprehend the major effects and interaction effects in RSM.[46] Visual representations of measured responses are provided by contour plots. Figure 7 combines three-dimensional response surface plots and a contour plot to illustrate the interaction between specific responses and the variables demonstrating the variables' influence. The best fit model equations derived from the responses are as follows:

$$GT = +44.20-3.78A-1.70B+1.33AB-2.19A^2-1.44B^2$$

$$DR = +48.20-8.97A+10.21B+8.74AB+10.11A^2-20.54B^2$$

Using the global desirability function (D), several series of models derived from the experimental study were optimised. The optimisation of their design space included the inclusion of all independent factors. On the desirability plot, the maximum D value for the responses was found as 0.821. This value was attained at the ideal independent variable concentrations. Using this desirability method, it can be determined that a formulation containing 1.80% HPMC and 22% Poloxamer 407 can satisfy the criteria for the optimal formulation and result in higher activity (Figure 8).

Evaluation of *in situ* Gels

Appearance, pH, and Drug Content

The developed Dolutegravir loaded polymeric nanoparticles based *in situ* gel compositions were assessed based on fundamental factors like clarity, pH, and medication concentration. All formulations were seen to be transparent, clear, and free of any turbidity or particles upon visual inspection. Since the nasal mucosa's physiological pH is 6.3, *in situ* gel having a pH of 4.5-6.5 can soothe nasal irritation as described in the literature.[13] The pH of *in situ* gels that have been prepared ranges from 4.8 to 5.6, and

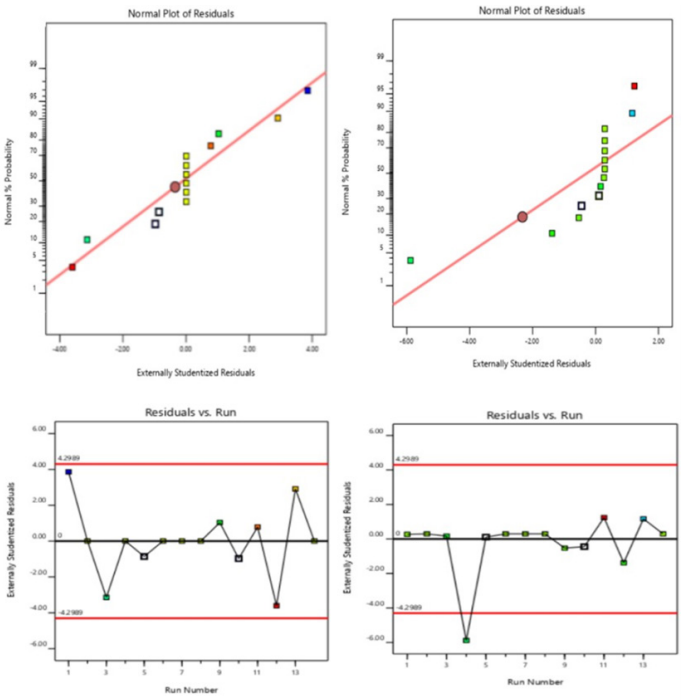

Figure 6: The correlation of actual versus predicted values and residuals' normal probability graphs for gelation temperature and drug release.

it did not significantly differ between the formulations examined. As a result, the manufactured compositions are secure and may be applied topically to the nostrils. The amount of medication found in the formulations shows that the optimised *in situ* gel contain enough Dolutegravir (>97%).

Gelation Temperature

The developed formulations observed gelation temperature has a value of 37°C to 47°C. In fact, when the amount of HPMC in the *in situ* gel was increased from 1.2-1.9% w/v, there was a level of significance ($p<0.05$), which is in agreement with various investigations reported.[14,16,17,47]

Viscosity and Spreadability

The formulation of *in situ* gels and their efficacy are both influenced by the rheological qualities, which include viscosity

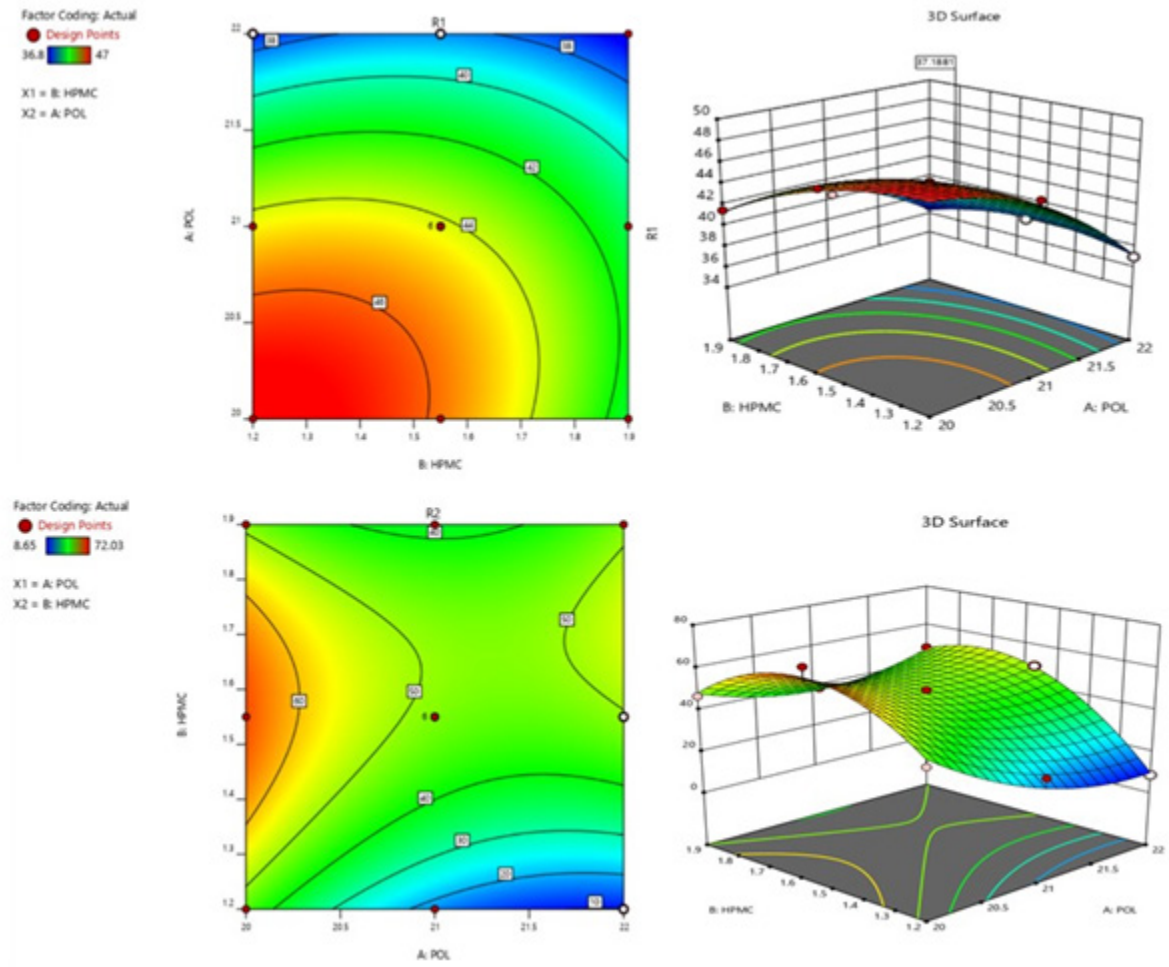

Figure 7: Response surface graphs for Gelation Temperature (GT) and Drug Release (DR).

Table 4: Dolutegravir pharmacokinetic characteristics in the rat brain and plasma after intravenous and nasal injection.

Parameters	Brain		Plasma	
	Nasal	IV	Nasal	IV
C_{max} (ng/mL)	370±23.3*	150±17.1	150±18.2*	545±30.1
T_{max} (h)	4	4	6	1
$AUC_{(0-t)}$ (h.ng/mL)	1244±34.2*	470±11.1	604±29.2*	1490±17.2

*The level of significance was $p<0.0001$ when compared to the IV counterpart.

and spreadability.[34] In order to prolong the nasal residence period, enough viscosity is required. The viscosity of the optimised formulation was determined to be 3400 cPs at 37°C. Spreadability is a critical component for any nasal formulation as it evaluates the ability to be applied and spread on the nostril while avoiding leakage after application. It was found that the spreadability of the gel was 15.19 cm^2/min. Indeed, the data observed with optimised *in situ* gel formulation showed sufficient spreading potential and may be appropriate for nasal administration, as reported by another study.[2]

Drug Release

Optimal drug release from *in situ* gel formulations is vital for therapeutic response and absorption. In addition, substantial knowledge of the formulation behaviour under *in vivo* settings is provided by the *ex vivo* permeation investigation.[48] The diffusion of drug/carriers over the biological membrane is influenced by the physicochemical characteristics of the drug/carrier, the physiological characteristics of the membrane, and the permeation pathways that are accessible to diffusant.[25,49] To ensure effective pharmaceutical release across the nasal mucosa, meticulous design of *in situ* nasal gel formulations is essential to extend residency in the nasal cavity. Evaluation of the total

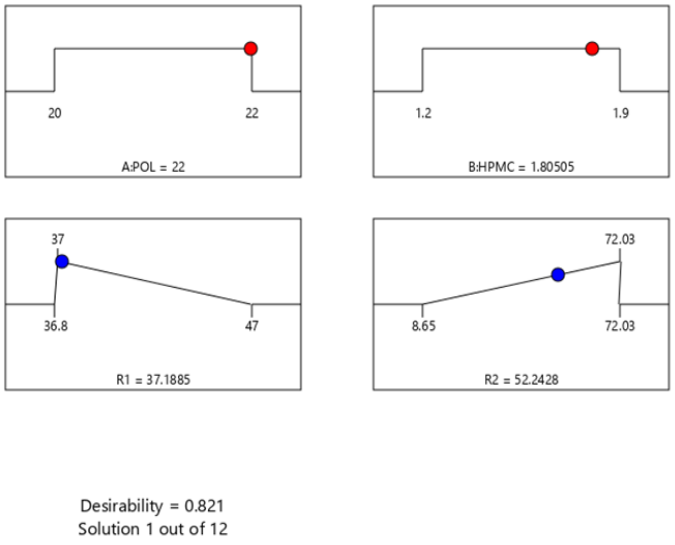

Figure 8: Desirability plot of optimization result.

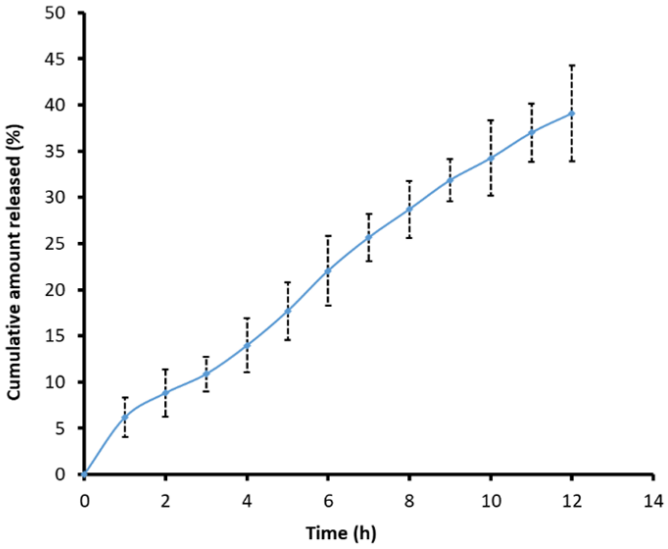

Figure 9: *In vitro* drug release profile of optimised formulation.

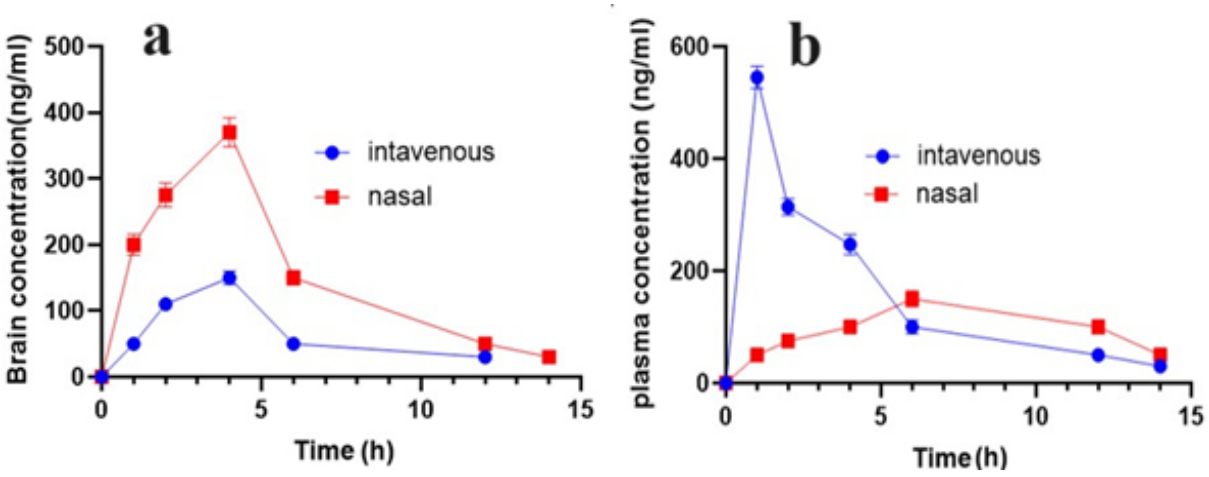

Figure 10: Dolutegravir sodium concentration noticed in rats after applying *in situ* gel through the nostril or intravenously in the brain tissue (a) and in the plasma (b).

released medication following a 12 hr *in vitro* drug release test on a specifically tailored nasal *in situ* gel revealed slow and controlled release of Dolutegravir, as depicted in Figure 9. The lower amount of drug release noticed here could be related to the eudragit polymer as observed in various investigations.[30,50] The Dolutegravir release from the optimized gel was found to be the Korsmeyer-Peppas model, as signified by a greater r^2 value of 0.9902. Indeed, the drug release from the prepared nanoparticles was influenced by its rate of diffusion, causing the sustained release as described earlier.[51]

Animal Experiments

Figure 10a shows the brain drug concentration-time profiles of Dolutegravir after intravenous administration of the solution and single application of the optimised *in situ* gel in the left nostril in rats. Table 4 provides a summary of the measured pharmacokinetic parameters. Greater brain drug absorption was noticed with intranasal delivery (Figure 10a). Figure 10b represents the Dolutegravir plasma drug concentration-time profile following intravenous and nasal delivery. Figure 10b shows that, in contrast to intranasal delivery, the intravenous method produced a high Dolutegravir amount in the plasma. The calculated AUC_{0-t} achieved in the brain for the intranasal route was three times greater than the AUC_{0-t} obtained for the intravenous method. Dolutegravir was only minimally exposed to the systemic environment via the paracellular transport route, according to a low drug plasma concentration-time profile after nostril application (Figure 10b). Comparing the nasal administration of Dolutegravir to an intravenous dose given at the same time, it is evident that the AUC_{0-t} and C_{max} values were significantly higher while the T_{max} was relatively the same (Table 4). The results here signify that the intranasal route decreased the permeation of the medicine into the systemic circulation. Indeed, the intra nasal delivery using *in situ* gel formulations generally can

increase the amount of drug reaching the target site (i.e., brain), which is in agreement with earlier investigations demonstrated with various drugs.[52-54]

CONCLUSION

Utilizing nose-to-brain delivery represents a promising strategy for the efficient administration of medications to the brain, particularly in the context of Central Nervous System (CNS) diseases. To address the challenges posed by Neuro AIDS, the development of a patient-friendly intranasal formulation has become crucial. A particularly promising approach involves the creation of a nanoparticle-loaded *in situ* gel. This innovative *in situ* gel formulation is meticulously designed to serve as an effective vehicle for drug delivery to the CNS. One of its key features is the incorporation of nanoparticles, enhancing the overall efficacy of drug transport. The formulation aims to capitalize on the unique advantages of intranasal delivery, such as direct access to the CNS and the avoidance of first-pass metabolism. A pivotal aspect of this study involves the optimization of a Dolutegravir-containing *in situ* gel. The goal is to create a formulation that not only addresses the specific challenges associated with Neuro AIDS but also ensures a sustained and controlled release of the drug. The *in situ* gel is strategically formulated to prolong its retention in the nasal cavity, facilitating a gradual and enhanced transfer of Dolutegravir from the nasal route to the brain, as evidenced by the *in vivo* data. In summary, this study delves into the development and evaluation of an intranasal *in situ* gel formulation, enriched with nanoparticles, with a focus on its potential for efficient nose-to-brain transfer of Dolutegravir. Such innovative approaches hold promise for advancing therapeutic interventions in the realm of CNS diseases, particularly for conditions like Neuro AIDS.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HPMC: Hydroxypropyl Methylcellulose; **EE:** Entrapment Efficacy; **SEM:** Scanning Electron Microscope; **FTIR:** Fourier Transform Infrared Spectroscopy; **RSM:** Response Surface Methodology; **PEG:** Poly Ethylene Glycol.

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