

PLGA Nanoparticle-Embedded Oral Films for Sustained Eletriptan Delivery

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ABSTRACT

Objectives: The study aimed to fabricate and characterize Oral Dispersible Film (ODF) containing PLGA polymeric nanoparticles of Eletriptan Hydrobromide (EH). The ODF system is designed to circumvent pre-systemic metabolism of drug and thereby augment the issue of low oral bioavailability of EH. **Materials and Methods:** Polymeric nanoparticles were prepared by the nanoprecipitation method using PLGA (50:50) as the polymer and poloxamer 188 as the surfactant. A Box-Behnken Design was employed to achieve optimized nanoparticle size, higher drug entrapment efficiency and Polydispersity Index (PDI) of PNPs. The oral dispersible film was prepared by using the pullulan as the polymeric film former and propylene glycol as the plasticizing agent, employing the solvent casting technique. The optimized film formulation was characterized in terms of physicochemical attributes, *in vitro* release behaviour, pharmacokinetic performance, and histopathological safety. **Results:** The optimized PNPs exhibited a mean particle size of 205 ± 0.42 , a high drug entrapment efficiency of $82 \pm 0.6\%$, and a narrow PDI of 0.195 ± 0.11 . The designed film formulation appeared opaque, uniform and well distributed. The *in vitro* data revealed that the PNPs-loaded ODF has the highest (91.14%) and extended release of drug (24 hr) occurred as compared to ODF containing free or un-encapsulated drug. Furthermore, histopathological study showed that the ODF is safe and effective formulation for transmucosal administration. **Conclusion:** The PNP-based ODF disintegrated rapidly in mouth so that unabsorbed drug could results quick therapeutic action. Therefore, the incorporation of PLGA-based nanoparticles into ODF provides a promising strategy to achieve both rapid therapeutic onset and prolonged release of drug.

Keywords: Box-Behnken Design, Eletriptan hydrobromide, ODF: Oral Dispersible Film, PLGA 50:50, Polymeric Nanoparticles, Solvent Casting Method.

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INTRODUCTION

Migraine is a chronic, excruciating, recurrent neurological condition, affecting 10 out of 100 people worldwide.¹ These remarkable numbers of people who suffer from migraine present a considerable economic hardship in terms of exorbitant medical costs, psychological impairment, and unemployment. Patients of migraine suffer from a wide range of visual, auricular, auditory, and dysosmia impairments as well as nausea and emesis disorder.² Moreover, migraine is also related to phobia, mental illness, quadriplegia and other "severe neurological diseases."³ Originally, it comes from the Greek word 'hemicrania' which means 'half side of the head'. Sometimes the pain is bilateral or,

rarely all over the body and face.⁴ It is mainly characterized by the pulsating headache, which comes in attacks, when it persists for 4 to 72 hr. The most frequent cause of migraine is headaches, which can occur from mild to severe and is exacerbated by any regular physical activity.⁵ The exact pathophysiology of migraine was not clear, but the activation of trigeminal nerve fibre by neurogenic inflammation causes migraine.⁶ Activation and sensitization of the trigeminal nerve depend upon both the central and peripheral part stimulation.⁷ Activation of the Trigeminal Nucleus Caudalis (TNC) generates the expression of c-Fos by releasing neurotransmitters such as Calcitonin Gene-Related Peptide (CGRP), neurokinins, and Substance P (SP).⁸ For treatment of migraine, patients generally emphasize the need for formulations that ensure rapid absorption and a quick onset of therapeutic action.⁹ The triptan class of antimigraine drugs are most commonly used for moderate to severe migraine attacks. Eletriptan hydrobromide is a selective serotonin 5-hydroxytryptamine (5-HT_{1B/1D}) receptor agonist utilized for the management of migraine.¹⁰ It binds or attaches to the 5-HT_{1B} receptor in intracranial arteries and the 5-HT_{1D}



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receptor situated on peripheral trigeminal sensory nerve terminals, inhibiting the stimulation of the trigeminal nerve by neurogenic vasodilation.¹¹ The pharmacological activity of EH is mediated through the inhibition of CGRP and SP-releasing substances.¹² It further exerts its effect by suppressing nociceptive transmission, preventing the activation of second-order sensory neurons within the brainstem, and reducing c-Fos expression in the trigeminal nucleus caudalis.^{13,14} In spite of their effectiveness, EH oral dosage forms have several disadvantages, like low oral bioavailability (40%), extensive first-pass metabolism, difficult to swallow and the lowest onset of action.¹⁵ Generally pediatric, geriatric, nauseous, bedridden, dysphagia, mucositis, parkinson's disease, and vomiting tendency patients also have problems in swallowing the traditional formulations because they have problem to take more volume of water.^{16,17} The factors outlined above emphasize the requirement for an advanced dosage form designed to alleviate the drawbacks of conventional oral systems. One such newly developed, originaive, beneficial, and patient-focused revolution referred in this path is oral dispersible film. They are non-adhesive and instantly disperse when placed on the tongue. ODF would also exhibit a lesser extent of mucoadhesion because of essential attributes like the chemical nature and molecular weight of the selected polymer utilized for its preparation.¹⁸ ODFs are highly flexible and very thin films incorporating active pharmaceutical ingredients that dissolve or disintegrate in the oral mucosal fluid rapidly without requiring any liquid or mastication. The absorption of the drug in ODF is facilitated through the oral mucosa and subsequently reaches systemic circulation by inhibiting the pre-systemic metabolism.¹⁹ The rapid onset of action associated with these dispersible films is attributed to their relatively larger surface area and reduced thickness compared to conventional tablets.²⁰ They also improve the bioavailability and half-life of the drug. ODFs are mainly fabricated using the solvent casting technique, in which drug and solvent are dispersed into aqueous or organic solvent with evaporation under higher pressure. The film is initially prepared in a wide sheet which is subsequently cut into unit-dose segments and packaged in various pharmaceutical-grade packaging options.²¹ The oral mucosa exhibits greater vascularity and permeability due to its comparatively lower thickness (500-600µm), so there is no need for a penetration enhancer in formulation.²² Eletriptan hydrobromide is a substrate of P-glycoprotein (P-gp), which consequently reduces its permeability across the blood-brain barrier compared with other agents. Polymeric nanoparticles are prepared to improve the permeability and to inhibit the P-gp efflux protein extracellular transport.²³ Nanoparticle-based delivery systems have become a major focus of contemporary research due to their capacity to efficiently transport therapeutic agents and enable targeted drug administration. From the previous research studies, it was found that biodegradable polymers like gelatin, Poly (D, L-lactic-co-Glycolic Acid) (PLGA), Polylactide (PLA), chitosan, alginate, albumin and Poly-Cyanoacrylate (PCA).²⁴

PLGA is most commonly used because it has low toxicity, higher mechanical strength, more compatibility and also increases the biodegradation properties of the formulation. PLGA may also enhance the drug absorption through mucous membranes.²⁵ Conventional tablets are reported to have delayed onset of action and reduced bioavailability due to first-pass metabolism. The study aims to prepare and characterize Polymeric Nanoparticles Loaded Oral Dispersible Films (PNP-ODF) to overcome these issues by promoting rapid absorption via the oral mucosa and providing sustained drug release. PLGA nanoparticles were also prepared to minimize P-gp-mediated drug efflux and improve the delivery characteristics of eletriptan hydrobromide. The ODF was anticipated to undergo rapid disintegration within the oral cavity, enabling the unabsorbed portion of the drug could rapidly trigger its intended pharmaco-dynamic action. The small size of polymeric nanoparticles may facilitate fast absorption and contribute to enhanced drug bioavailability. The developed formulation has the potential to enhance bioavailability by circumventing first-pass metabolism while simultaneously improving patient compliance. Furthermore, the incorporation of polymeric nanoparticles within the film supports the requirement for sustained drug release from the dosage form.

MATERIALS AND METHODS

Materials

Eletriptan hydrobromide was obtained from Goa Antibiotics and Pharmaceutical Limited, Solan, Himachal Pradesh. PLGA 50:50 and Poloxamer 188 (pharmaceutical grade) were procured from Sigma Aldrich. PVA, pullulan, HPMC, xanthum gum, chitosan, propylene glycol and PEG-400 were purchased from Microgen Hygiene Pvt. Ltd., (Kala Amb, HP). Methanol and acetonitrile (HPLC grade) were obtained from Rankem, India. All other reagents employed in the study were of certified analytical quality.

Methods

Optimization design

A Box-Behnken experimental design was employed to optimize the EH-loaded polymeric nanoparticles, incorporating four independent variables and two response parameters. The optimization study was conducted using Design Expert software (version 25.03, Stat-Ease 360). Polymer concentration (A, 20:40:60), surfactant amount (B, 2:8:14), aqueous/organic phase ratio (C, 1:3:5), and amount of drug (D 2:4:6) were selected as independent variables. Particle size (R¹) and drug entrapment efficiency (R²) were considered as dependent responses. The influence of the independent variables was evaluated at three predetermined levels (low, medium, and high), as presented in Table 1. The software generated batches F1-F26, and the best-performing formulation was identified on the criteria of achieving the smallest particle size and the highest entrapment efficiency.²⁶ Box-Behnken design was used because it provides

efficient optimization of multiple formulation variables with a reduced number of experimental runs while enabling the evaluation of linear, quadratic, and interaction effects. The selected independent variables and their ranges were established based on preliminary screening studies and literature reports, as they were considered critical factors influencing particle size and entrapment efficiency. The interaction and quadratic terms were generated automatically by Design-Expert® software according to the Box-Behnken design model.

Fabrication of polymeric nanoparticles

Polymeric nanoparticles of eletriptan hydrobromide were formulated by the nanoprecipitation method. The aqueous phase was prepared by dissolving 60 mg of drug and 0.75% w/v of surfactant poloxamer 188 into purified water (10 mL) with constant stirring for 20 min. For the preparation of the organic phase, PLGA 50:50 (0.75% w/v) was dissolved in acetone (10 mL) with continuous stirring at ambient temperature. Subsequently, this organic phase was added dropwise into the aqueous phase under continuous stirring to form a uniform dispersion. The organic solvent was removed by evaporation under reduced pressure. Then, the nanoparticles were purified by centrifugation at 10,000 rpm for 15 min using a refrigerated centrifuge (REMI R-4C, Vasai, India). The obtained formulation was subsequently lyophilized using a freeze dryer (Vir Tis Lyophilizer (Wizard 2.0, USA) at -80°C for 48 hr for further studies.²⁷

Screening of film-forming polymers and plasticizers

The integrity of oral dispersible film is based upon appropriate selection of both the polymeric film former and associated plasticizer. To identify the most suitable combination, various polymers such as chitosan, HPMC, pullulan, and xanthan gum were evaluated along with plasticizers including propylene glycol, and PEG-400 in a 1:1 ratio. By using these polymers and plasticizers various formulations were prepared and the optimum batch was selected on the basis of their physical parameters such as visual appearance, disintegration time.

Optimization of film forming-polymer and plasticizer concentration

Formation of oral dispersible film also depends upon the amount of film-forming polymer and plasticizer. Concentration of film-forming polymer and plasticizer affects the disintegration time, folding endurance, and tensile strength of oral dispersible film. The formulations were developed by using pullulan at concentrations of 5, 10, 15 and 20% w/v with plasticizer at 10, 15, 20, and 25% w/v respectively. The optimum batch was selected in accordance with optimum disintegration period, folding endurance, and tensile strength.

Preparation of oral dispersible film containing polymeric nanoparticles

Polymeric nanoparticles-loaded ODF was prepared by solvent casting technique.²⁸ Pullulan polymer (15% w/v) was prepared and added into drug-encapsulated polymeric nanoparticle dispersion (20 mL). This solution was continuously stirred at 400 rpm on the magnetic stirrer for 1hr to achieve a uniform mixture. Propylene glycol (20% w/v) was dissolved in 10 mL of water to obtain the required aqueous solution. This solution was subsequently incorporated into the drug-loaded polymeric nanosuspension. The mixture was then adjusted to a final volume of 30 mL. The resulting nanoparticle-embedded film-forming solution was cast into a petri dish and dried in a hot-air oven at 60°C for 24 hr under ambient laboratory humidity conditions. After drying, the oral dispersible film was removed from the petri dish and cut into the appropriate size for future evaluation.

Characterization and Evaluation of Polymeric Nanoparticle Systems

Particle size and Polydispersity Index (PDI)

The particle size and polydispersity index of eletriptan hydrobromide containing polymeric nanoparticles were characterized using a Dynamic Light Scattering (DLS) instrument (Malvern's Zetasizer, U.K). All DLS measurements were done at 25°C with an angle detection of 90°. Double-distilled water was used to dilute the samples to achieve the desired scattering intensity. The polydispersity index was used to assess the uniformity of particle size distribution.²⁹ For each formulation, three repeated measurements were conducted, and the outcomes were summarized as mean±standard deviation.

Entrapment Efficiency

The drug content in the polymeric nanoparticle formulation was estimated by centrifugation or indirect methods.³⁰ The polymeric nanoparticle formulation was subjected to centrifugation at 12,500 rpm for a duration of 30 min. The concentration of unincorporated drug present in the supernatant was quantified using a UV-visible spectrophotometer. After separation of supernatant, further dilution was made and analyzed by using an ultraviolet spectrophotometer (UV 3000, Labindia, India) at 272 nm. The drug quantification was performed by using a calibration curve prepared in the concentration range of 5-30 µg/mL. The method exhibited good linearity with a correlation coefficient (R^2) of 0.998. The method was further validated in accordance with ICH Q2 (R^1) guidelines with respect to accuracy, precision, recovery, selectivity, LOD and LOQ. The amount of entrapped drug was determined by calculating the difference between the initial drug load and the non-entrapped drug. All the measurements were done in triplicate, and the average of three determinations for each sample was found out. The entrapment efficiency (%) was calculated by the given equations.

$$EE \% = \frac{\text{Total drug added} - \text{Free drug in the supernatant}}{\text{Total drug added}} \times 100$$

Surface morphology by Scanning Electron Microscopy (SEM)

The outer surface structure, particle size, and aggregation of the polymeric nanoparticles were examined using a SEM. Prior to imaging, the samples were sputter-coated with gold using a JEOL ion coater. SEM micrographs were captured using a JEOL JSM-840, Japan instrument.³¹

Characterization of polymeric nanoparticle-loaded ODF

Visual appearance

The optimized film formulation was evaluated for the presence of any aggregates, colour deposition, smoothness, cracks and distribution of drug in film.

Thickness

The measurement of the thickness of the ODF is one of the crucial factors that showed the uniform distribution of all the components of the film formulation. A digital Vernier caliper (500-196-30, Mitutoyo, Japan) was employed to measure the thickness of the polymeric nanoparticle-loaded ODF. The film thickness was tested at various points that is, the four corners and the center location of the dispersible film. The analysis was conducted on three samples, and the corresponding average was estimated.³²

Disintegration period

The disintegration behaviour of the developed film formulation was measured by the petri plate method. The analysis was performed by keeping the film strip in a Petri plate filled with simulated salivary fluid or phosphate buffer at pH 6.8. When the film was completely disintegrated, the time was noted down. Three independent measurements were performed, and the average value was estimated.

Folding Endurance

The brittleness of polymeric nanoparticle-loaded ODF was analyzed by measurement of folding endurance. The film was repeatedly folded at the same point until it broke.³³ The number of folds sustained without any cracks or break was taken and the average of three measurements was reported in the results.

Surface pH determination

The pH measurement of the optimum film formulation is a crucial parameter, as an excessively acidic or alkaline nature may induce irritation or potential tissue damage. It was measured by using the pH meter (Hicon®, Grover Enterprises, New Delhi). A film sample was kept in distilled water (1 mL) for 1 hr at room temperature. The electrode was then placed on the film surface, which was allowed to equilibrate for one min, and the pH was evaluated in triplicate and recorded.³⁴

Tensile Strength Measurement

Tensile Strength (TS) refers to the maximum stress that a film can withstand at the point of rupture. It was measured by texture analyzer (Brookfield CT3 Texture Analyzer, USA) as per the ASTM International test method. The initial grip spacing of analyser was set to 20 mm, and the crosshead speed was maintained at 1 inch/min. The analysis of film ended when the film reached its breaking point. It is measured as the load applied per unit area, calculated by dividing the maximum applied load by the film's initial cross-sectional area.³⁵ Experiment was conducted three times, and resulting mean was determined.

$$\text{Tensile strength} = \frac{\text{Maximum Force (N)}}{\text{Original Cross-sectional area of film (cm}^2\text{)}}$$

Morphological Study: Scanning Electron Microscopy (SEM)

The outer surface characteristics of the polymeric nanoparticles-loaded ODF were analyzed by the Scanning Electron Microscopy (SEM) technique. Prior to imaging, a thin gold coating was applied to the pellets using a JEOL ion sputter coater. SEM photomicrographs of polymeric nanoparticles-loaded ODF were recorded using a JEOL JSM-840 scanning electron microscope.

Table 1: Factors used for optimization of polymeric nanoparticles.

Independent variables	Low	Medium	High
A: Polymer concentration (w/v)	20	40	60
B: Surfactant concentration (w/v)	2	8	14
C: Aqueous/organic phase ratio (v/v)	1	3	5
D: Drug concentration (w/v)	2	4	6
Dependent Variables			
R ¹ : Particle size (nm)			
R ² : Percent drug entrapment efficiency			

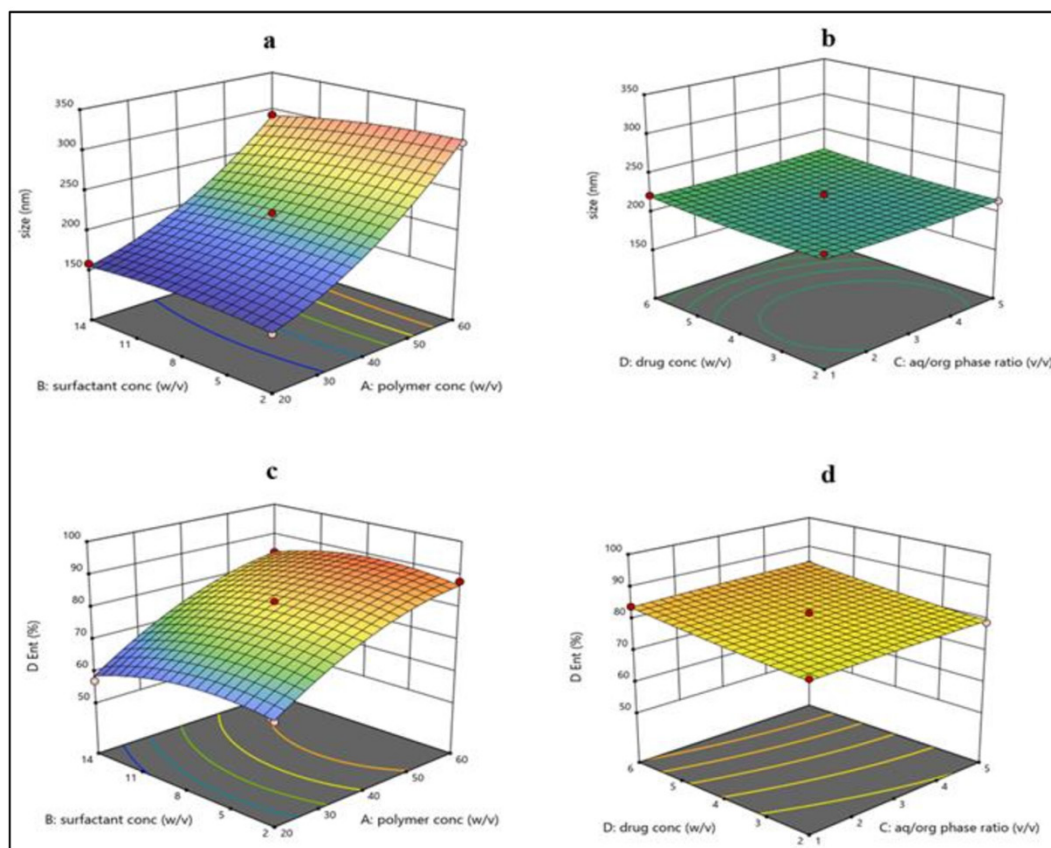


Figure 1: (a) 3-d response surface graph showing the combined effect of; polymer (A) and surfactant (B) on the particle size, (b) aqueous/organic phase ratio (C) and drug concentration (D) on the particle size; (c) polymer (A) and surfactant (B) on % drug entrapment efficiency; (d) aqueous/organic phase ratio (C) and drug concentration (D) on % drug entrapment efficiency.

X-ray Diffraction Studies (XRD)

To examine potential changes in the crystalline nature of pure eletriptan hydrobromide upon its incorporation into polymeric nanoparticles and subsequent loading into the Oral Dispersible Film (ODF), X-ray diffraction analysis was performed using a Rigaku Miniflex 600 diffractometer. The diffractometer equipped with Ni-filtered Cu K α radiation ($\lambda=1.5406$ Å), operated at a voltage of 40 kV and a current of 15 mA. Diffraction patterns were recorded by employing a vertical goniometer across a 2θ interval of 5° - 65° , with a scan rate of $10^\circ/\text{min}$ and 0.02° step size.³⁶

In vitro drug release

The *in vitro* drug release from polymeric nanoparticles-loaded ODF (test film) with respect to ODF containing free drug (control film) was evaluated by employing a USP Type II dissolution apparatus (Labindia DS 8000 series, India). To prevent the floating of film, each strip was kept on the glass slide and then placed carefully at the bottom of the dissolution vessel prior to the commencement of the test. The experiments were performed in 160 mL of phosphate buffer solution (pH 6.8) under controlled conditions of $37\pm0.5^\circ\text{C}$ and a paddle speed of

50 rpm. A dissolution medium volume of 160 mL was selected to ensure complete immersion of the film and to maintain adequate sink conditions throughout the dissolution study. The solubility of eletriptan hydrobromide in phosphate buffer (pH 6.8) was 11.19 mg/mL, providing sufficient solubilization capacity for the drug content present in the formulation. A 10 mL aliquots of the dissolution testing medium was collected at predefined time points of 5, 10, 15, and 30 min and 1, 2, 4, 6, 8, 12 and 24 hr. The withdrawn sample was replaced with an equal amount of temperature-equilibrated fresh buffer solution to sustain sink conditions throughout the dissolution study. The samples of film were passed through a membrane of $0.45\ \mu\text{m}$ and drug concentration was measured with a UV-visible spectrophotometer at 272 nm. To know about the pattern of drug release followed by the film matrix, the optimized film formulations were passed through the various types of kinetic modeling approaches like Zero-order, First-order, Higuchi and Korsmeyer-Peppas model. The highest regression coefficient (R^2) model was selected as the best-fitting model for the formulation. All the analysis were done three times, and the cumulative percentage of drug release was calculated accordingly.^{37,38}

In vivo bioavailability or pharmacokinetic studies

The pharmacokinetic analysis was carried out after the authorization granted by the Institutional Animal Ethics Committee, Maharishi Markandeshwar (MM) College of Pharmacy (Protocol no. MMCP- IAEC-180, dated 16/3/2024). The female Wistar albino female rats, weighing 200-250 g, were maintained in the animal house under standardized environmental conditions ($24 \pm 2^\circ\text{C}$, $60 \pm 5\%$ RH). The selected animals were kept in polypropylene enclosures within a controlled light-dark environment. The rats were randomly distributed into two groups, with six animals per group. Group 1: Polymeric nanoparticle-loaded ODF of EH; Group 2: EH drug solution as a control group. In one group the polymeric nanoparticle-loaded oral dispersible film of EH (10 mg/kg) was sectioned into appropriate pieces and kept on the surface of the rats' tongues. In another group, the same amount of dose of EH was given orally. During administration, the animals

were positioned on a table with their lower jaws held horizontally, and oral dispersible films were carefully placed on the rat tongue. The blood samples were taken from the retro-orbital venous plexus at predetermined time points of 1, 2, 4, 6, 8, and 12 hr. 1, 2, 4, 6, 8 and 12hr after the administration of the drug to each rat and immediately transferred to heparinized tubes. The centrifugation of obtained blood was done at 5000 rpm for 20 min to isolate the plasma fraction. The separated supernatant was subsequently vortexed for 10 min after the addition of 3 mL methanol, followed by centrifugation at 5000 rpm for 20 min. After centrifugation, the organic supernatant layer was gently collected in a clean tube and dried using at 40°C by placing the test tubes in the water bath. The collected supernatant was subjected to quantitative analysis using a UV-visible spectrophotometer at 272 nm. The experiment was performed after the injection of ketamine anesthesia administered intraperitoneally at 5 mg/

Table 2: Formulation detail and Influence of process variables on the response variables of EH-loaded PNPs.

Batches	PLGA50:50 (mg/mL)	Poloxamer188 (mg/mL)	Aq/org phase ratio	Drug conc. mg/mL	Size (nm)	% Drug entrapment efficiency	PDI
F1	40	8	5	2	215 $\pm$ 0.17	79 $\pm$ 1.4	0.174 $\pm$ 0.04
F2	20	8	1	4	164 $\pm$ 0.7	65 $\pm$ 1.7	0.123 $\pm$ 0.01
F3	60	14	3	4	293 $\pm$ 0.6	84 $\pm$ 0.5	0.057 $\pm$ 0.15
F4	40	14	3	6	201 $\pm$ 1.3	78 $\pm$ 0.8	0.189 $\pm$ 0.09
F5	20	14	3	4	158 $\pm$ 0.8	57 $\pm$ 1.3	0.057 $\pm$ 0.07
F6	40	8	3	4	205 $\pm$ 0.42	82 $\pm$ 0.6	0.195 $\pm$ 0.11
F7	40	2	3	2	211 $\pm$ 1.7	78 $\pm$ 0.2	0.188 $\pm$ 0.14
F8	60	8	3	2	305 $\pm$ 0.6	87 $\pm$ 0.4	0.281 $\pm$ 0.13
F9	60	8	5	4	316 $\pm$ 0.8	90 $\pm$ 1.5	0.275 $\pm$ 0.18
F10	40	2	5	4	221 $\pm$ 1.8	80 $\pm$ 1.7	0.221 $\pm$ 0.08
F11	40	8	3	4	223 $\pm$ 0.6	81 $\pm$ 0.8	0.207 $\pm$ 0.05
F12	60	2	3	4	310 $\pm$ 1.3	88 $\pm$ 0.7	0.254 $\pm$ 0.12
F13	20	8	3	2	169 $\pm$ 1.1	62 $\pm$ 0.5	0.084 $\pm$ 0.16
F14	60	8	1	4	300 $\pm$ 0.5	86 $\pm$ 0.8	0.278 $\pm$ 0.3
F15	40	8	5	6	217 $\pm$ 1.4	84 $\pm$ 0.5	0.242 $\pm$ 0.07
F16	20	8	3	6	162 $\pm$ 0.8	70 $\pm$ 1.2	0.136 $\pm$ 0.13
F17	20	2	3	4	154 $\pm$ 1.2	64 $\pm$ 0.7	0.072 $\pm$ 0.05
F18	40	2	1	4	213 $\pm$ 0.6	79 $\pm$ 1.3	0.208 $\pm$ 0.04
F19	40	14	5	4	210 $\pm$ 1.3	76 $\pm$ 0.2	0.174 $\pm$ 0.85
F20	20	8	5	4	156 $\pm$ 0.12	67 $\pm$ 0.3	0.089 $\pm$ 0.03
F21	40	8	1	6	222 $\pm$ 0.6	84 $\pm$ 0.9	0.224 $\pm$ 0.02
F22	40	8	1	2	223 $\pm$ 1.04	79 $\pm$ 1.1	0.192 $\pm$ 0.21
F23	60	8	3	6	325 $\pm$ 1.6	93 $\pm$ 1.9	0.312 $\pm$ 0.06
F24	40	2	3	6	225 $\pm$ 1.7	86 $\pm$ 0.8	0.216 $\pm$ 0.01
F25	40	14	3	2	196 $\pm$ 0.29	74 $\pm$ 1.4	0.159 $\pm$ 0.08
F26	40	14	1	4	209 $\pm$ 1.07	76 $\pm$ 0.9	0.172 $\pm$ 0.03

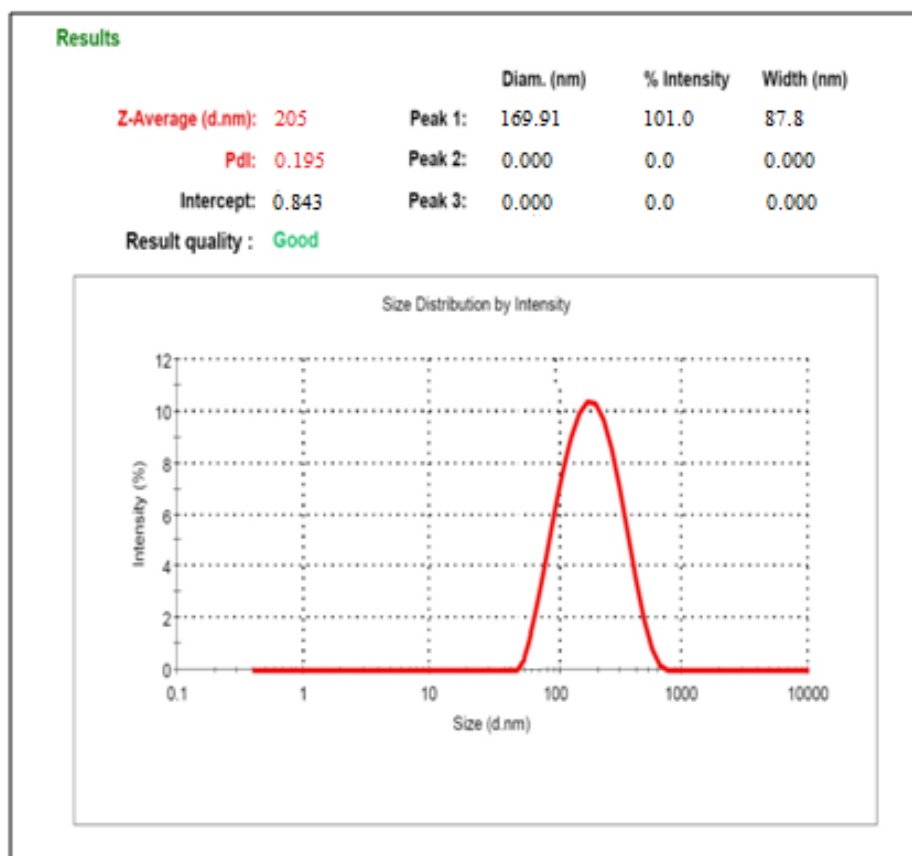


Figure 2: Particle size distribution of optimized polymeric nanoparticles formulation.

kg body weight. Different types of pharmacokinetic parameters such as C_{max} , T_{max} , $t_{1/2}$, AUC and Mean Residence Time (MRT) (hr) of oral dispersible film and oral solution of drug were studied. The resulting concentration-time data were processed using Non-Compartmental Analysis (NCA) in Microsoft Excel version 2010 (Microsoft Corporation, Redmond, WA, USA) to derive the pharmacokinetic parameters.

Statistical Analysis

The statistical comparisons between groups were performed by Graph pad prism version 8. Comparisons between the optimized polymeric nanoparticle-loaded oral dispersible film and the EH drug solution were carried out using Student's *t*-test. Differences were considered statistically significant at $p < 0.05$. The pharmacokinetic and experimental data were expressed as mean $\pm$ Standard Deviation (SD) ($n=3$).

Stability studies

The physical stability testing of the polymeric nanoparticle-loaded ODF was conducted on the basis of ICH Q1A (R^2) specifications. The samples were stabilized at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ Relative Humidity (RH) for a period of six months. The formulation was sealed in foil wrapper and stored within a stability assessment chamber (Narang Scientific Works Private Limited, New Delhi). The investigation of formulation was carried out after fixed period

of time in triplicate. Various parameters, including physical feature, disintegration period, tensile strength, and folding endurance of dispersible film were analyzed.³⁷

Histopathological measurement

The optimized film was tested for any sensitivity or irritation to oral mucosa. After performing the pharmacokinetic study the rats were sacrificed and their buccal mucosa were separated and washed by using acetate buffer (pH 4.5). A small part of obtained tissue was dried, fixed in a formalin buffered solution (10%) and thereafter treated with Hematoxylin and Eosin (H&E) to assess any abnormalities or lesions, histological alterations in the epithelium and surrounding connective tissue. After that it was examine under a digital microscope. The control oral mucosa was also treated with same treatment for ensuring the safety of film.⁴⁰

RESULTS

Polymeric nanoparticles factors optimization by Box-Behnken experimental design

A total of 26 experimental runs, including 2 center points, were designed using the Box-Behnken statistical approach to optimize the formulation parameters of polymeric nanoparticles. Four independent variables and two response variables were evaluated. All the prepared nanoparticle formulations were characterized for mean particle size, PDI, and percentage drug entrapment

efficiency, as shown in Table 2. Particle size and entrapment efficiency were selected as response variables for optimization, while PDI was evaluated as a supplementary characterization parameter. The impact of the selected formulation factors on the observed responses was analyzed, and corresponding 3D surface graphs were constructed.

Parameters affecting particle size

The overall particle diameter of the formulated PLGA nanoparticles was found within 154-325 nm, confirming the successful development of nanoscale dispersions. The relationship between the independent variables and the particle size response was fitted to a quadratic polynomial model expressed as:

$$R1 = +214.00 + 73.83 A - 5.58 B + 0.3333 C + 2.75 D - 5.25 AB + 6.00 AC + 6.75 AD - 1.75 BC - 2.25 BD + 0.7500 CD + 20.54 A^2 - 5.83 B^2 + 2.29 C^2 + 2.92 D^2$$

The 3-dimensional response surface graph of polymer (A), surfactant (B), aqueous/organic phase ratio (C), and drug concentration (D) on the particle size, shown in Figures 1a and 1b. The finding of ANOVA confirmed that the quadratic model showed a significant effect supported by its elevated F-value of 104.90 and $p < 0.0001$, indicating that the observed variations were not due to experimental noise. The adjusted (0.9831) and predicted (0.9612) R^2 values were in close alignment, showing excellent model predictability. Additionally, the adequate precision value of 31.817 (greater than the desirable limit of 4) suggested a strong signal, validating the suitability of the model for navigating the design space.

Impact on entrapment efficiency

The entrapment efficiency of the PLGA nanoparticles was observed within a range of 57-93%, confirming the strong affinity of PLGA to encapsulate the drug effectively. The influence of formulation factors on drug entrapment was described using a quadratic polynomial model:

$$R2 = +81.50 + 11.92 A - 2.17 B + 0.5833 C + 2.67 D + 0.7500 AB + 0.5000 AC - 0.5000 AD - 0.2500 BC + 0.0000 CD - 4.21 A^2 - 3.83 B^2 - 0.2083 C^2 + 0.4167 D^2$$

The 3-dimensional response surface graph of polymer (A), surfactant (B), aqueous/organic phase ratio (C), and drug concentration (D), on % drug entrapment efficiency illustrated in Figures 1c and 1d. Statistical evaluation demonstrated that the model was highly significant, evidenced by an F-value of 80.40 and a p -value below 0.0001. Additionally, the predicted (0.9447) and adjusted (0.9780) R^2 values were closely matched, indicating good model predictability. The adequate precision value of 32.588, which exceeds the desired threshold of 4, further validated the suitability of the model for optimization and design space exploration. Formulation F4 was identified as the ideal formulation with superior entrapment efficiency and desired characteristics for further development. The final optimized polymeric nanoparticle formulation exhibited mean particle size of 205 ± 0.42 nm, illustrated in Figure 2.

Morphological Assessment through Scanning Electron Microscopy (SEM)

The outer surface features of the polymeric nanoparticles were characterized by Scanning Electron Microscopy (SEM) analysis,

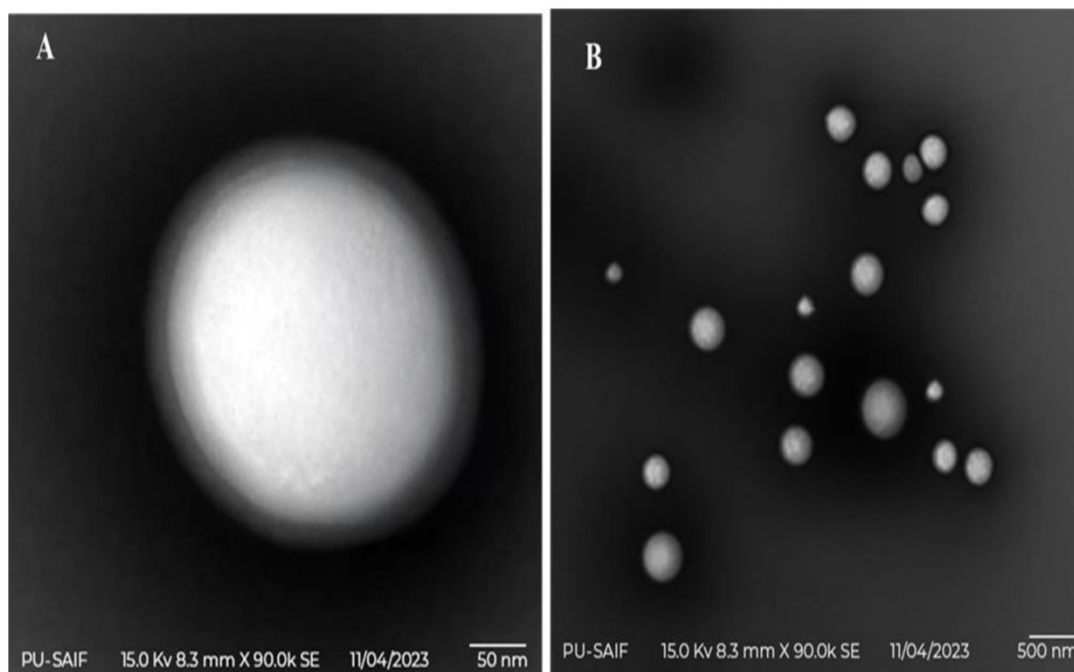


Figure 3: SEM image of polymeric nanoparticle at magnification A) 50 nm B) 500 nm.

and images of optimized polymeric nanoparticles at 50 nm and 500 nm are shown in Figure 3. The surface measurements indicate that the nanoparticles are smooth, uniformly distributed and spherical in shape. The absence of surface fractures or imperfections showed that the drug was successfully encapsulated within the PLGA matrix and that the formulation remained stable during the drying process. A narrow distribution of particle size is ensured by the low PDI found from particle size determination.

Characterization of polymeric nanoparticles loaded oral dispersible film

Optimization-oriented screening of the polymer-plasticizer combinations

The selection of polymer and plasticizer for film preparation mainly depends on the physical appearance and disintegration time of the film. The plasticizer type may impart mechanical flexibility to the film, whereas the film-forming polymer significantly influences the disintegration behaviour. For selection

of appropriate types of polymer and plasticizer, different types of formulations were evaluated (B1-B8), by visual appearance, disintegration time and the corresponding findings are presented in Table 3 and Figure 4. The chitosan-based films (B1, B5) were brittle and thick, and their disintegration time ranged from 134 to 146 sec. HPMC-based films (B2, B6) yielded consistent sheets; however, the PEG 400-containing film (B2) was thick and broke down in 125 sec, while the propylene glycol-based film (B6) was transparent and broke down in 87 sec. Pullulan performed exceptionally well; B3 (PEG 400) produced clear films that broke down in 69 sec. The combination of pullulan with propylene glycol yielded a flexible and uniformly opaque film that exhibited the fastest disintegration, with a disintegration time of 51 ± 0.21 sec (B7). The films made of xanthan gum (B4, B8) had the longest disintegration times (185- 189 sec) and were sticky, abrasive, and challenging to peel. Based on the obtained results, the formulation containing pullulan and propylene glycol was identified as the most suitable combination for further optimization, owing to its favorable film properties, including satisfactory appearance,

Table 3: Preliminary screening of polymeric film former and associated plasticizers.

Formulation	Film-forming polymer	Plasticizer	Visual appearance	Disintegration time (sec)
B1	Chitosan	Polyethylene glycol 400	Thick and brittle film	134 ± 1.5
B2	HPMC	Polyethylene glycol 400	Thick	125 ± 0.8
B3	Pullulan	Polyethylene glycol 400	Transparent	69 ± 0.5
B4	Xanthan gum	Polyethylene glycol 400	Sticky, Rough	185 ± 3.6
B5	Chitosan	Propylene glycol	Thick film	146 ± 2.8
B6	HPMC	Propylene glycol	Transparent	87 ± 2.3
B7	Pullulan	Propylene glycol	Opaque	51 ± 0.21
B8	Xanthan gum	Propylene glycol	Sticky, difficult to peel	189 ± 3.59

Table 4: Optimization of Polymer and Plasticizer Concentration.

Formulations	Pullulan (%w/v)	Propylene Glycol (%w/v)	Disintegration time (sec)	Folding endurance (count)	Tensile Strength (gcm^{-2})
B9	5	10	38 ± 0.46	46 ± 0.87	87 ± 0.53
B10	10	25	42 ± 0.87	73 ± 1.64	131 ± 1.34
B11	5	15	33 ± 0.67	51 ± 102	79 ± 0.13
B12	10	15	37 ± 0.53	56 ± 1.43	82 ± 1.20
B13	20	10	66 ± 1.23	129 ± 1.72	142 ± 1.42
B14	5	25	31 ± 0.21	78 ± 2.14	118 ± 0.21
B15	10	20	45 ± 0.10	71 ± 1.05	73 ± 0.36
B16	15	10	48 ± 0.43	56 ± 0.43	134 ± 0.45
B17	15	15	47 ± 1.6	63 ± 1.21	119 ± 0.93
B18	15	20	52 ± 0.15	85 ± 0.52	102 ± 0.27
B19	15	25	74 ± 0.13	126 ± 2.78	167 ± 1.34
B20	20	25	89 ± 2.8	149 ± 4.26	182 ± 2.62
B21	5	20	42 ± 0.43	66 ± 3.62	74 ± 1.16



Figure 4: Photographic images of different formulations (B1-B8) of PNPs-loaded ODF.

enhanced flexibility, convenient handling characteristics, and the lowest disintegration time among all formulations evaluated.

Optimization of polymer and plasticizer ratio for film formation

A series of ODF formulations (B9-B21) were prepared by varying the concentrations of pullulan polymer and propylene glycol. The film-forming polymer concentration significantly influenced disintegration duration, folding endurance, tensile strength of ODF and the obtained data are presented in Table 4. The disintegration time of the films ranged from 31 ± 0.21 sec (B14) to 89 ± 2.8 sec (B20). Disintegration time increases with increasing the concentration of pullulan from 5% w/v to 25% w/v. However, disintegration time of formulations decreases with gradual increases in plasticizer concentration from 10% w/v to 25% w/v. The constituent concentration of polymer and plasticizer both affects the folding endurance. Folding endurance values varied significantly, ranging between 46 ± 0.87 (B9) and 149 ± 4.26 (B20). At a constant amount of film-forming polymer (15% w/v) with varying concentrations of plasticizer from 10% w/v to 25% w/v, the folding endurance was found to increase from 56 ± 0.43 to 126 ± 2.78 . But, on further increasing the concentration of propylene glycol (25% w/v) and pullulan (20% w/v) more thick and brittle film formed with higher disintegration time, folding endurance and tensile strength. Tensile strength results, revealed a similar pattern, with values ranging from 73 ± 0.36 g/cm² (B15) to 182 ± 2.62 g/cm² (B20). Additionally, it was shown that significantly increasing the polymer concentration (as shown in formulations B13, B16, B19, and B20) enhanced the tensile strength of the ODF. The optimized formulation (B18)

has a disintegration time of 52 ± 0.15 sec, a folding endurance of 85 ± 0.52 and a tensile strength of 102 ± 0.27 , respectively.

Visual appearance

The visual inspection of the final optimized polymeric film showed that it was thin, elastic, non-sticky and homogeneous, with no flaws or spots seen on its surface, and it could be easily pulled out from the petri dish.

Thickness

Thickness of film is a measured physical parameter for uniformity of film and for accuracy of dose distribution. It should not be so thin and thick. The optimized formulation exhibited a film thickness of 0.69 ± 0.02 mm. The low statistical deviation of film indicates the uniformity of oral dispersible film.

Disintegration Time

The optimum disintegration time of the formulated ODF was found to be 56 ± 0.42 sec. In contrast, the films prepared from other polymers resulted in significantly longer disintegration times (exceeding 100 sec). The rapid disintegration was observed when pullulan was utilized as the film-forming polymer and propylene glycol functioned as the stabilizer.

Folding Endurance

Flexibility and brittleness of the ODF depend upon the folding endurance characteristics of film. The optimized formulation showed no signs of fracture up to 200 times of folds. However, a fine crease was observed at approximately 260 folds. Folding

endurance was evaluated for three film formulations, yielding an average value of 287 ± 0.53 folds.

Surface pH determination

Preliminary safety measurement of film was analyzed by pH determination. However, extreme acidic or basic conditions can lead to irritation or potential damage to oral mucosal tissues. The optimum pH value of the PNPs-loaded ODF was found to be 6.5 ± 0.31 indicating that the optimized formulation was in

the neutral pH range and would not irritate the oral cavity once placed there.

Tensile Strength

Tensile strength is an important mechanical property that reflects the robustness of a film when subjected to external stress or force during handling, manufacturing, and packaging. An oral dispersible film should possess an optimum tensile strength, because a more rigid film gives an unpleasant feel in the mouth,

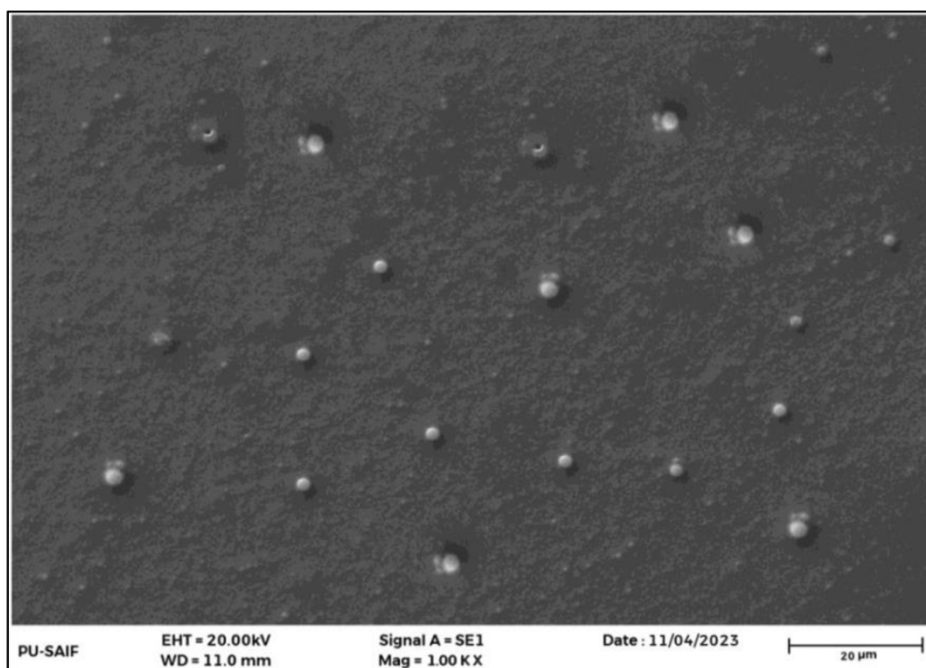


Figure 5: Scanning electron micrograph of PNPs-loaded ODF.

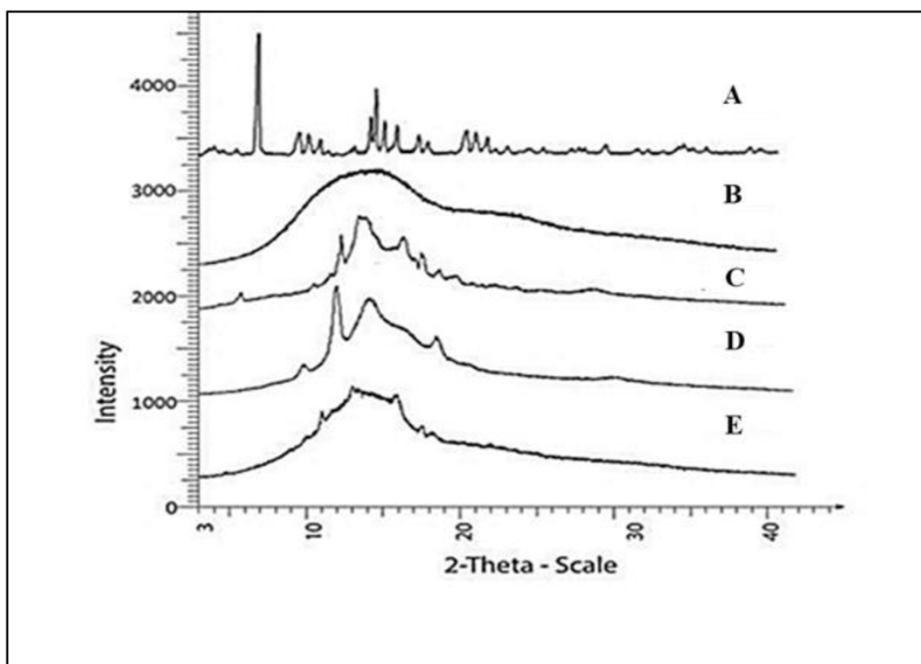


Figure 6: XRD profile of (A) eletriptan hydrobromide, (B) PLGA, (C) the physical mixture, (D) PNPs (E) PNP-loaded ODF.

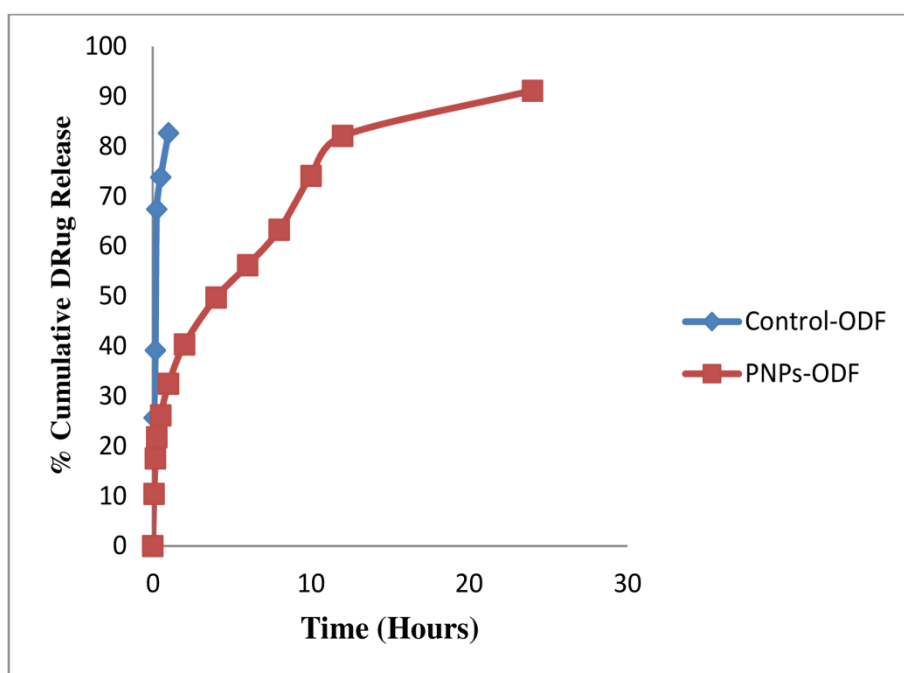


Figure 7: Drug release pattern of control ODF and PNP-loaded ODF.

Table 5: Release kinetics of ODF containing free drug and PNPs-loaded ODF.

Formulations	Cumulative % Drug Release	Kinetics value (R ²)			
		Zero order	First order	Higuchi model	Korsmeyer-Peppas
Control-ODF	82.65%	0.6842	0.0187	0.895	0.0285
PNPs-loaded ODF	91.14%	0.79	0.1084	0.963	0.3649

while insufficient strength can result in mechanical failure. A tensile strength of the formulated film was determined to be 213 ± 0.14 g/cm² which ensured that the film bear optimum toughness during stress conditions.

Morphological Study by Scanning Electron Microscopy (SEM)

The surface analysis of PNPs-loaded ODF of eletriptan hydrobromide is illustrated in Figure 5. The visual inspections of film showed a smooth appearance free from any mark or surface irregularities. It was evident from the results that the PNPs of EH were properly miscible and uniformly distributed in the ODF formulations. Some aggregation occurred in the film, which may be happened due to the casting process or during the drying of the film.

X-ray Diffraction (XRD)

The diffraction profile of eletriptan hydrobromide manifests several sharp and intense peaks at 5°, 8.2°, 10.3°, 15.1°, 16.4°, 19.3°, 21.1° and 23.5° respectively, which indicates its crystalline nature. However, the PLGA polymers exhibited a broad peak at 2θ of about 18-20°, which characterized its amorphous structure.

The physical mixture displayed a combination of distinct crystalline peaks of EH with a broad pattern of PLGA, indicating the presence of an intact crystalline drug in the physical blend. However, the quantity and intensity of the EH crystalline peaks were significantly reduced in the PNP formulation. Additionally, the ODF formulation showed a fully diffused pattern devoid of any noticeable crystalline peaks. X-ray diffraction of pure drug, physical mixture, polymeric nanoparticles and PNPs-loaded ODF are shown in Figure 6.

In vitro drug release

The *in vitro* release study of PNPs-loaded ODF of EH (formulated film) and ODF containing un-encapsulated drug (control film) was tested in pH 6.8 phosphate-buffered solution. As mentioned in Figure 7, 82.65% drug release from control ODF within 60 min. The PNPs-ODF illustrates a biphasic release pattern that is initially a burst and then followed by a sustained pattern of drug. During the first half hr, PNPs-loaded ODF showed fast release (26.13%). Subsequently, the release behaviour transitioned to a slower, sustained phase. The cumulative % drug release of 91.14% was measured within 24 hr. The kinetics of drug release from ODF formulation was determined by using the zero order, first order, Higuchi and Korsmeyer-Peppas model. The Higuchi model

demonstrated regression coefficients of 0.963 for the PNP-loaded ODF and 0.895 for the control ODF (Table 5).

In vivo bioavailability or pharmacokinetic study

The pharmacokinetic profiles of EH oral solution and PNPs-loaded ODF were compared, and the findings are shown in Figure 8. The C_{max} of the PNPs-loaded ODF formulation (87.42 ± 1.89 ng/mL) was slightly higher than that of the EH oral solution (80.72 ± 1.91 ng/mL), indicating an improved peak plasma concentration with the nanoparticle-loaded film. The T_{max} was extended from 2 hr (oral solution) to 4 hr (PNPs-ODF), suggesting a slower and more sustained release pattern from the ODF matrix. The elimination half-life ($t_{1/2}$) of the PNPs-loaded ODF was markedly prolonged (7.20 ± 1.06 hr) compared to the oral solution (4.06 ± 0.14 hr), which reflects the sustained presence of the drug in systemic circulation due to nanoparticle encapsulation and controlled release from the film. A significant enhancement was observed in the AUC_{0-t} which nearly doubled from 587.48 ± 11.57 ng·h/mL (oral solution) to 1231.46 ± 50.84 ng·h/mL (PNPs-loaded ODF). Similarly, the Mean Residence Time (MRT) increased from 5.65 ± 0.09 hr (oral solution) to 11.15 ± 0.17 hr (PNPs-loaded ODF). The t-test was conducted under the null hypothesis, which assumes no significant difference between the means of the compared groups. A significance level of $p < 0.05$ was considered as the criterion for all analyses, and a two-tailed approach was utilized to detect the differences in both directions. This method allows for the acceptance or rejection of the null hypothesis with greater reliability.

Stability studies

The stability testing studies of polymeric nanoparticles-loaded ODF under accelerated conditions ($40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH) for 6 months are summarized in Table 6. Even after six months the disintegration time, folding endurance and tensile strength of film were 57 ± 0.16 sec, 85 ± 0.72 and 134 ± 0.43 g/cm², respectively. There was no marked variation in the visual appearance of the oral dispersible film formulation.

Histopathological measurement

The PNPs-loaded ODF was delivered through the transmucosal route. Therefore, it is necessary to evaluate any sensitivity of film to oral mucosa. It was performed on a portion of rat oral mucosa, as shown in Figure 9. The experimental observations confirmed

that the cellular membrane was unharmed and the epithelial layer remained intact. There was no evidence of cell necrosis. There was no surface eruption, and the buccal mucosa of rats was in normal condition. Every cell layer was in good condition. There were no indications of inflammation.

DISCUSSION

The present study focused on the development and evaluation of an Oral Dispersible Film (ODF) containing PLGA-based polymeric nanoparticles of Eletriptan Hydrobromide (EH) to overcome the issues associated with its low oral bioavailability and extensive first-pass metabolism. By employing the nano-precipitation method and optimizing the formulation through a Box-Behnken Design,³⁹ and successfully prepared polymeric nanoparticles with desirable characteristics, which were subsequently embedded into a pullulan-based ODF using the solvent casting technique. The optimized PNPs and PNP-loaded ODF were systematically characterized through physicochemical, *in vitro*, pharmacokinetic, and histopathological assessments to determine their suitability for transmucosal delivery and their potential to provide both rapid and sustained therapeutic effects. During polymeric nanoparticles factor optimization, a noticeable increase in particle size was observed with elevated polymer concentration (factor A), which may be attributed to the rise in organic phase viscosity. Higher viscosity tends to reduce shear force efficiency during emulsification, resulting in larger droplets and eventually larger nanoparticles. Moreover, higher polymer levels allow more drugs to be entrapped within the matrix. In contrast, surfactant concentration (factor B; poloxamer 188) demonstrated a negative effect on particle size, as shown in Figure 1a. Higher surfactant levels facilitate the formation of smaller droplets by enhancing interfacial stabilization. Reduction in surfactant concentration leads to insufficient surface coverage, thereby inducing nanoparticle coalescence and aggregation, which increases the mean diameter. The variables C (aqueous/organic phase ratio) and D (drug concentration) showed minor positive effects compared to A and B (Figure 1b). Although increasing drug concentration did not significantly influence particle size, an increase in the aqueous-to-organic phase ratio from 2:1 to 10:1 tended to enlarge nanoparticles. This could be due to a lower volume of organic phase available for efficient droplet formation during emulsification. Among the formulation variables, polymer

Table 6: Stability parameters of optimized PNPs-loaded ODF.

Time (Months)	Disintegration time (sec)	Folding endurance (count)	Tensile strength (gm/cm ²)	Visual appearance
Initial (0)	54 ± 0.42	87 ± 0.53	136 ± 0.14	Opaque
1	52 ± 0.32	84 ± 1.10	135 ± 0.23	Opaque
3	56 ± 0.2	86 ± 0.64	138 ± 0.02	Opaque
6	57 ± 0.16	85 ± 0.72	134 ± 0.43	Opaque

concentration exhibited a major influence on particle size. Interpretation of the polynomial regression revealed that increasing polymer concentration (factor A), organic-to-aqueous phase ratio (factor C), and drug concentration (factor D) resulted in higher entrapment efficiency. Conversely, a rise in surfactant concentration (factor B) negatively influenced drug incorporation as shown in Figures 1c and 1d. A possible explanation is that a higher polymer amount increases organic phase viscosity, reducing drug diffusion out of the droplets during emulsification and thus promoting retention of drug molecules inside nanoparticles. Furthermore, larger particles likely provide a longer diffusional path for drug escape into the aqueous medium, minimizing drug loss and enhancing encapsulation. An increase in drug concentration also elevated the entrapment efficiency due to enhanced drug-polymer interactions and improved miscibility of the drug within the organic phase. SEM characteristics of polymeric nanoparticles may provide better stability, better drug entrapment efficiency, and sustained release behavior of EH. The screening of the polymer-plasticizer combinations unequivocally show that the physical and functional characteristics of oral thin films are greatly influenced by the plasticizer selection as well as the film-forming polymer. Chitosan's cationic character and limited aqueous solubility resulted in thick, brittle films that disintegrated slowly. HPMC, a hydrophilic cellulose derivative, on the other hand, produced films that were smoother and had superior disintegration properties. Propylene glycol's superior performance (87 ssec) over PEG 400 (125 sec) could be explained by its smaller molecular size and greater hydrophilicity, which promote water penetration and polymer chain flexibility. Overall, the study showed that pullulan is the highly promising film-forming polymer for creating fast-disintegrating ODF, especially when combined with propylene glycol. The ratio of

polymer and plasticizer affects the overall characteristics of film formulation. As illustrated in Table 4, the disintegration time of formulations decreases with gradual increases in plasticizer concentration may be due to the fact that plasticizers increase the flexibility and enhance the water solubility of film-forming polymers that allow water to penetrate easily and disintegrate the film more rapidly. At a constant amount of film-forming polymer (15% w/v) with varying concentrations of plasticizer from 10% w/v to 25% w/v, the folding endurance was found to increase due to the fact that the enables more movement and deformation of the film by widening the gap between polymer chains. Since the film becomes more malleable and less prone to cracking. As per the data presented in Table 5, upon increasing the plasticizer concentration from 5% w/v to 20% w/v resulted significant decrease in the tensile strength of the ODF. This is because plasticizers weaken the connections that hold polymer chains together by inserting themselves between them, creating a more flexible but weaker film. The kind of plasticizer used, its concentration, and the kind of polymer can all affect the precise result. One possible reason behind this could be due to the polymer chains forming a densely packed network of polymer chain, which strengthens the matrix. An ideal oral dispersible film should possess sufficient tensile strength to withstand mechanical stress; however, excessive tensile strength may negatively impact the film's flexibility and slow down the drug release from the polymeric film matrix. The rapid disintegration of the film formulation may be explained by the high hydrolytic nature of pullulan. Furthermore, pullulan provides additional stabilization to the nanoparticles, thereby improving the overall stability of the formulation. This type of mechanical strength of film showed superior flexibility of the film. The presence of pullulan polymer attributed structural integrity and enhanced

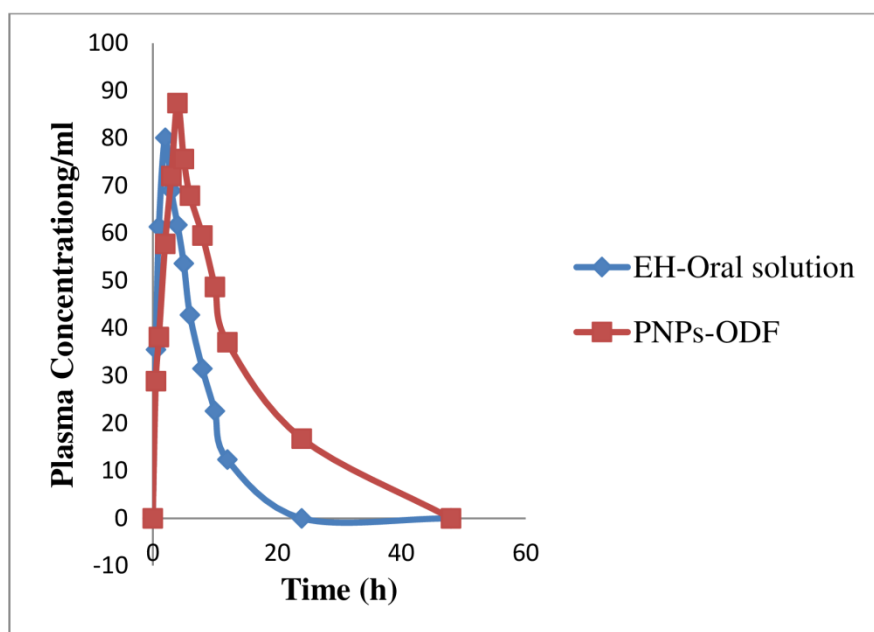


Figure 8: Pharmacokinetics profile of EH-oral solution and PNPs-loaded ODF.

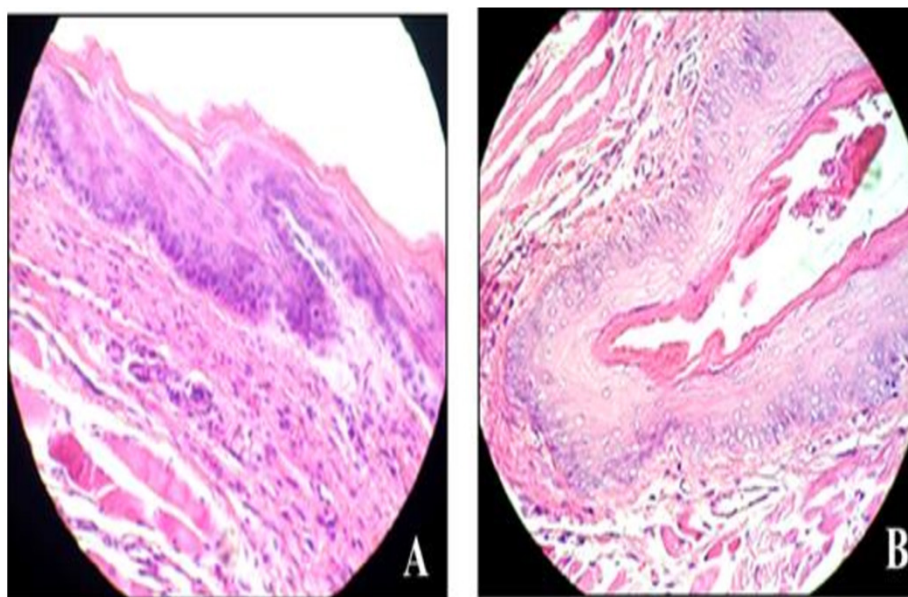


Figure 9: Histopathological images on portion of rat oral mucosa.

the mechanical strength of the film, whereas the use of propylene glycol as plasticizer conferred the required flexibility. The surface analysis showed smooth surface and uniform distribution of PNPs which indicate proper incorporation of nanoparticles into the film matrix. The minor aggregation observed may be attributed to processing parameters such as casting or drying. The X-ray diffraction exhibited a reduction or disappearance of EH crystalline peaks which implies that the EH was either amorphously changed or molecularly distributed within the PLGA nanoparticles. The ODF formulation showed complete amorphization, which may improve solubility, dissolution, and oral bioavailability. The *in vitro* study of PNPs-loaded ODF illustrates a biphasic release pattern that is initially a burst and then followed by a sustained pattern of drug. Initial burst release possibly resulted from the presence of unencapsulated or weakly bonded drug. The sustained phase is due to PLGA hydrolysis and controlled drug diffusion. Although the oral dispersible film rapidly disintegrates upon contact with the dissolution medium, the sustained drug release is primarily governed by the PLGA-based polymeric nanoparticles rather than the film matrix itself. Rapid film disintegration facilitates the release of nanoparticles, which subsequently act as drug reservoirs. The encapsulated drug is released gradually through a combination of diffusion from the polymeric matrix and progressive PLGA degradation, thereby extending the release profile up to 24 hr. This biphasic release behavior, characterized by an initial burst release followed by a prolonged sustained phase, is advantageous for achieving rapid onset of action while maintaining therapeutic drug levels for an extended period. The Higuchi model correlation indicates diffusion-controlled release. The findings of pharmacokinetic study, clearly indicates that the PNPs-loaded ODF significantly enhanced the pharmacokinetic performance compared to the conventional oral solution. The higher C_{max}

value, prolonged T_{max} , extended half-life, nearly a two-fold increase in AUC, and longer MRT of PNPs-loaded ODF can improve bioavailability and provide a prolonged therapeutic action, thereby reducing the frequency of administration and improving patient adherence. The t-test evaluation indicating the significant improvements ($p < 0.05$) in the PNPs-loaded ODF formulation, demonstrating its superior performance. The accelerated stability study confirms that the ODF formulation retained its mechanical integrity and physicochemical stability under accelerated storage conditions for an extended period. Histological measurements indicate that the PNPs-loaded ODF is safe for transmucosal delivery, as it did not trigger irritation, necrosis, inflammation, or structural damage to the oral mucosa. However, comprehensive bioavailability studies and clinical evaluations are essential to substantiate these preliminary observations. Furthermore, *ex vivo* transmucosal permeation studies and mucosal retention investigations would provide additional insight into the transmucosal delivery potential of the developed formulation and may be explored in future studies.

CONCLUSION

In the present research study, oral dispersible film containing PLGA (50:50) polymeric nanoparticles of eletriptan hydrobromide were manufactured by the solvent casting method. The characteristics of oral dispersible film and polymeric nanoparticles depend upon the components utilized for the preparation of film formulation. X-ray diffraction showed the diffuse amorphous pattern of polymeric nanoparticles and PNPs-loaded ODF, confirming the transition of the drug structure from crystalline to amorphous phase. The SEM image of PNPs-loaded ODF demonstrates that the polymeric nanoparticles were homogeneously distributed within the film formulation. The *in vitro* evaluation revealed

that the nanoparticles retained the drug within their structure and facilitated a sustained release profile. This suggests that the medicine is released by the nanoparticles over a significantly longer period of time (24 hr), whereas the film releases the nanoparticles in less time. Furthermore, non-entrapped (free) drug in the polymeric nanoparticles provides a rapid onset of action that is needed in anxiety or migraine attack situations. In vivo pharmacokinetic evaluation revealed that the formulated film exhibited significantly different characteristics ($p < 0.05$) compared to the drug solution (reference), demonstrating distinct plasma concentration-time profiles. The PNP-ODF showed a prolonged mean residence time, indicating sustained systemic exposure relative to the reference formulation. Stability data indicates that the optimized film formulation was stable for 6 months. Mucosal histological testing ensured the safety of transmucosal administration of the formulation. Generally paediatric, geriatric, nauseous, bed-ridden, dysphagic, mucositis, Parkinson's disease, vomiting tendency patients also have problems swallowing the traditional formulations, because they have difficulty to take larger volumes of water. From the study it was concluded that the fabrication of PNPs-loaded ODF had more benefits than oral administration, such as rapid disintegration, thereby circumventing first-pass metabolic degradation, showing the ability to improve the systemic bioavailability, and ultimately promoting patient adherence.

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ABBREVIATIONS

w/v : Weight/Volume; **mg**: Milligram; **mL**: Milliliter; **µm**: Micrometer; **nm**: Nano Meter; **OTF**: Oral Thin Film; **QbD**: Quality by design; **EMA**: European Medicines Agency; **ICH**: International Council for Harmonization; **BBD**: Box-Behnken Design, **ODF**: Oral Dispersible Film, **SCM**: Solvent Casting Method, **EH**: Eletriptan Hydrobromide; **PDI**: Polydispersity Index; **TNC**: Trigeminal Nucleus Caudalis; **CGRP**: Calcitonin Gene-related Peptide; **5-HT**: 5-Hydroxytryptamine; **P-gP**: P-glycoprotein; **PLGA**: Polylactide; **PLCA**: Poly-CyanoAcrylate; **DLS**: Dynamic Light Scattering; **rpm**: Revolutions Per Min; **MRT**: Mean Residence Time; **AUC**: Area Under Curve; **RH**: Relative Humidity; **SEM**: Scanning Electron Microscopy; **XRD**: X-ray Diffraction; **PNPs**: Polymeric Nanoparticles; **HPMC**: Hydroxypropyl Methylcellulose; **PVA**: Polyvinyl Alcohol; **PEG-400**: Polyethylene Glycol 400; **NCA**: Non-Compartmental Analysis; **H&E**: Hematoxylin and Eosin; **TS**: Tensile Strength.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

In this study, we develop Oral Dispersible Films (ODFs) incorporating PLGA containing polymeric nanoparticles of eletriptan hydrobromide by employing the solvent casting technique. All the findings indicated high precision and accuracy, and the formulation was more convenient to administer to paediatric, geriatric, nauseous, bed-ridden, dysphagic, and vomiting tendency patients. Therefore, it may serve as a promising approach for the emergency treatment of migraine.

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