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Solid lipid nanoparticle-loaded oral dispersible films of eletriptan hydrobromide for enhanced bioavailability and sustained migraine relief

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ABSTRACT

The present study aims to develop and characterize a solid lipid nanoparticle-loaded oral dispersible film of eletriptan hydrobromide for migraine treatment. Eletriptan hydrobromide is a selective serotonin 5-HT1B/1D receptor agonist drug which is mainly used in the treatment of migraine. Solid lipid nanoparticles (SLN) were prepared using high-pressure homogenization and optimized through Box–Behnken design. The drug-loaded SLN were evaluated by their size, polydispersity index, drug entrapment efficiency, and *in vitro* drug release. Oral dispersible films were prepared using the solvent casting method, with pullulan as the film-forming polymer and propylene glycol as the plasticizer. X-ray diffraction was used to assess the drug's solid-state characteristics. Oral dispersible film containing SLN showed higher (87.02%) and sustained drug release over a period of 24 hours as compared to free drug loaded in oral dispersible film. A transmission electron microscope study illustrated that the SLN were dispersed uniformly in the film and spherical in shape. Results of the study demonstrate that our formulation enhances the poor oral bioavailability of the drug, avoids first pass metabolism, provides a rapid onset of action, and sustained drug release.

1. INTRODUCTION

Migraine are very painful recurrent episodes of the nervous system. Approximately 15% of people worldwide suffer from this persistent neurological condition [1]. Patients with migraine suffer from excruciating and incapacitating health conditions. It shows recurrent, unilateral, throbbing headache episodes that range in intensity from moderate to severe [2]. Headache is the second most prevalent cause of migraines, and other common symptoms include nausea, vomiting, photophobia, and/ or phonophobia [3]. The symptoms could progressively get worse. After 2–12 hours, migraine discomfort peaked and then gradually subsided. But it comes into attack if it lasts for 4–72 hours [4]. Although the exact pathogenesis of migraine is unknown, it is generally accepted that migraine is caused by activation and sensitization of trigeminal nerve fibers brought about by neurogenic inflammation [5]. Trigeminal neurons contain one axon, which is divided into central and peripheral stimuli, with both capable of sensitizing and activating these neurons [6]. There are different types of migraine triggers, such as physiologic, dietary, and environmental factors that cause activation of the trigeminal nerve fiber, which may turn into migraine attacks [7]. Neurogenic inflammation in the cerebral dura mater is the first cause of migraine headache. The physiological circumstances surrounding trigemino-vascular activation provide opportunities for new antimigraine medications and enable *in vivo* research into the molecular causes of cephalic discomfort [8]. Therefore, medications with a rapid pharmacological action are frequently selected to restore the patient's functioning capacities as quickly

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as possible. Ibuprofen and acetaminophen are good nonsteroidal anti-inflammatory medications, but triptans such as eletriptan, sumatriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan, and rizatriptan are necessary for severe and chronic migraines [9,10]. Eletriptan hydrobromide is a selective serotonin 5-HT1B/1D receptor agonist of an orally fast-acting triptan class anti-migraine drug. They act by inhibiting the stimulation of the trigeminal nerve, calcitonin gene-related peptides, and SP release substance. They also act by inhibiting nociceptive transmission, avoiding the activation of second-order sensory neurons in the brainstem, and decreasing the c-fos expression in the trigeminal nucleus caudalis [11]. The absorption of the drug was very rapid, but the absolute oral bioavailability is low, about 40–50%, due to first-pass metabolism. The conventional dosage form (tablets) has the slowest onset of effect. Therefore, it is necessary to create dosage forms that provide immediate headache relief while also reducing the first-pass effect to increase bioavailability [12]. The aforementioned factors clearly suggest the need for a better pharmaceutical dosage form that would attenuate the issues while using conventional dosage forms. Somewhat new, "innovative, useful and patient-driven progress directed towards is oral dispersible film (ODF) [13]. Oral dispersible films are flexible, ultra-thin film that contains an active pharmaceutical ingredient that dissolves or disintegrates in the salivary fluid within a second without using any solvent or chewing. The fast release action of the thin film is due to the larger surface area and lesser thickness of the film as compared to a tablet. They are typically composed of plasticized hydrocolloids, which can be manufactured by hot-melt extrusion or the solvent casting method [14]. Transmucosal administration provides a better pathway for systemic availability of the drug since the drug is absorbed directly into the bloodstream, which prevents the degradation of the drug in the GI tract and avoids the hepatic first pass metabolism [15]. Better patient acceptability is also anticipated because this approach is advantageous for patients with dysphagia or swallowing difficulties, because it does not need to be ingested like traditional dosage forms [16]. Furthermore, the thin non-keratinized sublingual mucosa has a high blood supply and low enzymatic activity, enable extraordinarily good drug absorption to achieve high plasma drug concentration, which results in a prompt migraine response. However, some of the problems associated with transmucosal administration are the washout effect of saliva, involuntary swallowing, and mucoadhesion of the film. As per the literature survey, oral dispersible film must have mucoadhesive qualities to prevent the dosage form from being removed by the flushing action of saliva and to guarantee a prolonged retention of the dosage form with the sublingual mucosa surface. For this context, various types of mucoadhesive polymer, such as carbopol, chitosan, hydroxypropyl methylcellulose (HPMC), other cellulose derivatives, and so on, have been utilized for sublingual administration to enhance mucoadhesion. In the present research work, pullulan was used as a mucoadhesive polymer for film preparation [17]. To prolonge the retention time of the dosage form, were employed in an oral dispersible film. They are made up of a solid lipid core that is stabilized by one or more surfactants [18]. They can be delivered by oral dispersible films and redispersed from the film matrix without losing their nanoparticulate features. Additionally, the lipid particles could be stabilized to a significant degree in the metastable polymorphism state. When lipid nanosuspensions are embedded in a film-forming polymer to generate orodispersible, they can be dried at more moderate temperatures [19]. Oral dispersible films based on solid lipid nanoparticles (SLN) exhibit a variety of characteristics, including controlled release, mucus penetration, mucoadhesion, and deformation ease [20,21]. Overcome the use of penetration enhancers, which irritate the mucosa [22,23]. A few research studies focused mainly on the loading of SLN in oral film formulations. Didanosine SLN were effectively produced by researchers Jones *et al.* [24] and administered by buccal route to prevent rapid breakdown of the Active Pharmaceutical Ingredient in the gastrointestinal system. To facilitate buccal medication distribution, the film matrix was composed of HPMC, triethyl citrate, and eudragit® RS 100 [24]. Another study manufactured SLN of coumarin loaded in hydroxypropyl methyl cellulose film to examine the quality and mucoadhesive properties of film formulations [25]. SLN have been described as a taste-masking approach, and loading in oral dispersible films allows longer residence time on the mucosal surface area [26]. The discernible benefits of employing SLN over more widely used polymeric nanoparticles are their excellent biocompatibility, particularly when phospholipids are used [27]. The aim of the present research work was to establish the foundation for the enlargement of a solid lipid nanoparticle-loaded oral dispersible film of eletriptan hydrobromide for migraine. SLNs comprise a solid lipid (glyceryl monostearate) and a surfactant (poloxamer-188) and were prepared by the high-pressure homogenization process. Special attention was on the SLN, that how the presence of lipid-based system affected the films' mechanical characteristics, mucin interaction, and uniformity.

2. MATERIALS AND METHODS

2.1. Materials

Eletriptan hydrobromide was received as a gift sample from Goa Antibiotics and Pharmaceutical Limited, Solan, Himachal Pradesh. Solid lipids such as glyceryl palmitostearate, glyceryl monostearate, stearic acid, dynasan 114, gelucire 44/14, surfactant poloxamer-407, PEG-40, poloxamer-188, soy phosphatidylcholine, and polysorbate 80 were purchased from Microgen Hygiene Pvt Ltd, Kala Amb, Himachal Pradesh. Acetonitrile and phosphate buffer were purchased from Rankem, India. The remaining solvents and compounds were of analytical grade.

2.2. Methods

2.2.1. Screening of solid lipid

Screening of solid lipid depends upon the higher solubility of the drug in lipids. The solubility of eletriptan hydrobromide was determined in various types of lipids like glyceryl palmitostearate, glyceryl monostearate, stearic acid,

dynasan 114, and gelucire 44/14 by the shake flask method [28]. Eletriptan hydrobromide (10 mg) and solid lipid (100 mg) were weighed accurately and transferred to a flat-bottom screw caps glass vial. Vials were then heated in the water bath above the solid lipid's melting point. They were mixed and placed in a shaker for 24 hours. The mixture was centrifuged at 3,000 rpm for 20 minutes by maintaining the system at 70°C and then filtered. 2 ml of supernatant was taken from the mixture and analyzed by UV Spectrophotometer at 272 nm. The dilutions were made, and the sample was tested in triplicate.

2.2.2 Screening of surfactant

The screening of surfactants was conducted using different types of hydrophilic surfactants, including poloxamer-407, PEG-40, poloxamer-188, soy phosphatidylcholine, and polysorbate 80. The SLN were prepared using a selected solid lipid glyceryl monostearate, and different types of surfactants at a constant concentration of 1% w/v. The selection of surfactant depends upon particle size and polydispersity index (PDI). The experiment was performed on three samples, and average values were calculated.

2.2.3. Optimization of SLN by Box–Behnken design

The optimization of solid lipid nanoparticle formulation was done by Box–Behnken experimental design expert [29]. Concentration of solid lipid (% w/v) (X1), surfactant concentration (% w/v) (X2), and homogenization speed (rpm) (X3) were taken as independent variables. Dependent variables are Particle size (nm) (Y1), Polydispersity index (Y2), and Entrapment efficiency (%) (Y3). The effect of these variables on dependent variables was analyzed at three different levels, such as low, medium, and high, as shown in Table 1. 13 batches were prepared by software, and the resulting data are shown in Table 2.

2.2.4. Preparation of SLN

The high-pressure homogenization technique was employed for the preparation of SLN. The aqueous phase was prepared by dissolving poloxamer 188 (1% w/v) in water by heating at 90°C to obtain an emulsifier mixture. Separately, the lipid phase was prepared by heating glyceryl monostearate (1.5% w/v) at 90°C. The drug was added to the emulsifier mixture. Then the solution containing eletriptan hydrobromide was added to the lipid melt at 90°C. After mixing the two phases at the same temperature, they were stirred for 1 minute at 15,000 rpm using a mechanical stirrer. The micro-emulsion was transferred into cold water under continuous homogenization at 75,000 rpm for 15 minutes. The resulting SLN were analyzed by particle size and polydispersity index [30].

Table 1. Dependent and independent variables.

Converting a coded value to real units			
Independent variable	**Variable levels**		
	Low	**Medium**	**High**
Amount of solid lipid (%w/v) (A)	1%	1.5%	2%
Amount of surfactant (%w/v) (B)	0.5%	1%	1.5%
Homogenization speed (rpm) (C)	5,000	7,500	10,000
Dependent variable			
Particle size (nm) (Y1)			
Poly dispersity index (Y2)			
Entrapment efficiency (%) (Y3)			

2.2.5. Preparation of solid lipid nanoparticle-loaded oral dispersible film

The solvent casting method was used for the preparation of an oral dispersible film. Pullulan polymer (15%w/v) and plasticizer propylene glycol (20% w/v) were incorporated into 20 ml of the drug-containing solid lipid nanoparticle solution. To form dispersion, the solution was magnetically agitated for one hour at 400 rpm using a magnetic stirrer. The propylene glycol aqueous solution, 20% w/v of the total volume of solution, was prepared in 10 ml of water. This plasticizer solution was immersed in the SLN emulsifier mixture of the drug. The total volume of the solution was prepared up to 30 ml. The final solution of nanoparticles containing film was cast into a petri dish and placed for 24 hours in a hot air oven at 60°C for drying the film. The final, prepared oral dispersible film was removed from the petri dish and cut into a desired size for further use [31].

2.3. Characterization of SLN

2.3.1. Particle size and polydispersity index

The particle size of the optimized formulation of SLN was analyzed by dynamic light scattering (Zetasizer, Delsa Nano C, Beckman Coulter, USA) at 25°C at an angle of 90°. Average particle size and PDI have been measured in triplicate by calculating the three measures' average. Distilled water was added to the particle dispersion until the required number of counts was achieved [32].

2.3.2. *Entrapment efficiency (EE%)*

The entrapment efficiency of SLN was obtained by determining the amount of free drug in an aqueous medium by using the centrifugation method. The formulations of SLN were centrifuged (C-24, BL, REMI, India) at 15,000 rpm for 30 minutes. The amount of free drug in the clear supernatant was determined by UV-visible spectrophotometer (UV 3,000, Labindia, India) at 272 nm using supernatant. The concentration of incorporated drug was measured by calculating the initial drug minus the free drug. The entrapment efficiency (%) was determined by the given equations. The measurement was done in triplicate.

$$EE\ \% = \frac{amount\ of\ drug\ added - amount\ of\ drug\ in\ the\ supernatant}{amount\ of\ drug\ added} \times 100$$

2.3.3. Surface morphology by Transmission Electron Microscope (TEM)

Morphology of the optimized the solid lipid nanoparticle formulation was performed by TEM. TEM was used to observe the internal morphology of the SLN

formulation. The sample was put on top of a nitrocellulose-covered copper grill. Without being negatively stained, it was allowed to dry at ambient temperature before being analyzed using a TEM (JEOL-1200EX, Japan) at an accelerating voltage of 90 KV [33].

2.4. Characterization of solid lipid nanoparticle-loaded oral dispersible film

2.4.1. Thickness

The thickness of solid lipid nanoparticle-loaded oral dispersible film was measured by digital venire caliper. The measurement was obtained at different points of the oral dispersible film, which are the four corners and the center location of the film [34]. This is necessary to ascertain the film's uniformity in thickness because it has a direct effect on the dose accuracy of the film [35]. All the measurements were done in triplicate, and the mean value was calculated.

2.4.2. Weight variations

Individual films were weighed in order to get the average weights for weight variation. The unique weight of each film is then deducted from the average weight of the film. A large weight variance suggests that the procedure used was ineffective and that the drug content was not uniform [36]. The testing was done three times, and the mean data is reported.

2.4.3. Surface pH

The pH of the oral dispersible film was analyzed to investigate the risk or any irritation to the oral mucosa. The surface pH of oral film should be closer to 7.0. Three oral dispersible films were selected randomly and moistened with 1 ml of purified water for approximately 2 minutes. The pH of films was analysed by placing the electrode on the surface of wet oral dispersible films [37]. The mean values of triplicate data for each oral dispersible film are reported.

2.4.4. Disintegration time

The petri plate method was used for the analysis of the disintegration time of the oral dispersible film. It was measured by placing the film strip on a wire mesh of stainless steel, which had been kept at 37 ± 0.5°C in a petri dish with phosphate buffer (pH 6.8). The time taken by the film to break down was noted as the disintegration time of the film [38]. The analysis was measured in triplicate.

2.4.5. Folding endurance

The folding endurance of the oral dispersible film was manually analyzed. The same location on a strip of film was folded repeatedly until it broke. The folding endurance of film is measured by the number of times it can be folded in the same spot without breaking [39]. The folding endurance also provides brittleness to the film. The test was done in triplicate.

2.4.6. Tensile strength measurement

A texture analyzer was used to measure tensile strength. Tensile tests were performed on the texture analyzer using the ASTM International Test Method for Thin Plastic Sheeting. The grip spacing was 20 mm, and the starting crosshead speed was 1 inch/minute. The test was considered to be over when the film broke. To evaluate the films' tensile properties, tensile strength was computed using the cross-sectional area and the load required to break the oral dispersible film. The tensile strength is the maximum load applied to a spot where the thin film breaks and is expressed in force per unit area. It can be measured by dividing the maximum load by the specimen's initial cross-sectional area [40]. The mean value of tensile strength is reported.

$$\text{Tensile strength} = \frac{Force\ (N)}{cross\ sectional\ area\ of\ film(cmx^2)}$$

2.4.7. Morphological study: transmission electron microscope

TEM was used to observe the uniform distribution of solid lipid nanoparticle-loaded oral dispersible film. The TEM was performed by placing an oral film sample on the carbon-coated copper grid. A sample of film was dried at room temperature and examined using a TEM (JEOL-1200EX, Japan) at an accelerating voltage of 90 KV without being negatively stained.

2.4.8. X-ray diffraction studies (XRD)

An X-ray diffraction study was performed to determine any change in crystallinity of the pure form of the drug when delivered in solid lipid nanoparticle form and in SLN-loaded-oral dispersible form. It was measured by a Rigaku Miniflex X-ray diffractometer with Ni-filtered Cue K radiation. During the X-ray diffraction study, a 40 kV voltage with 15 mA current was used. The vertical goniometer was used for the measurement of radiation scattered on the samples. At different 2θ values between 5° and 65°, X-ray diffraction patterns were obtained at a scan speed of 10°/minute with a width of 0.02 degrees.

2.4.9. Differential scanning calorimetry studies

Shimadzu, Japan's differential scanning calorimetry (DSC) 60 with TA60 software, was used for DSC investigations. The DSC thermograms were observed for eletriptan hydrobromide, glyceryl monostearate, poloxamer 188, physical mixture, solid lipid nanoparticle, and solid lipid nanoparticle-loaded oral dispersible film. The samples were weighed accurately, placed on aluminum plates, sealed with aluminum lids, and provided with constant heat at 5ºC /minute over a temperature range of 0ºC–250ºC.

2.5. *In vitro* drug release study

The *in vitro* drug release investigation was done by using a dialysis bag. Drug release from oral dispersible film containing SLN of eletriptan hydrobromide was studied with respect to a reference oral dispersible film containing free drug. Therefore, reference and test films having approximately 10 mg of drug were put into test tubes (20 ml) that were fastened at one end with a dialysis membrane (12,000 Da). After that, it was submerged in 150 milliliters of pH 6.8 phosphate buffer. The whole compartment was set at a temperature of 37ºC at 100 rpm. At a particular period of time, 1 ml of the sample was

withdrawn at intervals of 5, 10, 15, 30 minutes, and 1, 2, 4, 6, 8, 12, and 24 hours. After withdrawal of samples, an equal amount of fresh phosphate buffer at pH 6.8 was replaced [41]. The measurement was performed in triplicate, and cumulative percentage drug release was observed.

2.6. Accelerated stability studies

A stability study of an optimized solid lipid nanoparticle-loaded oral dispersible film was performed as per ICH guidelines. A sample of film was wrapped in aluminum foil and kept in a stability chamber. The accelerated stability studies were conducted at a temperature of 25°C with 60% relative humidity over a 3-month period. After fixed periods of time, 0, 30, 60, and 90 days, samples were taken and evaluated by physical appearance, folding endurance, and disintegration time [42]. All measurements were taken in triplicate, and the averages were computed for the results presented.

3. RESULTS AND DISCUSSION

3.1. Preliminary trial batches

On the basis of trial batches, glyceryl monostearate was selected as a solid lipid, and poloxamer 188 was selected as a surfactant. Based on the trial batches, poloxamer 188 showed a low particle size (275.48 ± 1.82nm) and the highest entrapment efficiency (62.37% ± 0.72%) as compared to other surfactants. Therefore, poloxamer 188 was taken as a better surfactant for further analysis. Glyceryl monostearate (1% w/v), poloxamer 188 (1% w/v), and a homogenization speed of 5,000 rpm for 15 minutes were selected for the preparation of SLN. From the trial batches, the levels selected for further study were 0.5%–1.5% w/v, 1%–2% w/v, and 5,000–10,000 rpm for concentration of surfactant, concentration of solid lipid, and homogenization speed, respectively.

3.2. Optimization of factors affecting SLN by Box–Behnken experimental design

Dependent variable responses for 15 batches by Box–Behnken statistical software are shown in Table 2. When various values of independent variables were combined, particle size, polydispersity index, and entrapment efficiency ranged from 119 nm to 589.5 nm, 0.214% to 0.473%, and 52.9% to 74.12%, respectively. The best-fitted models were selected for each value based on the correlation coefficient (R^2), projected R^2, adjusted R^2, and standard deviation (S.D.). A quadratic model was selected as best best-fitted model for particle size, PDI, and % entrapment efficiency. Quadratic model for particle size (R^2 = 0.9,983), PDI (R^2 = 0.9,748), and % entrapment efficiency (R^2 = 0.9,608), respectively. The regression equation was created using the analysis of variance, which is tabulated in Table 3. The regression equation shows that the results of the dependent variables were caused by all independent variables.

3.2.2. Effect on particle size

The particle size of SLN was affected by varying the speed of the homogenizer from low to high and the concentration of surfactant and lipid. At a very low speed of the homogenizer 5,000 rpm, a very large particle size resulted. It may be due to the aggregation of particles at low speed. When the speed of the homogenizer increases from 5,000 rpm to 10,000 rpm, the particle size decreases. However, it is also noticed that the amount of surfactant and lipid added during the preparation of SLN also affects the particle size. Additionally, SLN were greater at extremely low surfactant concentrations (0.5% w/v) because the emulsified globules were comparatively larger at low surfactant concentrations. As a result, the surfactant was further optimized using the optimal range. In the same way, a very high concentration (2% w/v) of lipid led to a larger particle size. The 1.5% w/v of lipid was found to be the optimum concentration for the preparation of SLN. Optimization of

Table 2. Optimization of SLN.

Formulations	Lipid Amt (%w/v)	Surfactant (%w/v)	Homogenizer speed (rpm)	Entrapment efficiency (%)	Particle size (nm)	PDI
F1	1	0.5	10,000	60.25 ± 1.41	155.5 ± 0.83	0.26 ± 1.16
F2	1	1.5	7,500	56.21 ± 2.16	172.2 ± 1.42	0.289 ± 1.05
F3	2	0.5	7,500	71.04 ± 2.24	368.5 ± 2.35	0.402 ± 1.74
F4	1	0.5	7,500	63.8 ± 0.64	272.8 ± 1.78	0.315 ± 1.91
F5	1.5	0.5	5,000	73.4 ± 2.15	515.6 ± 3.17	0.473 ± 1.83
F6	1	1	10,000	56.31 ± 2.72	136.8 ± 2.48	0.237 ± 0.56
F7	1.5	1.5	10,000	52.9 ± 1.83	119 ± 1.84	0.214 ± 0.78
F8	2	1.5	7,500	66.16 ± 1.52	293.4 ± 2.28	0.336 ± 1.33
F9	2	1	10,000	64 ± 0.93	259.2 ± 1.30	0.31 ± 1.76
F10	2	1	5,000	74.12 ± 3.14	589.5 ±3 .85	0.452 ± 2.5
F11	1.5	1.5	5,000	65.8 ± 1.81	409.2 ± 3.66	0.372 ± 2.83
F12	1.5	1	7,500	65.51 ± 0.68	149.2 ± 0.59	0.274 ± 0.71
F13	1	1	5,000	65.89 ± 1.85	442.7 ± 3.55	0.391 ± 1.15
F14	1.5	1	7,500	64.32 ± 2.76	136.8 ± 2.47	0.256 ± 1.92
F15	1.5	1	7,500	62.54 ± 3.61	140.5 ± 1.51	0.224 ± 1.26

Table 3. Regression analysis results for SLN.

Responses	Model	R^2	R^2 Predicted	R^2 Adjusted	Std Dev	Polynomial equation
Particle size	Quadratic model	0.9983	0.9,754	0.9,951	10.79	$Y_{1=}$+142.17 + 60.76A –39.83B –160.81C + 6.37AB –10AC+17.48BC+ 95.89A^2 +38.67B^2 +118.99 C^2
PDI	Quadratic model	0.9,748	0.7,848	0.9,294	0.0,217	Y_2= +0.2513 + 0.0335A – 0.0299B – 0.0834C – 0.0100 AB + 0.0030 AC + 0.0137 BC + 0.0510 A^2 + 0.0332 B^2 + 0.0452 C^2
Entrapment efficiency	Quadratic model	0.9,608	0.9,248	0.9,501	1.35	Y3= +64.14 + 4.12A – 3.45B – 5.72 C

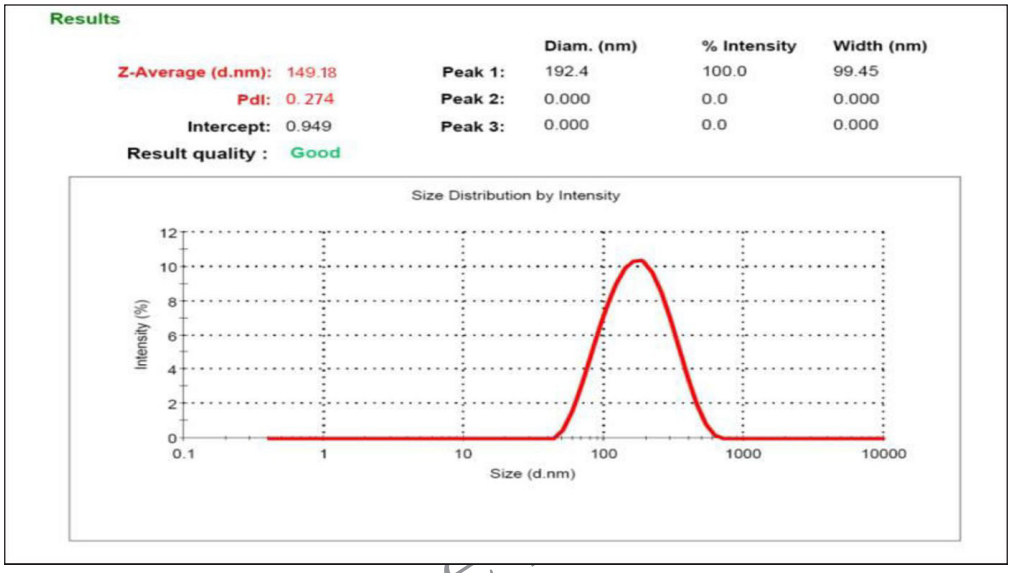

Figure 1. Zeta sizer of final optimized SLN formulation.

particle size is important while manufacturing SLN because it affects the nanoparticles' biocompatibility and bioactivity. Furthermore, it demonstrates the formulation's stability. The optimized batch of SLN had an average particle size of 149.189 ± 0.87 nm (Fig. 1). The surface response plot shown in Figure 2 and the polynomial equation suggest that factors interact with each other and affect the particle size of SLN.

3.2.3. Effect on PDI

Table 2 showed that at very low homogenizer speeds (5,000 rpm), the PDI resulted, a larger size of particles, signifying a less uniform distribution. However, an increase in the PDI may be due to the fact that at lower speeds, the lipid dispersion may not be sufficiently broken down. Higher lipid concentration (2% w/v) also increases PDI. However, surfactant concentration had a non-significant effect on the polydispersity index of the formulation. The PDI of 0.274 was found to be optimum as it showed a narrow and uniform particle size distribution that stabilized the formulation.

3.2.4. Effect on entrapment efficiency

As per the data mentioned in Table 2, the result was that a high concentration of surfactant (1.5% w/v) showed low entrapment efficiency. Increasing surfactant concentrations might result in increased drug partitioning from the internal to the exterior phase, thus solubilizing the drug and lowering the amount accessible for encapsulation. Moreover, a more densely packed polymer layer caused by high surfactant concentrations may impede drug entrapment and penetration into the nanoparticles. High homogenization speed (10,000 rpm) might result in low entrapment efficiency. Because of things like increased shear stress and heat generation, which could harm the encapsulated substance. The structure and characteristics of the lipid matrix may also be impacted by high homogenization speeds, which may result in the development of unstable solid lipid nanoparticles (SLNs) or modifications to the drug's solubility in the lipid matrix. From the result, it was observed that 1% w/v of surfactant concentration, 1.5% w/v of lipid amount, and 7,500 rpm homogenizer speed were found to be optimum since they have a desired particle size of 149.2 nm, a narrow PDI range of 0.274, and maximum drug entrapment efficiency of 65.51%. From the overlay plot, lipid concentration 1.58,883% w/v, surfactant 0.883% w/v, and 7,795 rpm homogenization speed were selected as the optimum formulation. Based on results obtained from the preliminary trial batches, which were further optimized by design of experiments, formulation F12 was selected as optimum for the preparation of SLN.

3.2.5. Morphology

Transmission electron microscopy was performed to physically check the prepared solid lipid nanoparticles (SLNs). The SLN that were located as almost spherical in shape were also found to be smooth, in the nano range, and devoid of any

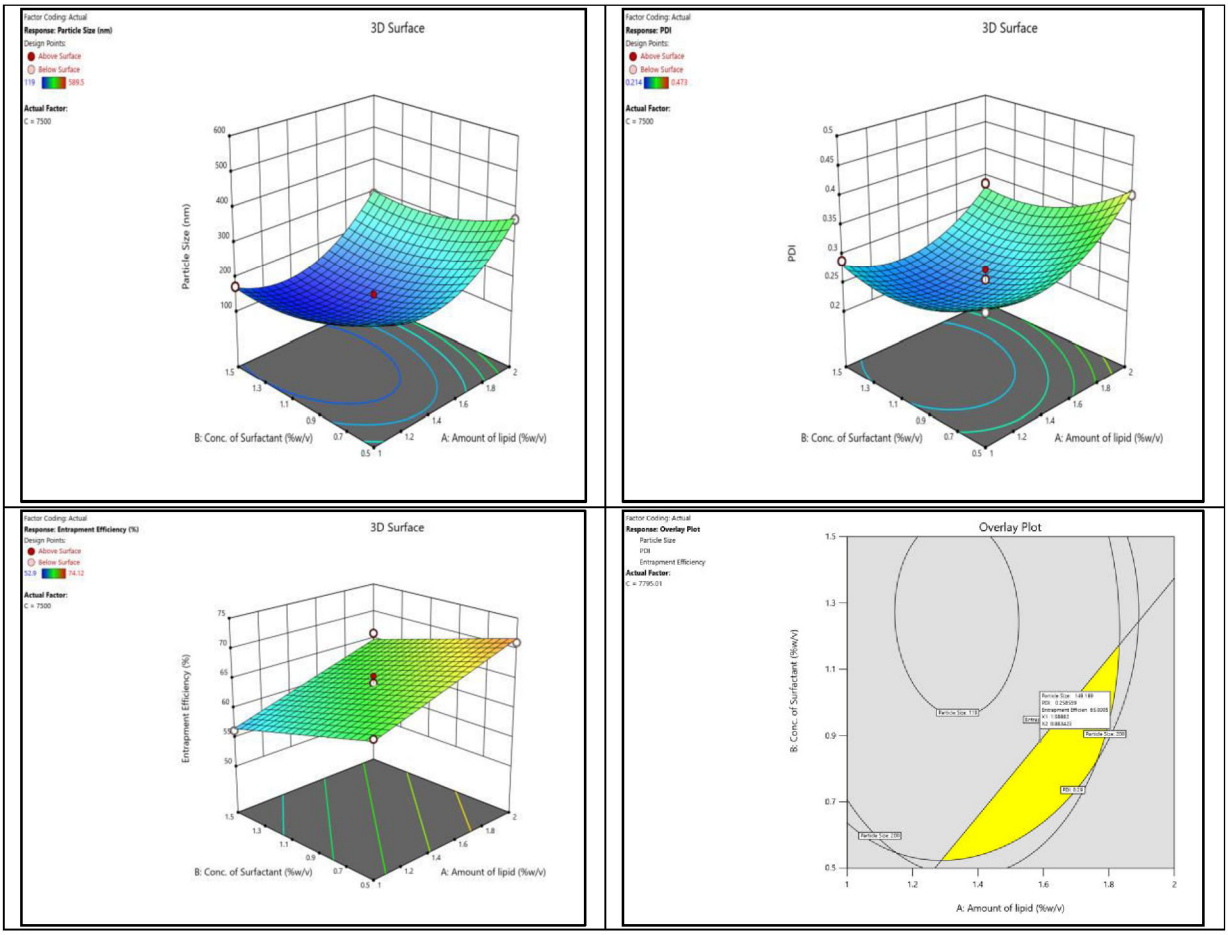

Figure 2. Surface response plot displays the following dependent variables of SLN: (A) particle size; (B) PDI; (C) entrapment efficiency; and (D) overlay plot.

debris (Fig. 3). The SLN were found to be in the 150–200 nm range.

3.3. Evaluation of solid lipid nanoparticle-loaded oral dispersible film

3.3.1. Weight variation

The weight variation analysed the uniform distribution of the drug and other excipients of the film. The individual films were weighed accurately, and the mean value was calculated. The weight variation of the optimized formulation was 567.5 ± 2.11 mg. A low value of standard deviation indicates uniformity in the weight of the film.

3.3.2. Surface pH

The pH of oral film administered to the oral mucosa must be near 7.0 to prevent any damage to the oral mucosa. The pH value of the solid lipid nanoparticle-loaded film was 6.7, which is close to that salivary. Result of the study suggests that the films would be easy to administer and would not irritate the oral mucosa. In the present work, only physicochemical evaluation, including pH measurement, was performed as a preliminary safety indicator. No cytotoxicity or mucosal irritation studies were performed.

3.3.3. Thickness

Thickness is one of the main physical attributes of oral dispersible film that demonstrates its consistency in film casting. The thickness of the oral dispersible film depends on the concentration of the film-former polymer. The coating should not be so thick that it takes a longer time to dissolve, or so thin that it cannot be removed without causing damage. Furthermore, the film thickness also affects how accurately the dose is distributed. However, the ideal thickness value of oral film should be between 50 and 1,000 µm. The thickness of the optimum batch was found to be 387.41 μm ± 0.024 m. The consistency of the film was evidenced by the minimal standard deviation.

3.3.4. Disintegration time

The optimized formulation's disintegration time was 54 ± 0.32 seconds, which is less than a minute and suggests a rapid onset of action of the film. Results showed that pullulan film former polymer alone gives faster disintegration without the addition of any super-disintegrant. The hydrophilic nature

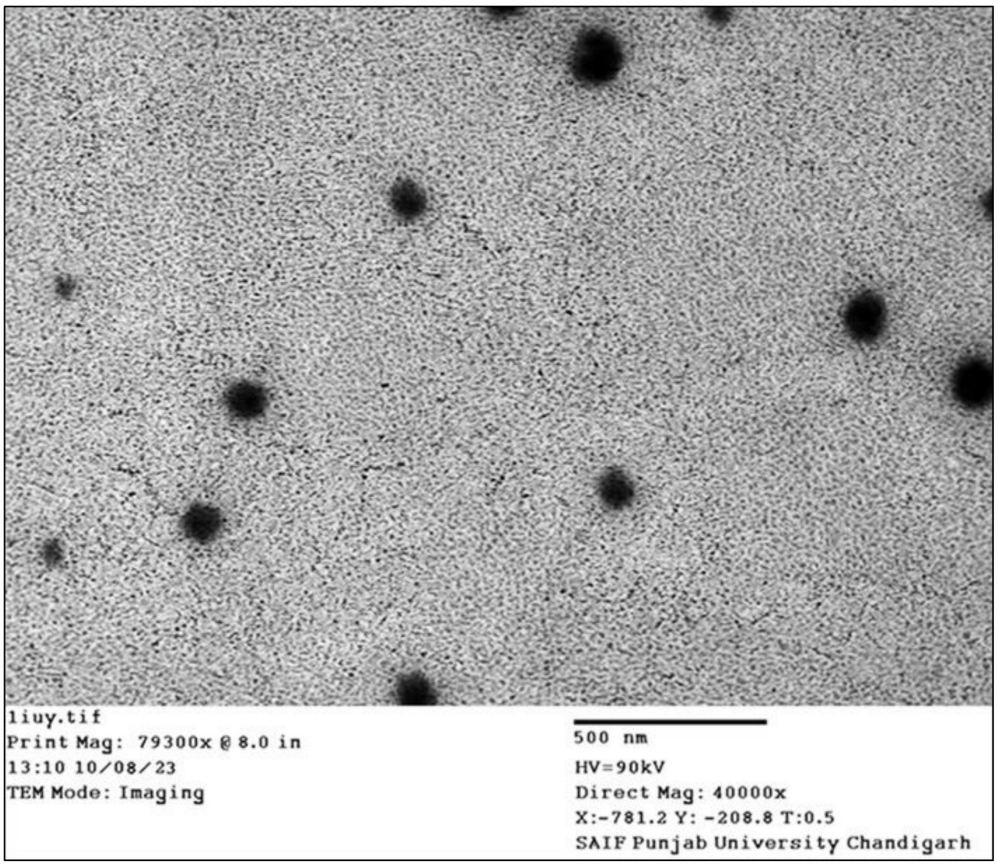

Figure 3. TEM images of SLN at magnification of 500 nm.

of pullulan polymer exhibits hydration on the surface of the film and gives rapid disintegration.

3.3.5. Folding endurance

Folding endurance determines the brittleness or flexibility of oral dispersible film. Folding endurance increases as we increase the concentration of polymer and plasticizer. The optimized formulation gives no sign of breaking until 82 folds. But after 90 folds, a thin line was seen on the surface of the film. The test was performed in triplicate, and the optimum value of folding endurance was found to be 106 ± 1.43 folds. The result of the study showed that pullulan film-forming polymer gives excellent strength to film, and plasticizer propylene glycol provides flexibility to the oral dispersible film.

3.3.6. Tensile strength

Tensile strength is also one of the main mechanical characteristics of oral dispersible film that indicates the toughness of the film. It analysed the force or stress that is endured by the film during manufacturing, packaging, and transport. Tensile strength of the film should be optimum, as too-thick film gives a bad or uncomfortable feel in the mouth. Tensile strength of formulated oral dispersible film was found to be 153 ± 0.18 g/cm^2, which revealed that the film has better strength to bear force during processing and handling of the film.

3.3.7. Morphology study by transmission electron microscopy

TEM images of SLN loaded oral dispersible film demonstrated that the SLN were uniformly dispersed in the film matrix (Fig. 4). The SLN had an almost spherical in shape and a very smooth surface.

3.3.8. X-Ray Diffraction

X-ray diffraction study was performed to determine the diffraction pattern of eletriptan hydrobromide in pure form, physical mixture, solid lipid nanoparticle, and for oral dispersible film loaded with nanoparticle. X-ray study of pure drug eletriptan hydrobromide was detected at 2 theta angle, which showed many sharp peaks at 10°, 11.5°,13.2°, 15.1°, 16.5°, 18.2°, 20.2°, 22.5°. These sharp peaks indicate drug exists in pure crystalline form. All these peaks shift to some extent, but also appear in a physical mixture to some lesser extent. However, distinct sharp peaks disappear in the solid lipid nanoparticle and the solid lipid nanoparticle-loaded film. This type of halo pattern of characteristics peaks of SLN and SLN-loaded oral dispersible film showed a change of the crystalline nature of the drug into an amorphous form. The type of polymer, surfactant, and lipid was responsible for the loss of crystalline nature of the drug. They get absorbed on the surface of SLN and inhibit the recrystallization of the drug, which stabilizes the amorphous form of the formulation. An amorphous form of oral dispersible film incorporated with SLN suggests a higher rate of dissolution of the formulation. X-ray diffractograms of

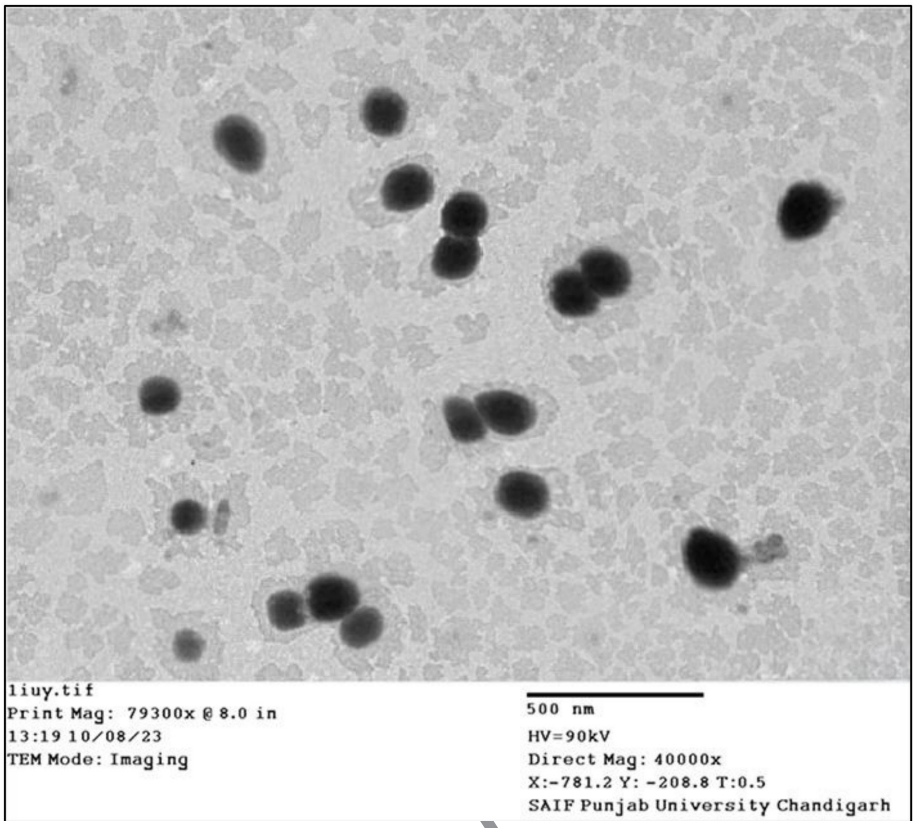

Figure 4. TEM image of SLN-loaded oral dispersible film.

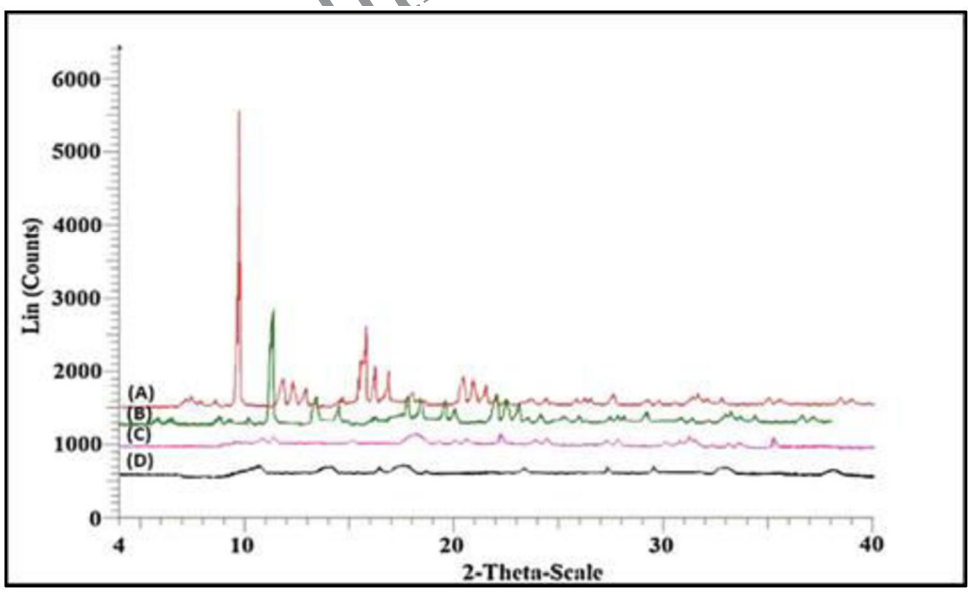

Figure 5. Comparison of x-ray diffractograms of: A) Eletriptan hydrobromide; B) Physical mixture; C) SLN; D) SLN -loaded oral dispersible film.

eletriptan hydrobromide, physical mixture, SLN, and SLN-loaded oral dispersible film are shown in Figure 5.

3.3.9. Differential scanning calorimeter

The DSC thermogram of eletriptan hydrobromide showed a melting peak at 165°C. The individual melting peaks of glyceryl monostearate and poloxamer 188 were revealed at 65°C and 54°C, respectively. The physical combination thermogram likewise showed these independent melting peaks at about the same value. However, melting peaks in solid lipid nanoparticle (SLN) and solid lipid nanoparticle-loaded oral dispersible film formulations (SLN-ODF) were almost absent.

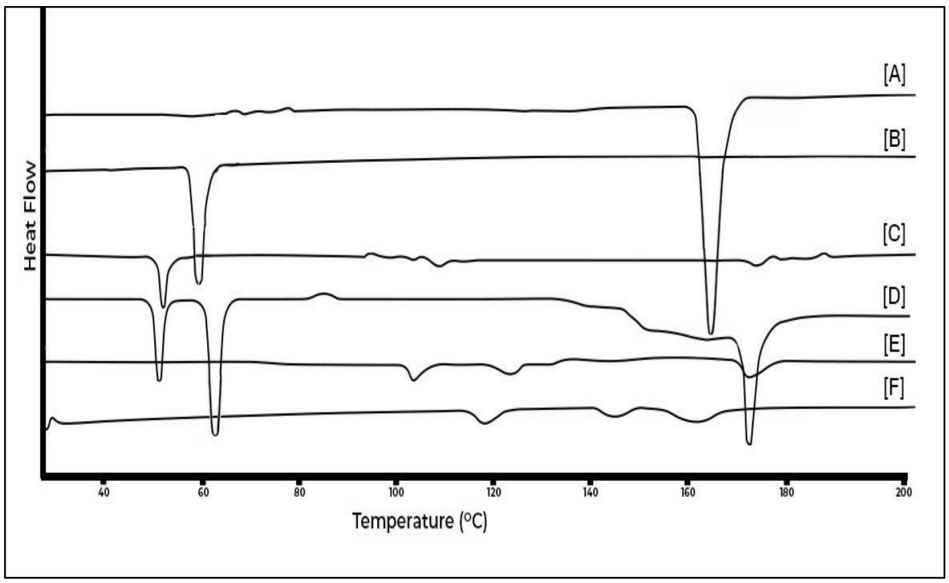

Figure 6. DSC profile of SLN-loaded oral dispersible film: A) Eletriptan hydrobromide; B) glyceryl monostearate; C) poloxamer 188; D) Physical mixture; E) SLN; F) SLN -loaded oral dispersible film.

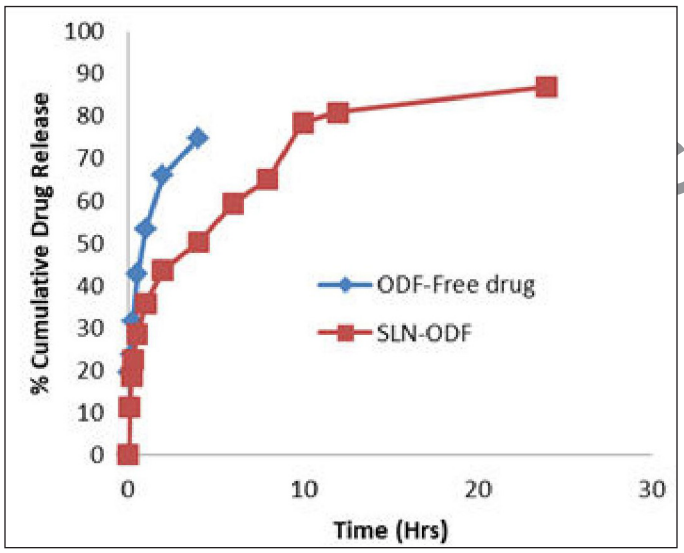

Figure 7. % Cumulative drug release of ODF-free drug and SLN-ODF.

The absence of the melting peak of eletiptan hydrobromide in SLN and SLN-ODF suggests that the drug exists in amorphous form or disperses molecularly in the lipid matrix (Fig. 6).

3.4. In vitro drug release

In vitro drug release of oral dispersible film containing SLN of eletriptan hydrobromide (Test film) was compared with oral dispersible film containing free drug (Reference film) in phosphate buffer pH 6.8. Figure 7 resulted, 74.67% drug release from ODF containing free drug with a period of 4 hours. The solid lipid nanoparticle-loaded oral dispersible film illustrates that 26.51% of the drug is released from the film in half an hour. Initially, film exhibits burst release, which can be due to the presence of an unentrapped amount of drug in the matrix of the oral dispersible film. The quick release of the drug within the first half hour may be due to the presence of a hydrophilic film-forming polymer, pullulan. However, after a resulting burst release in half an hour, the oral dispersible film containing SLN of eletriptan hydrobromide showed a slower drug release rate than the oral dispersible film containing free drug, which can be due to the presence of entrapped drug in SLN. Since glyceryl monostearate is well known for its ability to provide sustained drug release through its matrix. The drug is embedded in a matrix created by glyceryal monostearate, which reduces the drug's mobility inside the matrix and causes a slower release. Moreover, the surfactant poloxamer 188 stabilizes the nanoparticles and may have an impact on release rates by influencing the drug's position within the SLN loaded in ODF. The cumulative percent drug release of 87.02% was measured within 24 hours. A controlled and prolonged release results from the lipid's solid state at body temperature, which limits the movement of the drug. Drug release pattern of oral dispersible films was analysed by applying zero order, first order, Korsmeyer–Peppas, and Higuchi models. The R^2 value of the Higuchi model was 0.9,386 for SLN-ODF and 0.9,335 for ODF-free drug, which indicates that the release of the drug is primarily followed by Higuchi's model.

3.5. Stability studies

The results of stability studies of optimized SLN loaded oral dispersible film at 25°C temperature and 60% relative humidity for 3 months are shown in Table 4. Even after 90 days at 25°C and 60% relative humidity, the film folding endurance and tensile strength were found to be 103 ± 0.38 and 150 ± 0.27g/cm^2, which were in an acceptable range. The disintegration time of film was 57 ± 0.45 seconds. Likewise, there was no discernible variation in the disintegration time. The physical appearance of the formulation also remains opaque. The stability of the formulation under ambient conditions (25°C/60% RH) was supported by the whole data of the examined parameter. Only preliminary (long

Table 4. Stability studies of optimized SLN loaded oral dispersible film.

Formulation	Time (days)	Disintegration time (seconds)	Folding endurance (count)	Tensile strength (gm/cm²)	Visual appearance
SLN-ODF	Initial	54 ± 0.32	106 ± 1.43	153 ± 0.18	Opaque
	30	56 ± 0.27	101 ± 0.41	151 ± 0.25	Opaque
	60	55 ± 0.18	102 ± 0.53	152 ± 0.38	Opaque
	90	57 ± 0.45	103 ± 0.38	150 ± 0.27	Opaque

term) stability was performed, and accelerated stability testing under ICH conditions is planned for future studies to confirm shelf-life claims.

4. CONCLUSION

In the present research study, the oral dispersible film containing SLN of eletriptan hydrobromide was manufactured successfully by using pullulan as a film-forming polymer and propylene glycol as a plasticizer. The incorporated SLN were manufactured by glyceryl monostearate as a solid lipid and poloxamer-188 as a surfactant. All the parameters of optimized formulations depended on the types and concentration of excipients used for the preparation of oral dispersible film. The oral dispersible film showed sufficient mechanical strength. Studies using DSC, XRD, and TEM further validate the development of the film. X-ray diffraction study demonstrated that the crystallinity of the drug changed into an amorphous form after incorporating into the oral dispersible film. The *in vitro* drug release data clearly show that a solid lipid nanoparticle-loaded oral dispersible film of eletriptan hydrobromide provides controlled and sustained drug release as compared to free drug-loaded oral dispersible film. However, unentrapped drug present on the surface of the film provide fast action of drug, which is needed in migraine situation. The SLN-ODF illustrated sustained drug release up to 24 hours. Stability study data showed that the film was stable at 25°C/60% RH for 3 months. From the study, it was concluded that oral dispersible films do not require water during dose administration, avoid first-pass metabolism, show potential to enhance bioavailability, and improve patient compliance. Bioavailability studies and clinical validation are required to confirm these findings. Mucoadhesion and transmucosal absorption were discussed as potential advantages based on the properties of the polymer and lipid carriers. However, experimental mucoadhesion and tissue permeation studies are necessary to validate the assumptions of mucoadhesion strength and transmucosal permeation across sublingual tissue. *In vitro* cytotoxicity assays and mucosal histological analysis will be essential in future studies to fully establish safety for sublingual administration.

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6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

10. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

11. PUBLISHER'S NOTE

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12. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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