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Research Article

Formulation and Characterization of Clozapine Nanosuspension as a Sublingual Film

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Abstract

Background: Clozapine (CLZ) is a potent antipsychotic drug that suppresses the symptoms of schizophrenia and mania. Clozapine falls into Class II (BCS); its poor bioavailability is attributed to low water solubility and an extensive first-pass effect. ***Objective***: To prepare CLZ as a nanosuspension (NS) to improve its low water solubility and load it in a sublingual film to enhance oral bioavailability. ***Methods***: CLZ nanosuspensions are prepared by the "solvent anti-solvent precipitation" method using Soluplus as a stabilizing agent. We evaluated the polydispersity index (PDI) and the particle size of the CLZ nanosuspension formulations. The optimized formula of CLZ nanosuspension is loaded directly onto a sublingual thin film, eliminating the need for freeze-drying for solidification by the solvent casting approach. The sublingual films were characterized by thickness, surface pH, folding endurance, disintegration time, and in vitro dissolution rate. ***Results***: We selected the formula F1 sublingual film as the best, as it demonstrated a uniform thickness of 0.087mm, good flexibility, and a surface pH of 6.7. It disintegrated quickly in 13 seconds and had a faster in vitro dissolution rate (3 min) compared to the CLZ ordinary films. ***Conclusions***: The results confirmed the success of CLZ NS as a sublingual thin film for dissolution rate enhancement, which may improve oral bioavailability.

Keywords: Bioavailability, Clozapine, Nanosuspension, Sublingual film.

صياغة وتوصيف معلق كلوزابين النانوي كفيلم تحت اللسان

الخلاصة

الخلفية: كلوزابين (CLZ) هو دواء قوي مضاد للذهان يثبط أعراض الفصام والهوس. يصنف كلوزابين الفئة الثانية (BCS)؛ ويعزى ضعف التوافر الحيوي إلى عدم كفاية الذوبان في الماء وتأثير المرور الأول الواسع النطاق. **الهدف**: تحضير CLZ كمعلق نانوي (NS) لتحسين ذوبانه في الماء وتحميله في فيلم تحت اللسان لتعزيز التوافر الحيوي الفموي. **الطرق**: يتم تحضير معلقات النانو CLZ بطريقة "الترسيب المضاد للمذيبات المذيبة" باستخدام Soluplus كعامل استقرار. قمنا بتقييم مؤشر التشتت المتعدد (PDI) وحجم الجسيمات لتركيبات التعليق النانوي. تم تحميل الصيغة المحسنة للتعليق النانوي CLZ مباشرة على طبقة رقيقة تحت اللسان، مما يلغي الحاجة إلى التجفيف بالتجميد للتصلب من خلال نهج صب المذيبات. تميزت الأفلام تحت اللسان بالسماكة، ودرجة الحموضة السطحية، والقدرة على التحمل للطي، ووقت التفكك، ومعدل الذوبان في المختبر. النتائج: اخترنا فيلم الصيغة F1 تحت اللسان كأفضل فيلم ، حيث أظهر سمكا موحدا يبلغ 0.087 مم ، ومرونة جيدة ، ودرجة حموضة سطحية تبلغ 6.7. تفككت بسرعة في 13 ثانية وكان معدل ذوبان أسرع في المختبر (3 دقائق) مقارنة بأفلام CLZ العادية. الاستنتاجات: أكدت هذه النتائج نجاح CLZ NS كغشاء رقيق تحت اللسان لتعزيز معدل الذوبان ، مما قد يحسن التوافر البيولوجي عن طريق الفم. **النتائج**: اخترنا فيلم الصيغة F1 تحت اللسان كأفضل فيلم، حيث أظهر سمكا موحدا يبلغ 0.087 مم، ومرونة جيدة، ودرجة حموضة سطحية تبلغ 6.7. تفككت بسرعة في 13 ثانية وكان معدل ذوبان أسرع في المختبر (3 دقائق) مقارنة بأفلام CLZ العادية. **الاستنتاجات**: أكدت هذه النتائج نجاح CLZ NS كغشاء رقيق تحت اللسان لتعزيز معدل الذوبان، مما قد يحسن التوافر البيولوجي عن طريق الفم.

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INTRODUCTION

Clozapine (CLZ) is a potent antipsychotic drug that treats symptoms of schizophrenia, mania, and neuroleptic reactions and has good pharmacodynamic characteristics. "The Biopharmaceutics Classification System" places CLZ as a class II medication due to its poor aqueous solubility and excellent penetration through biological membranes. Its low solubility in water might hinder absorption, and its hepatic metabolism restricts its bioavailability [1]. However, clozapine exhibits significant biotransformation upon oral administration, which leads to a bioavailability of nearly less than 27%. Patients need to administer the medicine over a longer period of time due to the extensive hepatic metabolism of CLZ, which complicates oral administration for illness treatment. Therefore, addressing these issues is necessary to enhance CLZ bioavailability and minimize adverse effects. The design of a sublingual dosage form will enable sublingual drug delivery, which means inserting a drug under the tongue [3]. The sublingual area has many capillaries, which allow the drugs to reach circulation immediately without passing via the stomach, intestines, or liver [4]. Fast-dissolving sublingual film (FDSF) is prepared from a hydrophilic polymer and enables the dosage form to dissolve or disintegrate in the sublingual region of the mouth without the need for chewing or drinking within a minute [5]. FDSF will be beneficial and exhibit higher patient acceptance and convenience, particularly for pediatric, elderly, bedridden, anxious, and psychiatric patients [6]. To optimize the potential of CLZ sublingual mucosa absorption, CLZ nanosuspension (CLZ-NS) was prepared first before incorporation into FDSFs to increase the dissolution rate of CLZ. Nanosuspension is the colloidal dispersion of drug particles smaller than 1 µm, which is achieved by stabilizing the particles with an appropriate stabilizer. The dissolution rate is improved because of the increased surface area and saturated solubility that arise from reducing the particle size to the nanometer range [7].

METHODS

Materials

Clozapine (Kathy, China), Soluplus® and PVA (BASF SE, Germany), methanol (Thomas Baker, India), Hydroxy Propyl Methyl Cellulose HPMC E5 and E15 (Hyperchem, Hangzhou, China), Glycerine Fluka (Chemical AG, Switzerland), Tween 80 (Alpha Chemika, India), and PEG-400 (Mumbai, India).

Preparation of CLZ NS

CLZ nanosuspension was prepared by solvent anti-solvent. Briefly, 3 ml of an organic solvent (methanol, acetone, or ethanol) was used to dissolve 12.5 mg of CLZ. The antisolvent system is an aqueous solution with varying ratios of Soluplus added as a stabilizer. After that, the organic solution was injected drop by drop into the stabilizer aqueous solution at a rate that was done under stirring for one hour at 25±1 °C with varying mechanical agitation speeds (500 to 1500 rpm) using a magnetic stirrer to allow the organic solvent to evaporate [8]. Table 1 provides extensive information about the composition and various formula preparation conditions.

Table 1: The compositions of the prepared formulations of CLZ NS

Formula	Drug	Stabilizer	Ratio Drug:Stabilizer	Solvent	Speed (rpm)
A1	Clozapine (12.5 mg)	Soluplus®	1:1	Methanol	500
A2			1:2	Methanol	500
A3			1:3	Methanol	500
A4			1:4	Methanol	500
A5			1:5	Methanol	500
A6			1:3	Methanol	750
A7			1:3	Methanol	1000
A8			1:3	Methanol	1500
A9			1:3	Ethanol	1000
A10			1:3	Acetone	1000

Particle size and polydispersity index

A particle size (Malvern, UK), which measures variation in light scattering at room temperature with 90° as the scattering angle, was used to determine the average particle size and polydispersity index for all prepared formulas. Polymeric nanosuspension was dispersed appropriately and shaken well [9].

Saturation solubility determination

The best formula of CLZ NS was freeze-dried at a temperature of -50 °C and a pressure of 0.021mbar to obtain the powder form of the nanosuspension for the saturation solubility study. Pure drug and freeze-dried formula in excess amounts were added to different mediums (water and phosphate buffer (pH 6.8) with 1.5 and 1% w/v Brij-35, respectively) at room temperature and regularly shaken for 72 hours. The solutions were subjected to centrifugation, filtration, and UV spectrophotometer analysis. The absorbance of clozapine was measured in each medium at its maximum wavelength. [10].

Preparation of CLZ NS as FDSF

We developed sublingual films of pure CLZ and optimized CLZ nanosuspension using the solvent casting technique, employing hydrophilic polymers such as polyvinyl alcohol (PVA) and hydroxypropyl

methylcellulose E5 and E15. We dissolved an appropriate quantity of polymer in 10 ml of heated water at 60 °C, added 20% w/w plasticizer (polyethylene glycol 400 (PEG 400), glycerin, or propylene glycol) to the polymeric solution, continuously stirred with a magnetic stirrer for approximately 60 minutes to create a uniform polymeric solution, and then allowed the mixture to cool. The remaining excipients, such as cross-polyvidone, citric acid, tween 80, mannitol, and vanilla, were added to 2 ml of water and then mixed with the polymeric solution. Next, we mixed the optimized CLZ nanosuspension formula with the polymeric solution, stirred it for an additional hour, and set it aside to remove air bubbles. The obtained uniform solution was cast on a Petri dish (9cm) and dried overnight in a 40°C oven. Then, the film was removed from the petri dish and cut to an appropriate size (2 and 2 cm^2). An equivalent dose (6.25 mg) of CLZ was present in each film. After that, it was covered with aluminum foil for further analysis [11]. For an ordinary clozapine sublingual film containing pure clozapine, the same procedure was followed, but CLZ was added as a pure drug after dissolving in 3 mL of methanol and 5 mL of distilled water. The composition and quantities of each formula are shown in Table 2.

Table 2: Composition of clozapine nanosuspension fast dissolving sublingual film

Ingredients (mg)	Formula Code					
	F1	F2	F3	F4	F5	F*
Clozapine	6.25	6.25	6.25	6.25	6.25	6.25
Soloplus	18.75	18.75	18.75	18.75	18.75	-----
PVA	40	----	----	40	40	40
HPMC E5	----	40	----	----	----	----
HPMC E15	----	----	40	----	----	----
Cross povidone	2	2	2	2	2	2
PEG 400	8	8	8	----	----	8
Glycerin	----	----	----	8	----	----
PG	----	----	----	----	8	----
Citric Acid	2	2	2	2	2	2
Tween 80	2	2	2	2	2	2
Vanilla	2	2	2	2	2	2
Mannitol	9	9	9	9	9	9
Total Wt.	90	90	90	90	90	71.25

F*: The sublingual film contains pure clozapine

Characterization of FDSF

All produced sublingual film was examined for characteristics including surface, color, homogeneity, and transparency [12]. Ten films were weighed individually, and the average weight was determined. The accepted film weight should not significantly differ from the weighted average [13]. Using a magnetic stirrer, each film was dissolved in 10 mL of methanol for five minutes. The resultant liquid was diluted with a suitable volume of methanol. A UV spectrophotometer determined the CLZ content. The CLZ average content was calculated by applying the equation below [14].

Content uniformity= actual CLZ amount in FDSFs/theoretical CLZ amount in FDSFs × 100

We used a vernier caliper micrometer to measure each film's thickness at five distinct points (the center and four corners). The data were displayed as the mean ± SD of three assessments [15]. Folding endurance (the number of folds that can be made repeatedly at the same place without the film breaking) is used to assess the flexibility of sublingual films. Three films of each formulation were folded to test their durability, and the mean and standard deviation were noted [16]. The pH was measured using a pH meter by attaching the probe to a film dissolved in 2 mL of distilled water, and then the result was checked after a minute [17]. We determined the average of three measurements.

In-vitro disintegration time

This test was done using the Petri dish method; one film was placed on the Petri dish containing distilled water (2 ml), and the time required for the film to disintegrate completely was determined. This test was done for three films from each batch, and average values were calculated [18].

In vitro drug dissolution

The in vitro release of CLZ from the films was performed using the USP Drug Dissolution Apparatus II (paddle type). After precisely weighing each film, it was placed into dissolution containers with 500 ml of phosphate buffer (pH 6.8) and 1% w/v Brij-35, maintained at 37 ± 0.5 C and agitated at 50 rpm. To maintain the volume of the dissolving medium, 5 ml was withdrawn and replaced with an equal volume of fresh buffer at the designated intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 15 minutes. After filtering the withdrawn samples, analysis at 293 nm was used to determine the medication released [19,20].

Release kinetic models

Kinetic models were used to identify the best-fit model and release the kinetic mechanism. We assessed release data for the best formula, including Higuchi, zero-order, first-order, and Korsmeyer-Peppas, using a DD solver—a Microsoft Excel-based add-in program [20].

RESULTS

All the prepared CLZ nanosuspension formulations generated a particle size on the nanoscale. Formulas (A1-A5) were prepared at different ratios of the drug: soluplus (1:1, 1:2, 1:3, 1:4 and 1:5). As shown in Table 3 and Figure 1, a significant difference (p<0.05) was observed in the particle size among each ratio.

Table 3: The particle size and PDI of CLZ NS

Code	Particle size (nm)	PDI
A1	113.1	0.09
A2	100.9	0.14
A3	94.56	0.03
A4	98.1	0.14
A5	98.2	0.09
A6	87.32	0.01
A7	80.43	0.01
A8	104.2	0.21
A9	111.4	0.12
A10	85.2	0.08
A6	87.32	0.01

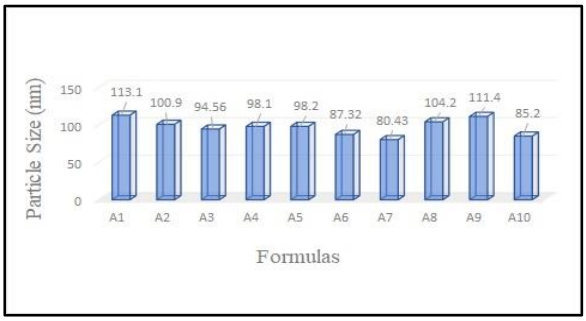

Figure 1: particle size of clozapine nanosuspensions.

Each ratio generates a distinct particle size. The results of particle size for formulas (A1-A5) were 113.1±1.48, 100.9±2.25, 94.56±0.706, 98.1±3.01, and 98.2±1.6 nm, respectively. The smallest particle (94.56±0.706 nm) size was obtained by a ratio of 1:3, represented by formula (A3), so this ratio was used to study the influence of other factors. To determine the effect of varying stirring speeds on the particle size of nanosuspension, formulas (A3 and A6-A8) were prepared using speeds ranging from 500 to 1500 rpm.

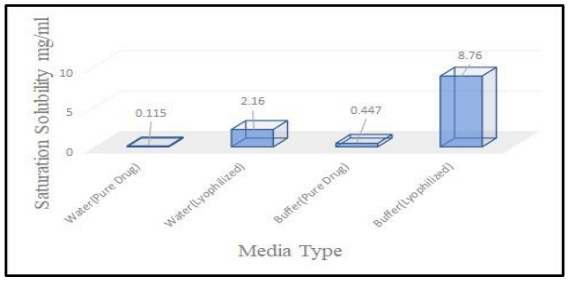

Figure 2: Saturation solubility of the pure clozapine and freeze-dried formula in water (1.5% Brij35) and phosphate buffer (1% Brij35).

As shown in Table 3 and Figure 1, the best result was obtained at a speed of 1000 rpm, represented by a formula (A7) that showed the smallest particle size (80.43 nm). The impact of organic solvent type on the particle size of CLZ nanosuspension was studied by formulas (A7, A9, and A10) using distinct solvents (methanol, ethanol, and acetone). The optimum solvent was methanol, which gave the smallest particle size (80.43±0.853 nm). The range of values for formulations' polydispersity index (PDI) typically was 0.01-0.21, as demonstrated in Table 3. The saturation solubility of the selected CLZ nanosuspension formula (A7) was studied in two different media (water and phosphate buffer), and the results demonstrated that clozapine solubility has increased significantly (p<0.05) in both media compared to the pure drug. Figure 2 shows that clozapine's water solubility increased from 0.115 to 2.16 mg/ml, while in phosphate buffer, the solubility increased from 0.447 to 8.76 mg/ml. Considering the outcomes, as mentioned earlier and taking into account the particle size and PDI, the most favorable characteristics were observed in formula A7, which exhibits a particle size of 80.43±0. 853 nm and a PDI of 0.01±0.002. Therefore, it was selected as the best formula and used for CLZ sublingual film preparation. All prepared CLZ sublingual films were subjected to several characterizations, including visual appearance, weight variation, drug content, the thickness of the film, folding endurance, surface pH, disintegration time, and in vitro drug dissolution. The results of these studies are summarized in Table 4.

Table 4: Some physicochemical properties of the prepared sublingual films of clozapine

Code	Weight of Film (mg)	Drug Content	Thickness (mm)	Folding Endurance	Surface pH	In vitro Dt (Sec)
F1	87±2.54	97.6±1.3	0.087±0.04	> 300	6.7± 0.1	13±1.9
F2	86±1.24	101.5±2.1	0.09±0.03	> 300	6.8 ±0.03	35±2.2
F3	88±0.66	94.9±1.5	0.09±0.03	> 300	6.9± 0.05	60±2.6
F4	83±2.38	93.6±2.3	0.092±0.031	> 300	6.7±0.05	18±1.0
F5	86±3.64	98±0.9	0.11±0.06	> 300	6.5± 0.11	22±1.6
F*	65±2.84	91±0.46	0.023±0.01	> 300	6.6 ± 0.1	75±2.3

After visual inspection, it was observed that all prepared formulas were uniform, homogenous, thin, with smooth textures, and translucent and tended to be yellow due to the color of the drug. The average weight of the sublingual films prepared with clozapine nanosuspension ranged from (65 ± 2.84mg) to (88 ± 0.66mg) mg, as shown in Table 4. Concerning the content uniformity, all the formulated films were practical and gave acceptable drug content (101.5±2.1 to 91±0.46). A vernier caliper micrometer was used to measure the thickness of the oral film that had CLZ NSs in it. It was found to be between 0.087±0.04 and 0.11±0.06 mm, while the thickness of the regular film was 0.023±0.01 mm, as shown in Table 4. The durability and flexibility of the sublingual film were determined by the folding endurance value; all clozapine nanosuspension sublingual films prepared displayed exceptional folding endurance of more than 300. To avoid any mucosal irritation, the surface pH of the sublingual films was measured and found to range from 6.5±0.11 to 6.9±0.07. The values of *in-vitro* disintegration time for clozapine nanosuspension films were evaluated, and the results ranged from 13±1.9 to 60±2.6 sec for CLZ NSs film, while for ordinary clozapine oral film, it was 75±2.3 sec. We assessed the dissolution of clozapine nanosuspension films and ordinary clozapine films using the USP dissolution test apparatus type II. The film (F1), composed of PVA as a polymer and PEG 400 as a plasticizer, exhibited a complete release within 3 minutes, as shown in Figure 3. Conversely, the PVA films, plasticized with glycerin (F4) and propylene glycol (F5), achieved a complete release within 4 minutes. The films containing HPMC E5 (F2) and HPMC E15 (F3) exhibited a complete release after 5 and 6 minutes, respectively. In contrast, the ordinary clozapine film (F*) demonstrated a release rate of only 26.8% during the same time frame. The study involved a comparison of the release patterns of films (F1, F4, and F5), as well as a pure clozapine film (F*)

that served as a reference. The similarity factor *f2* was utilized for this purpose.

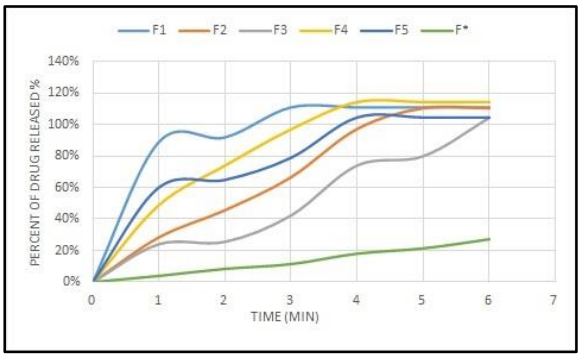

Figure 3: *In vitro* dissolution profile of the pure clozapine sublingual film and clozapine nanosuspension films in phosphate buffer (pH 6.8) containing 1% Brij35.

According to the data provided in Table 5, the obtained similarity factor values were found to be less than 50.

Table 5: Similarity factor *f2* values for the dissolution profiles of the sublingual films

Formulas name	*F*2 values	Formulas name	*F*2 values
F1 & F*	4.71	F1 & F4	37.88
F4 & F*	6.29	F1 & F5	35.5
F5 & F*	8.69	F4 & F5	48.36

Based on the above results, the formula (F1) was selected as the best formula regarding its acceptable appearance, weight, content uniformity, thickness, folding endurance, surface pH, quick disintegration time, and rapid dissolution rate, so it was used to determine the release kinetic mechanism. The dissolution profile of the selected clozapine nanosuspension sublingual film (F1) was fitted to different kinetic models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas models). The regression coefficient (R^2) was calculated for each model, as illustrated in Table 6. The highest R^2 (0.9487) value was seen with the first-order model, while the n value in the Korsmeyer-Peppas model that explains the drug release mechanism from the dosage form was 0.362.

DISCUSSION

The particle size and polydispersity index are essential characteristics because they impact nanoparticle release rate, bioavailability, and saturation solubility. The values for formulations' polydispersity index (PDI) typically ranged from 0.01 to 0.21; this means that all formulas were monodispersed, but the slight difference in the PDI values is highly related to the particle size; the larger particle size often generates a higher PDI [21]. Formulas A1-A5 were prepared at a ratio ranging from 1:1 to 1:5. As shown in Table 3 and Figure 1, the particle size decreases significantly (p<0.05) as the stabilizer ratio goes up. This suggests that the concentration of polymer is high enough to cover the nanoparticles [22]. Once we reached a ratio of 1:4, the particle size began to increase again. This might be explained by a rise in the viscosity of the anti-solvent solution, which could obstruct particle mobility and cause extra drug particle coating. These results were in agreement with Dora *et al*. [23]. Formulas A3 and A6-A8 were prepared at varying agitation speeds. As shown in Figure 1, the particle size decreased as the speed increased from 500 rpm to 1000 rpm. This can be explained by faster stirring rates, allowing the organic solvent to permeate the water phase more quickly and shear mixing more efficiently, leading to the rapid nucleation and formation of tiny drug particles [22]. While a high mixing speed will decrease the particle size, it may also increase the possibility of aggregation, increasing the particle size and accelerating the suspension's sedimentation rate, as happened in the case of 1500 rpm [24]. Using different organic solvents (methanol, ethanol, and acetone) in formulas A7, A9, and A10 demonstrated that methanol was the best solvent, providing the smallest size and controlling the number of crystal nuclei formation [25]. Using different organic solvents (methanol, ethanol, and acetone) in the formulas A7, A9, and A10 demonstrated that methanol was the best solvent by giving the smallest size by controlling the number of crystal nuclei formation [26]. According to the results of the particle size and polydispersity index study of the nanosuspension, formula A7 was selected as the optimized formula due to its smallest particle size (80.43±0. 853 nm) and lowest PDI (0.01±0.002), so it was used to prepare FDSF and its saturation solubility was determined. The saturation solubility study demonstrated a significant enhancement of drug solubility in both media (water and phosphate buffer) compared to the pure drug. In water, the solubility increased by about 18.7 times compared to pure drug, whereas in phosphate buffer, the enhancement was about 19.5 fold higher than pure drug. The enhancement in saturation solubility may be attributed to the increase in surface area due to the reduction in particle size. Concerning the sublingual films, the average weight of all sublingual films was acceptable. Only a slight difference was found in weight between ordinary CLZ films and CLZ nanosuspension films. This is because of the lack of stabilizer (Soluplus) in ordinary CLZ films. The very low standard deviation (SD) values indicate the uniformity of the film weight [27]. This study found that the thickness of the oral film with CLZ NSs was between 0.087±0.04 and 0.11±0.06 mm, while the thickness of the regular film was (0.023±0.01) mm, as shown in Table 4. The difference in thickness is due to the concentration of the excipient used in the formulation and the lack of a stabilizer (Soluplus®) in the regular CLZ films [14]. As Table 4 outlined, each film demonstrated a folding endurance of more than 300, indicating an acceptable result [28]. The surface pH of the sublingual films was measured and found to range from 6.5±0.11 to 6.9±0.07. Since these pH values are close to those of the oral mucosa, they don't cause any irritation [29]. The values of in vitro disintegration time for clozapine nanosuspension films ranged from 13±1.9 to 60±2.6 sec, and for ordinary clozapine oral film, it was 75±2.3 sec. There was a significant difference (p<0.05) between CLZ NS films and ordinary films, which

have the longest *in vitro* disintegration time (75±2.3 sec). CLZ sublingual films prepared with PVA had the shortest in vitro disintegration time compared to those made with HPMC E5 and HPMC E15, which had the longest disintegration time [30,31]. Regarding the in-vitro dissolution assessment, as depicted in Figure 3, formula F1 (PVA) required the shortest time for complete drug release (3 minutes). Along with PVA's high solubility, the polymer swelled more quickly and more extensively, which let more dissolution media enter the matrix and break up the drug particles more quickly [32]. Formulas F2 (HPMC E5) and F3 (HPMC E15) showed a complete release of the drug in 5 and 6 minutes, respectively. The difference in the viscosity grades of the HPMC film-forming polymer caused this slight difference in the drug release between F2 and F3. It takes longer for HPMC to release drugs than PVA does. This is because HPMC polymers control drug diffusion by making a gel layer that stops drug diffusion when they come into contact with liquid. Consequently, the viscosity increased, and the process slowed down [3 3]. The films plasticized with PEG400 had better drug release profiles than other plasticizers. This may be because the PEG400, when submerged in the dissolution medium, quickly leaches out of the film, leaving void spaces for drug diffusion, which optimizes the drug release profile. Also, PEG400's water vapor transmission, which determines the film's permeability, is higher than that of others [34]. The DD solver, a Microsoft Excel-based add-in program, yielded the highest R2 value for the selected clozapine nanosuspension sublingual film (F1), as shown in Table 6.

Table 6: Kinetic analysis data of release of CLZ nanosuspension sublingual film

R^2 value				n-value
Zero order	First order	Higuchi	Korsmeyer-Peppas	
0.0886	0.9487	0.7656	0.9889	0.142

This suggests that the dissolution behavior of CLZ NS sublingual film follows the first-order kinetic release. In the first order, the dissolution rate depends on the concentration gradient. The n value in the Korsmeyer-Peppas model explains the drug release mechanism from the CLZ NSs sublingual film. The value (n) represents the release exponent, which indicates the method of drug transport through the polymer. When $n < 0.5$, these represent Fickian diffusion since the n value was 0.362, which indicates that the release of CLZ NP sublingual film exhibits Fickian diffusion.

Conclusion

Preparing CLZ as NS improves its water solubility and dissolution rate by reducing particle size, and it outperforms commercially available preparations. Because the medicine enters systemic circulation directly, the strategy described below may improve bioavailability. The prepared CLZ-NS-FDSFs had a uniform thickness, good flexibility, quick disintegration, and outstanding dissolution properties. As a result, NS-FDSFs appear to be a potential strategy for increasing dissolving rate and bioavailability.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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