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Research Article

Preparation and Optimization of Olanzapine as Transdermal Nanoparticles Delivery System

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Abstract

Background: The treatment of schizophrenia typically involves the use of olanzapine (OLZ), a typical antipsychotic drug that has poor oral bioavailability due to its low solubility and first-pass effect. ***Objective***: To prepare and optimize OLZ as nanoparticles for transdermal delivery to avoid problems with oral administration. ***Methods***: The nanoprecipitation technique was applied for the preparation of eight OLZ nanoparticles by using different polymers with various ratios. Nanoparticles were evaluated using different methods, including particle size, polydispersity index (PDI), entrapment efficiency (EE%), zeta potential and an in vitro release study. The morphology was evaluated by a field emission scanning electron microscope (FESEM) and an atomic force microscope (AFM). We also perform differential scanning calorimetry (DSC). ***Results***: Characterization studies of OLZ nanoparticles showed that OLZ-6 was the best formula with a particle size of 115.76 nm, a PDI of 0.24, a high EE% of 78.4%, and a high zeta potential of -19.01 mV. The in vitro release of OLZ was higher than that of other formulations. FESEM reveals the spherical shape of the nanoparticles, and AFM screening confirms that the OLZ-6 size is comparable to what the Zeta sizer finds. The DSC results confirm the purity of OLZ and the compatibility between the drug and polymer. ***Conclusions***: OLZ-6, as a transdermal delivery system, is a promising formula to overcome the problems associated with oral drug administration and could enhance its bioavailability.

Keywords: Nanoparticles, Nanoprecipitation, Olanzapine, Polymers, Solubility.

تحضير وتحسين الاولانزابين كنظام جسيمات نانومترية عبر الجلد لعلاج الفصام

الخلاصة

الخلفية: أولانزابين (OLZ) يُصنف كدواء مضاد للذهان ويستخدم لعلاج الفصام، يمتلك توافر حيوي ضعيف 60% بسبب قلة الذوبان و الأيض الكبدي للمرور الاول. **الهدف:** يهدف العمل الحالي الى تحضير وتحسين OLZ كجسيمات نانومترية للتسليم عبر الجلد لتفادي المشاكل المرتبطة بالأدوية عن طريق الفم. **الطرق**: تقنية الترسيب النانوي تم تطبيقها لتحضير ثمانية جسيمات نانومترية من OLZ باستخدام بوليمرات مختلفة و بنسب مختلفة. تم تقييم الجسيمات النانومترية من خلال دراسات توصيف مختلفة مثل حجم الجسيمات، ومؤشر تعدد التشتت (PDI)، وكفاءة الانحباس (EE٪)، جهد الزيتا ودراسة تحرر الدواء في المختبر. تم فحص شكل الجسيمات النانومترية بواسطة المجهر الإلكتروني الماسح للانبعاثات الميدانية (FESEM)، ومجهر القوة الذرية (AFM) كما تم إجراء قياس السعرات الحرارية بالمسح التفاضلي (DSC). **النتائج**: نتائج دراسات توصيف جسيمات OLZ النانومترية تشيير أن الصيغة الأمثل لجسيمات OLZ النانومترية كانت OLZ-6 بسبب حجم الجسيمات المقبول (115.76 نانومتر)، PDI (0,24)، ارتفاع EE٪(78,4%)، جهد الزيتا العالي (-19.01 مللي فولت)، كان تحرر الدواء في المختبر عالي ومعنوياً بالمقارنة مع المستحضرات الأخرى والأدوية النقية. يُظهر FESEM الشكل الكروي للجسيمات النانوية، وكشف فحص AFM أن حجم OLZ-6 كان مشابهًا للحجم الذي تم الحصول عليه بواسطة zeta sizer. تؤكد نتائج DSC نقاء OLZ ووجود التوافق بين الدواء والبوليمر. **الاستنتاجات** : يمكن أن نستنتج أن OLZ-6 يعتبر صيغة واعدة للتغلب على المشاكل المرتبطة بتناول الدواء عن طريق الفم ويمكن أن يعزز التوافر الحيوي للدواء، عند تحضيره كجسيمات نانوية دقيقة مذابة للتسليم عبر الجلد في المستقبل.

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INTRODUCTION

The oral route is considered the most prevalent route for administering drugs to patients in order to achieve local or systemic action. Oral traditional dosage forms are manufactured to provide immediate therapeutic activity after administration. Furthermore, the oral route has advantages such as better patient compliance, self-administration, a safe route, low cost, and doesn't require a sterile environment [1]. Despite their obvious advantages, conventional oral formulations may exhibit limitations such as erratic drug absorption, which may be due to poor aqueous solubility, a specific absorption window, drug instability, or hydrolysis in the gastrointestinal tract (GIT) [2]. Other limitations include dose dumping, dose repeating, fluctuations in plasma drug levels, premature elimination, and the fact that some drugs suffer from extensive first-pass hepatic metabolism due to the low bioavailability of traditional oral medications [3]. Therefore, researchers have developed an advanced transdermal drug delivery system to circumvent the issues associated with oral administration. This system has garnered significant attention due to its capacity to enhance patient compliance by reducing pain associated with hypodermic needle usage, circumventing first-pass hepatic metabolism, enabling self-administration, and providing protection against enzymatic drug degradation [4]. Nanoparticle-loaded drugs are the most promising tool for administering drugs through the skin. Nanoparticles, as colloidal dispersions, have a size range of 10–1000 nm, in which the drug may be dissolved, entrapped, or encapsulated and sometimes the drug adheres to the matrix of the nanoparticle [5]. Due to their advantages, such as improved dissolution rate, controlled drug release, higher loading, delivery to the target size, and protection against enzymatic degradation, nanoparticle-loaded drugs represent an advanced system for the delivery of several drugs for the treatment of different diseases [6]. Nanoparticles offer numerous benefits for drug delivery, including enhanced solubility, stability, targeting, and improved permeation through the biological membrane [7]. OLZ is a typical antipsychotic drug with a molecular weight of 312.44 g/mol and a molecular formula of $C_{17}H_{20}N_4S$. OLZ has low oral bioavailability (60%), which is due to poor solubility and extensive first-pass hepatic metabolism [8]. So, the purpose of this work is to prepare and optimize OLZ as nanoparticles for transdermal delivery, which could enhance its bioavailability and improve patient compliance, in addition to the ease of administering OLZ to schizophrenic patients.

METHODS

Materials

A free sample of pure OLZ for laboratory use was obtained from Hyperchem in China. We obtained polymers such as polyvinyl alcohol (PVA) from Rhom Pharma, Germany. Polyvinylpyrrolidone (PVP) with different molecular weights, like PVP-K15 and PVP-K30, was purchased from Provizer Pharma, India. Soluplus® polymer was purchased from BASF, Germany. The methanol solvent was sourced from Sigma-Aldrich, Germany. We used all other solvents and chemicals of analytical grade.

Preparation of OLZ nanoparticles

OLZ nanoparticles were prepared by the bottom-up technique, which is the nanoprecipitation technique. This technique involves using an organic solvent, specifically absolute methanol (3 ml), to dissolve OLZ (10 mg). Next, a syringe pump drops the organic phase at a rate of 1 ml/min into an aqueous phase (30 ml), which is composed of deionized water with stabilizer. The dropping process occurs under continuous stirring (600 rpm), and the resulting nanosuspension precipitates instantaneously. In order to evaporate the organic solvent [9], The composition and variables of the OLZ nanoparticle are listed in Table 1.

Table 1: Composition and variables of OLZ nanoparticles.

Formula Code	OLZ (mg)	Polymer (Stabilizer)	Amount (mg)	D:P ratio	O:A ratio
OLZ-1	10	PVP-K30	10	1:1	3:30
OLZ-2	10	PVP-K30	20	1:2	3:30
OLZ-3	10	PVP-K15	10	1:1	3:30
OLZ-4	10	PVP-K15	20	1:2	3:30
OLZ-5	10	Soluplus®	10	1:1	3:30
OLZ-6	10	Soluplus®	20	1:2	3:30
OLZ-7	10	PVA	10	1:1	3:30
OLZ-8	10	PVA	20	1:2	3:30

OLZ: olanzapine; D:P, drug:polymer ratio; O:A, organic:aqueous ratio.

Characterization of OLZ Nanoparticles

The particle size and PDI were analyzed using a Zeta sizer instrument (Malvern, UK). The particle size was measured by the apparatus through the determination of the intensity of light scattered by particles present in the sample with a scattered angle of 90° at room temperature. The PDI was analyzed and is responsible for uniformity and particle size distribution within the sample [10]. A triplicate measurement was done. A zetasizer instrument (Malvern, UK) screened the zeta potential of the prepared formulations, and the values provided insight into the stability of the nanosuspension [11]. The indirect method was utilized to estimate the entrapment efficiency of OLZ nanodispersion. This method involves the estimation of free OLZ concentration in dispersion medium and is performed by placing 5 ml of drug nanosuspension in an Amicon® Ultra Centrifugal tube with a molecular cutoff (MWCO) of 10 kDa, followed by centrifugation at 3000 rpm for 20 min. The concentration of unentrapped OLZ present in ultrafiltration was diluted and determined spectophotometrically at 270 nm by using the following equation [12].

$$EE\% = \frac{WT-WF}{WT} X100 \ldots \text{Eq. 1}$$

Where, WT is the (total) initial weight of drug used, WF is weight of free OLZ that measured in the supernatant layer after ultrafiltration. The measurement was performed in triplicate and the values expressed as mean±SD.

In vitro release study

In vitro release of OLZ powder and its nanodispersion was performed by placing a suitable volume (9 ml) of OLZ nanodispersion containing 3 mg of drug and 3 mg of pure drug in a dialysis bag 8000–14000 Da (Hi Media Lab Pvt. Ltd., India). [13]. Followed by immersing the sealed bag in 500 ml of phosphate buffer pH 7.4 that contains 0.2% tween 20, drug release was done by the dissolution apparatus USP-II (paddle) at 37°C± 0.5 with a rotating speed of 50 rpm. A specified sample volume (5 ml) was taken at intervals of (5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 min), and each withdrawn volume was replenished by buffer to preserve sink condition. Then, samples were filtered by membrane (0.45 µm) and drug concentration was measured spectrophotometrically at the λ max of the drug [14]. A triplicate measurement was done.

Surface morphology of nanoparticle

Morphology screening of OLZ nanoparticles was made by using field emission scanning electron microscope FESEM (HITACHI S–4160, Japan), and atomic force microscope AFM (Nanosurf, Switzerland).

Powder X-ray diffraction study

Powder X-ray diffraction analysis of pure OLZ, a physical mixture of drug and polymer and OLZ nanoparticles was made to determine the crystallinity nature of these samples. We performed the analysis using X-ray diffractometery (XRD-6000, Shimadzu, Japan), operating at 30 mA and 40 kV, respectively. Scanning of samples was done at 2 Theta from 0-80° at a scanning rate of 5°/min [15].

Differential scanning calorimetry (DSC)

DSC is a thermal analysis technique that involves placing a quantity (5mg) of pure OLZ powder, a physical mixture of (drug: polymer), and a selected lyophilized formula in the aluminum pan of the DSC-60 Shimadzu, Japan, and heating it at a rate of 10°C/min at a temperature of 50 to 250 °C with a nitrogen flow of 40 ml/min.

Statistical analysis

Data from at least three independent experiments were analyzed using Excel 2016. All means are reported with a standard deviation. We performed a one-way analysis of variance (ANOVA) as appropriate. Statistical significance was defined as $p < 0.05$.

RESULTS

Depending on the characterization studies of OLZ nanoparticles, the results of measuring particle size and PDI exhibited that nanoparticle size was in the range 73.98 to 171.8 nm and PDI range was 0.152 to 0.385 (Table 2 and Figure 1).

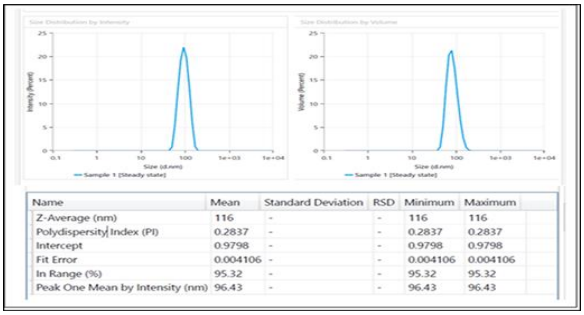

Figure 1: Particle size of optimized formula of nanoparticle (OLZ-6).

The investigation into the relationship between the drug:polymer ratio and particle size revealed a strong link (p<0.05) between the two. For example, OLZ-1, OLZ-3, OLZ-5, and OLZ-7 with a ratio of (1:1) had smaller particles than OLZ-2, OLZ-4, OLZ-6, and OLZ-8 with a ratio of (1:2) (Table 2). Zeta potential is a physical property of nanodispersion; it represents the potential difference between the bulk solution (dispersing medium) and the hydrodynamic shear's surface (slipping plane) [18]. The results show lower zeta potential values for all OLZ nanoparticle formulations; the zeta potential values ranged from -5.59 to -19.01 mV (Table 2 and Figure 2).

Table 2: Particle size, PDI, Zeta potential and entrapment efficiency of OLZ nanoparticles

Formula Code	Particle size (nm)	PDI	Zeta potential (mV)	EE%
OLZ-1	80.51±3.24	0.176±0.13	-7.04±0.12	56.4±2.21
OLZ-2	88.95±1.81	0.316±0.05	-13.1±0.15	71.6±6.43
OLZ-3	88.12±11.5	0.267±0.02	-5.59±0.09	56.2±3.78
OLZ-4	98.32±4.66	0.282±0.18	-17.09±2.1	73.6±6.11
OLZ-5	73.98±8.84	0.152±0.10	-13.11±1.3	68.2±4.87
OLZ-6	115.76±5.45	0.240±0.070	-19.01±1.8	78.4±5.46
OLZ-7	111.73±16	0.242±0.065	-10.65±0.23	65.3±2.67
OLZ-8	171.8±35.5	0.385±0.325	-16.2±0.78	72.6±6.93

Values were expressed as mean±SD; n=3.

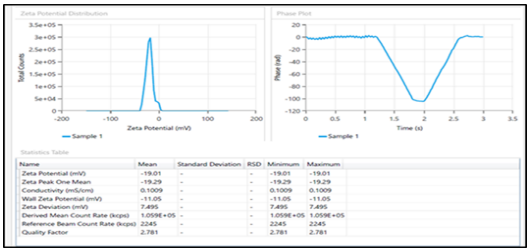

Figure 2: Zeta potential of optimized formula of nanoparticle (OLZ-6).

The entrapment efficiency (EE%) of nanoparticles indicates a relationship between the ratio of polymer and EE%; this can be described as the ratio of polymer raised, and the entrapment efficiency increased significantly (P<0.05). Table 2 explains the rise in EE% as the stabilizer ratio increased from (1:1) to (1:2) for all types of polymers used in the preparation of OLZ nanoparticles. We subjected the selected formulations OLZ-2, OLZ-4, OLZ-6, and OLZ-8 with different types of polymers to in vitro release screening based on characterization studies of drug nanoparticles, which include particle size, zeta potential, and entrapment efficiency. These formulations exhibited good particle size and high EE% compared to other formulations. *In*

vitro release of formulations was performed in phosphate buffer pH 7.4 with 0.2% tween 20 to promote drug solubility and preserve sink conditions [19]. The results give an indication that all formulations possess a higher and more significant release (p<0.05) when compared with pure drugs. Figure 3 explains the *in vitro* release profile of OLZ nanodispersion. After studying different types of OLZ nanoparticles and their properties, such as particle size, PDI, entrapment efficiency, and zeta potential, it was found that OLZ-6, which is made up of (OLZ: Soluplus®) in a 1:2 ratio, was the best formula.

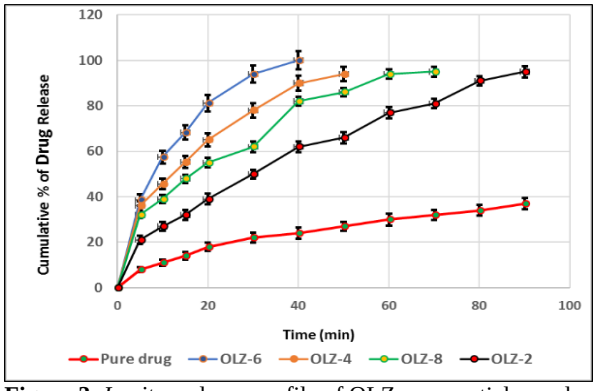

Figure 3: *In vitro* release profile of OLZ nanoparticles and pure drug.

This is because it had the smallest particle size (115.76 nm) compared to other formulations, the highest entrapment efficiency (78.4%), the most uniform distribution of particle size within the formula (PDI = 0.24), the highest zeta potential (-19.01 mV) compared to other formulations, and it released more drug (p<0.05) compared to other formulations and pure drug. The surface morphology of the OLZ nanoparticle that was screened by a field emission scanning electron microscope (FESEM) was spherical in shape, as shown in Figure 4.

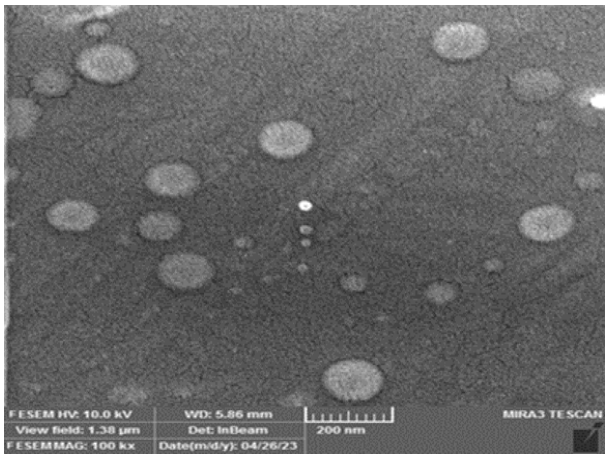

Figure 4: FESEM of optimized formula OLZ-6.

The atomic force microscope confirms that the Zeta sizer approximates the size of the nanoparticle (OLZ-6), as depicted in Figures 5 and 6. The pure OLZ X-ray diffractogram showed a sharp peak with high intensity at angles 2 Theta of 9°, 20°, 21°, 22°, and 24°, indicating the drug's crystalline nature. Figure 7 explains the X-ray diffractograms of the pure drug, physical mixture, and OLZ-NP. The results of DSC screening show a sharp endothermic peak for pure powder OLZ at 198.38 °C, which represents the melting point of OLZ and is identical to the reference readings (196 °C to 198 °C) [20,21].

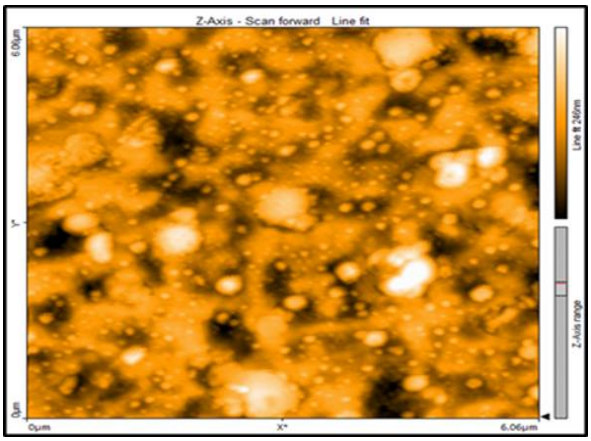

Figure 5: AFM picture of optimized formula OLZ-6.

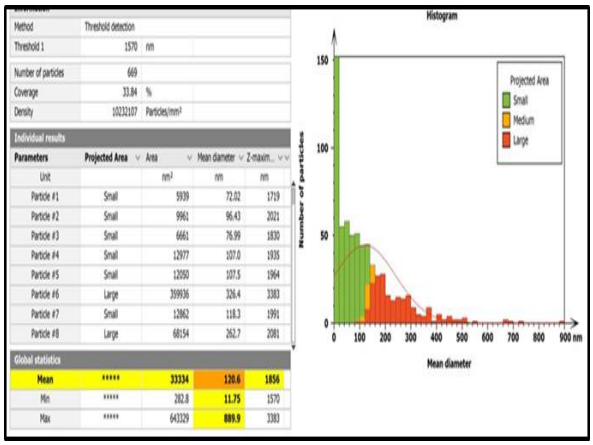

Figure 6: Histogram of mean particle size distribution of optimized formula OLZ-6.

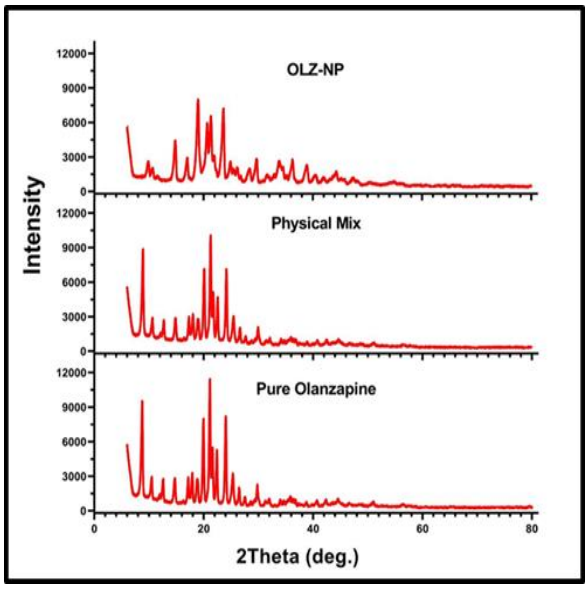

Figure7: X-ray diffraction of pure OLZ, physical mixture (drug: soluplus®) and OLZ nanoparticle (OLZ-NP).

The DSC thermograms of pure OLZ, a physical mixture of (drug: polymer), and OLZ nanoparticle OLZ-6 are explained in Figures 8A–C, respectively.

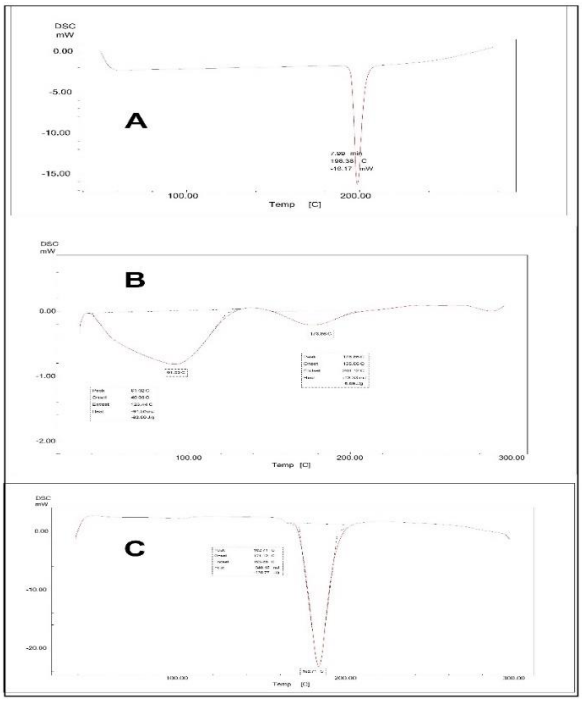

Figure 8: DSC thermogram, A) OLZ pure powder, B) physical mixture of (OLZ: Soluplus®), and C) OLZ nanoparticles (OLZ-6).

DISCUSSION

The size of all formulated OLZ nanoparticles that were formulated by different polymers was at the nanoscale level. Concerning PDI, it's regarded as an essential investigation about the distribution and uniformity of drug nanoparticles within a sample. When the values of PDI in the range (0.0–0.05) are considered monodisperse standards, (0.05–0.08) the sample is nearly monodispersing, (0.08–0.7) is mid-range polydispersity and more than 0.7 is very polysiperse. So, based on PDI results, OLZ nanoparticles are considered to have mid-range polydispersity because PDI values are less than 0.7 [22]. The effect of the drug:It is shown that the OLZ nanoparticle gets bigger as the amount of polymer increases. This might be because more stabilizer makes the solution thicker, which makes it harder for particles to move around in it and stops newly formed nanoparticles from being better covered. Having a lot of stabilizer also makes the coat that covers the nanoparticle thicker and stops the diffusion between solvent and antisolvent during the precipitation of nanoparticles [23,24]. Zeta potential manifested the degree of repulsion between adjacent and similarly charged particles in a dispersion medium. When stabilization is based on steric stabilizers, the measured zeta potential is lower because the adsorption layer of the stabilizer shifts the plane of shear, in which the zeta potential is measured, to a far distance from the particle surface. As a result, the zeta potential value (-19.01 mV) in nanoparticle OLZ-5 was sufficient for stabilization due to the steric effect [25]. There was an increase in entrapment efficiency when the polymer amount was raised. The explanation for this process is that when the stabilizer ratio was raised, the attachment of the polymer into the nanoparticle shell would be improved, thereby promoting the viscosity of the stabilizer solution and thereby slowing the diffusion of the drug into the external phase, resulting in good entrapment efficiency [26,27]. The dissolution rate of particles is regarded as a function of the surface area of the particle and this is explained by the Noyes-Whitney equation, which states that as the size of the particle decreases, the solubility will increase, thereby enhancing the dissolution rate. This description is compatible with gained by Ali *et al*. (2019), when they formulate a nanosuspension of atorvastatin calcium using different polymers by the nanoprecipitation method, and the results revealed an improvement in the dissolution rate of a pure drug when formulated as a nanoparticle, and the cumulative release was 44% and 90% for the pure drug and the formulated nanoparticle, respectively [28]. Additionally, the type of polymer influences the release of drugs from nanoparticles, which is dependent on the drug-polymer interaction and the mechanical characteristics of the polymer. Soluplus®, a co-polymer with amphipathic characteristics, functions as a wetting agent and surfactant, thereby reducing the interfacial tension between the OLZ nanoparticle surface and the anti-solvent. So, soluplus® lets water interact with the surface, which keeps the smallest nanoparticles while OLZ dissolves and is released more quickly than with other polymers. This is why OLZ-6 with soluplus® stabilizer showed a higher and more significant drug release ($P<0.05$) than pure OLZ and other formulations of PVP-K15, PVP-K30, and PVA. [29] The atomic force microscope confirms the spherical shape of nanoparticles and the size of the nanoparticle (OLZ-6) is approximated by the size obtained by the Zeta sizer. The OLZ X-ray diffractogram showed that the OLZ nanoparticle (OLZ-NP) has some sharp peaks that disappear, mainly two tetra of 9°, 21°, and 22°, and the intensity of other peaks goes down. This means that the crystallinity of OLZ has gone down [30,31]. The DSC results of the lyophilized nanoparticle OLZ-6 showed a wide endothermic peak that shifted, indicating a reduction in the crystallinity of OLZ through the use of different nanoparticle formulations.

Conclusion

The best nanoparticle formula, OLZ-6, is made up of 10 mg of OLZ and 20 mg of Soluplus®. It has good particle size, entrapment efficiency, and zeta potential, which are enough to keep the delivery system stable because the polymer creates steric hindrance. Additionally, this formula demonstrates higher and more significant drug release compared to the pure drug. So, the optimized formula (OLZ-6) can be considered a promising formula to improve the bioavailability of OLZ when formulated as a dissolved microneedle in the future.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

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

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