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# Preparation and characterization of Posaconazole as a Nano-micelles using d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) #

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## Abstract

Posaconazole (POCZ) is a newly developed extended-spectrum triazole that belongs to BCS class II. In patients with a weakened immune system, POCZ has been shown to be effective as an antifungal treatment for invasive infections caused by Candida and Aspergillus species. The aim of this study is the formulation of POCZ nano-micelles by using d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) to increase the solubility of practically insoluble POCZ. In order to increase their apparent solubility in water, nano-micelles are made by combining macromolecules that self-assemble into ordered structures capable of entrapping hydrophobic drug molecules in the interior domain. Dispersed colloidal systems, of which Nano-micelles are a subset, are a large and diverse group. POCZ nano-micelles are made with TPGS and tween 80. Six formulations were prepared and analyzed their micelles size, polydispersity index (PDI), entrapment efficiency (EE), drug loadings (DL), saturation solubility, and in-vitro release. The drug-loaded nano-micelles of the Posaconazole formula coded (POCZ6) were characterized, and their properties were found to be: micelles size (95.6±4.9 nm), PDI (0.34±0.09), EE (94.3±1.69%), DL (10.3%), and best solubility factor (1144). All POCZ formula contained TPGS: tween80 at (1:5:3) ratio showed better solubility than the pure drug. An in-vitro release study was conducted, and the results showed that the chosen formula POCZ6 released the entire dose of drug in 70 minutes, compared to only 23% for pure drug.

**Key words: Posaconazole (POCZ). Nano-micelles, Critical micelles concentration (CMC).**

# تحضير وتقييم البوساكونازول كمذيلات نانوية باستعمال الفا توكوفيريل بولي اثيلين كلايكول ١٠٠٠ سكسنيت #

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**الخلاصة**

البوساكونازول (POCZ) هو تريازول ممتد الطيف تم تطويره حديثا وينتمي إلى نظام التصنيف الحيوي من الفئة الثانية ولديه قابلية ذوبان قليلة. في المرضى الذين يعانون من ضعف الجهاز المناعي، ثبت أن البوساكونازول فعال كعلاج مضاد للفطريات للعدوى الغازية الناجمة عن أنواع المبيضات والرخيات في المرضى الذين يعانون من ضعف الجهاز المناعي. يمكن استخدام تقنية المذيلات النانوية لزيادة قابلية الذوبان البوساكونازول. من أجل زيادة قابليتها للذوبان الظاهرة في الماء، تصنع الجزيئات النانوية من خلال الجمع بين الجزيئات الكبيرة التي يتم تجميعها ذاتيا في هياكل مرتبة قادرة على استيعاب جزيئات الادوية الكارهة للماء في المجال الداخلي. الأنظمة الغروية المشتتة، والتي تعد السيلات النانوية مجموعة فرعية منها، هي مجموعة كبيرة ومتنوعة. تتكون من مرحلة منتشرة في حد ذاتها في جميع أنحاء الوسط (المرحلة المستمرة). تشكل المواد الخافضة للتوتر السطحي محلولا غروانيا عندما يكون تركيزها في المحلول أعلى من تركيزها الحرج (CMC). تصنع المذيلات النانوية من TPGS و80 tween. في هذه الدراسة، تم اعداد ست تركيبات مختلفة وتم تحليل حجم الجسيمات، ومؤشر التشتت المتعدد (PDI)، وكفاءة التحميل (EE)، وتحميل الأدوية (DL)، وقابلية الذوبان في التشبع، وتحرر الدواء في المختبر. تميزت الميسيل النانوية المحملة بالدواء لصيغة بوساكونازول ذ ات الترميز (POCZ6)، ووجد أن خصائصها هي: حجم الجسيمات ( 95.6±4.9نانومتر)، (0.34±0.09) PDI، 94.3±1.69 %EE(، DL (١٠,٣٪)، وأفضل عامل ذوبان (1144) كلها أفضل في TPGS: Tween80 (١:٥:٣) نسبة من الدواء النقي. أجريت دراسة تحرر الدواء في المختبر، وأظهرت النتائج أن الصيغة المختارة POCZ6 أطلقت الجرعة الكاملة من الدواء في ٧٠ دقيقة، مقارنة بنسبة ٢٣٪ فقط للدواء النقي.

**الكلمات المفتاحية: البوساكونازول، المذيلات النانوية، التركيز الحرج للمذيلات النانوية**

## Introduction

There are both quantitative and qualitative ways to characterize drug solubility [(1, 2)]. Quantitative solubility refers to how many grams of drug particles are needed to reach saturation in solution at a given temperature [(3, 4)]. A qualitative definition of solubility would be the ability of two phases to combine into a single phase. Large number of drug molecules are classified as class II (low solubility and high permeability) and have poor bioavailability because of their inability to dissolve completely [(5)].

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Methods that improve the solubility of poorly water-soluble drugs can be used to increase the bioavailability of class II drugs and produce the desired clinical efficacy. Increased apparent solubility in water was achieved through the formulation of nano-micelles using large molecular weight molecules that self-assembled into vesicle-like structures with an outer hydrophilic shell and an inner lipophilic core [6-9] .When surfactants are present in concentrations above their CMC, they form micelles and the solution becomes a colloidal suspension. The critical micelle concentration (CMC) is the lowest concentration at which micellization of an amphiphilic molecule can begin; this varies depending on the monomer. [10, 11])

Posaconazole is a triazole antifungal medication that is used to treat and prevent various fungal infections[12]. It is known for its broad spectrum of activity against a wide range of fungal pathogens and its effectiveness against drug-resistant strains. One of the challenges in using Posaconazole is its poor solubility, which can limit its bioavailability and effectiveness [13, 14]. POCZ can be formulated as nano-micelles by using TPGS and Tween80 to form mixed nano-micelles with hydrophobic inner core and hydrophilic shell, so these vesicles can entrap POCZ and can increase POCZ solubility as shown in Figure (1).

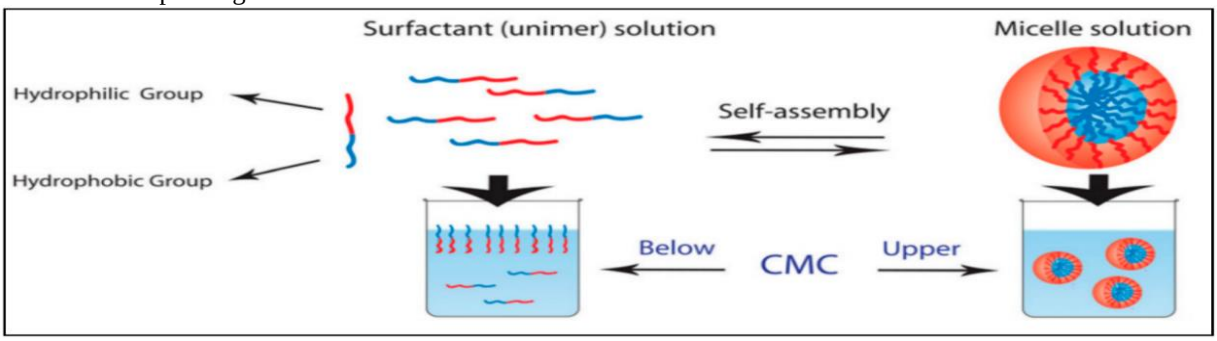



**Figure 1.Formulation and Structure of Nano-micelles [15] .**

## Materials and Method

Posaconazole (POCZ), d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) were purchased from Hangzhou, Hyperchem (China). Tween 80 from Indiamart (India), methanol from Alphachemica(India).

***Methods***

***Determination of critical micelles concentration***

To find the critical micelle concentration, iodine was used as a hydrophobic probe. 500 milligrams of potassium iodide and 250 milligrams of iodine were solubilized in 25 milliliters of deionized water to form a standard KI-I2 solution. In the dark, 25 microliters of a standard KI-I2 solution were added to a series of TPGS dilutions in deionized water (50µg/ml, 100µg/ml, 150µg/ml, 200µg/ml, 250µg/ml, 300µg/ml). TPGS concentration was plotted against UV absorbance measured at 366 nm for all samples. The concentration of TPGS at which absorption increases dramatically is called the critical micelle concentration. [16]

***Preparation of Posaconazole loaded nano-micelles***

POCZ nano-micelles were made by the thin-film hydration technique. In 30 mL methanol, all ingredients (POCZ, TPGS, and tween80) were dissolved. Next, the solvents were evaporated in a rotary evaporator at 150rpm 50 °C for 30 minutes with vacuum pressure 7.4Kpa, at which point a thin film had formed. Afterwards, 10 mL of deionized water was used to hydrate the film, and the micelles solution was sonicated for 5 minutes before being magnetically stirred at 500 rpm for 20 minutes. [17]

**Table 1. Composition of Nano-micelles**

| Formula | POCZ | TPGS (mg) | Tween80(mg) | POCZ: TPGS: tween80 |
|---|---|---|---|---|
| POCZ1 | 100mg | 300 | 100 | 1:3:1 |
| POCZ2 | 100mg | 300 | 200 | 1:3:2 |
| POCZ3 | 100mg | 300 | 300 | 1:3:3 |
| POCZ4 | 100mg | 500 | 100 | 1:5:1 |
| POCZ5 | 100mg | 500 | 200 | 1:5:2 |
| POCZ6 | 100mg | 500 | 300 | 1:5:3 |

***Characterization of POCZ nano-micelles***

***Micelles size determination***

The micelles size, poly dispersity index (PDI) and zeta potential of diluted formulation were determined using a Zetasizer (Malvern Instruments Ltd, United Kingdom).

***Drug Loading (DL%) and Encapsulation Efficiency (EE%)***

The drug loading capacity (DL%) and entrapment efficiency (EE%), which correspond to the percentage of POCZ encapsulated, were determined indirectly by measuring the concentration of free POCZ in nano-micelles. An ultrafiltration technique was used to determine the amount of free drug that was not trapped. In brief, 5.0 ml of POCZ nano-micelles solution was placed in the upper chamber of an Amicon® Ultra Centrifugal tube with a molecular cut off size (MWCO) of 10 KDa and centrifuged for 30 minutes at 5,000 rpm. After adequate dilution, the ultrafiltration containing the free drug and the concentration of unentrapped POCZ was measured using a spectrophotometer at 260nm.[18] The following equations were used to calculate the (EE%) and drug loading percent (DL%)[19].

$$\%DL = \text{Weight of pocz in nanomicelle} / (\text{weight of pocz} + \text{weight of excipients})$$

$$\%EE = \text{weight of pocz in nanomicelles} / \text{weight of pocz fed}$$

***Saturation solubility study of POCZ***

The solubilization properties of nano-micelles solutions were investigated by adding an excess of POCZ to 5 mL of empty micellar solutions in sealed glass bottles, which were then kept at 25C° in a water bath shaker. After 48 hours, the samples were centrifuged at 15,000 rpm for 20 minutes, and the concentration of POCZ in the supernatants was measured using a UV-spectrophotometer at 262nm after proper dilution with methanol. The solubility factor (Sf) was then calculated using the equation [20, 21].

$$Sf = Smic/Sw$$

Sf: solubility factor

Smic: solubility of POCZ in nano-micelles.

Sw: solubility of POCZ in water.

***In vitro release study***

Using a dialysis bag and a dialysis membrane from the MYM biological technology company in the United States (MWCO: 8-14 kD), in vitro release of POCZ from micelles was investigated in addition to pure POCZ powder. Phosphate buffer with a pH of 6.8 and 0.5% sodium lauryl sulfate as a surfactant to maintain sink condition (900ml) was used as a release media for selected formula. Using a USP dissolution apparatus (RIGGTEK, Dissilio TX8, Germany), the systems were maintained at 37C° while being stirred at 75 rpm. At regular intervals, 5 mL of the external medium was removed and replaced with fresh dissolution medium. In the same way that nano-micelles dissolution curves were obtained, so were POCZ powder dissolution curves is plotted. After measuring the absorbance at 260nm with a UV spectrophotometer, a triplicate test was conducted on the samples. The results acquired from the dissolution studies were statistically validated using a similarity factor(f2). The f2 was used to consider similar dissolution profiles (equation below).

$$f2 = 50 \cdot \log\left\{100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5}\right\}$$

Where (n) is the number of dissolution time points. (Rt), (Tt) are the reference and test dissolution values at time t respectively. The two dissolution profiles consider similar when f2 values greater than 50 (50– 100); otherwise, the profiles are not similar[22].

***FT-IR Spectroscopy.***

Pure POCZ and nano-micelles formulations were analyzed by using a Fourier transform infrared spectrophotometer (Shimadzu 4100, Japan).

***Field Emission Scanning Electron microscope (FESEM)***

FESEM was used to investigate the morphology of POCZ nano-micelles formulation (FESEM S-4160, Hitachi, Japan). Sample preparation is an important step in the imaging of samples using a Field Emission Scanning Electron Microscope (FESEM). The quality of the images obtained from the FESEM is largely dependent on the quality of the sample preparation. The sample preparation include collection of nano-micelles carefully to avoid contamination or damage, sample fixation in which preservation of structural integrity of the formula and dehydration of formula to remove water from nano-micelles, Critical point drying is a technique used to remove the solvent from the formula without causing damage to the morphology of the nano-micelles, mounting of the formula on a stub using a conductive adhesive carbon tape used, coating in order to prevent charging and improve image quality, the nano-micelles formula was coated with a conductive material platinum and finally imaging in which the nano-micelles formula is now ready to be imaged using the FESEM.

***Statistical study***

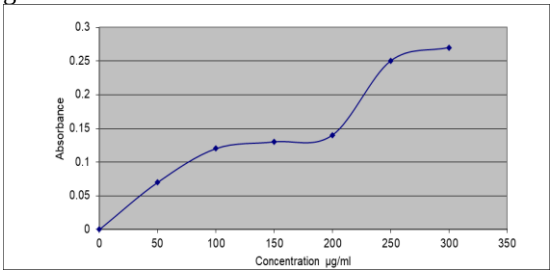
Results were expressed as mean values (±SD; n = 3), in-vitro release study was done by similarity factor f2 by using DD solver program.

## Results and Discussion

***Determination of critical micelles concentration (CMC)***

Figure (2) depicts a graph of Iodine absorbance in samples containing varying concentrations of TPGS. The CMC value was obtained from the graph as 200 µg/mL, which represents the sharp increase in absorbance intensity. This CMC value appears to be advantageous to the system because smaller

CMC caused greater stability of micelles in the gastrointestinal tract [16] .




**Figurer 2. critical micelles concentration of TPGS.**

***Micelles size and poly-dispersibility index***

Table (2) showed that as the concentration of TPGS and Tween80 increased, the particle size and PDI decreased, because high surfactant concentration decreases surface tension and forms more Nano-micelles particles, which will solubilize more drug molecules in the hydrophobic sites of the micelles [23, 24], and high surfactant concentration Tween80 and TPGS stabilizes newly developed surfaces during homogenization and production of smaller particles at the interface [21] .

***Drug loading and encapsulation efficiency***

The DL and EE for POCZ1 were 6%±0.4% and 30%±2.4%. POCZ6 had a DL of 10.3%±0.11% and an EE of 94.3%±1.69%. The DL and EE improved as the TPGS concentration in the preparation is increased, in comparison with a formulation with a low TPGS content. Increasing the solubility of hydrophobic drugs is the reason for the rise in popularity of TPGS [13.14]. In addition, the Food and Drug Administration in the United States has given its approval to TPGS for use in a number of different medication delivery systems. It was also shown that the micelle's DL and EE were affected by the polymer type and concentration, as well as the micelle's core forming block type and length and shell forming block length. So, increase TPGS and tween80 concentration will improve in DL and EE of the POCZ in Nano-micelles. [23, 25]

***Saturation solubility***

According to table (2), POCZ is only 0.9 µg/mL soluble in water, but its solubility is 26.56±3.95µg/mL and 1030.3±5.97µg/mL in POCZ1 and POCZ6, respectively. Thus, POCZ1 and POCZ6 have a solubility factor 29.5 and 1144 times higher than pure POCZ in water, respectively. The reasons for increasing the solubility are due to decreasing in size of nano micelles which will ultimately increase the surface area and wetting of drug molecules also increasing in TPGS and tween80 concentration cause more micelles to form in solution, which in turn entraps more POCZ in the hydrophobic core of micelles, increasing POCZ's solubility in water **[25, 26].** Figure (3) showed the relationship between decreasing in micelles size with increasing the solubility of POCZ.

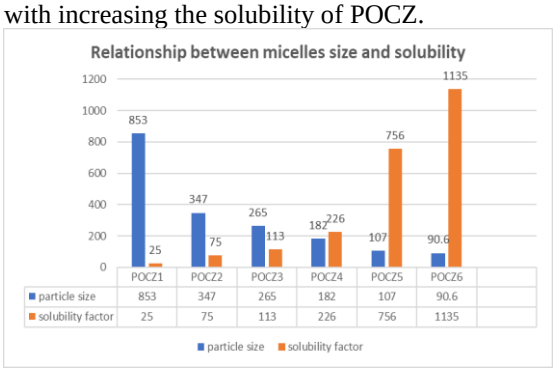



**Figure 3. Relationship between the micelles size and solubility factor for Posaconazole Nano-micelles.**

**Table 2. Characterization of Nano-micelles**

| Formula | Particle size(nm) | PDI | EE% | DL% | Solubility (µg/ml) | Solubility factor |
|---|---|---|---|---|---|---|
| POCZ1 | 843±64 | 0.71±0.07 | 30±2.4 | 6%±0.4 | 26.56±3.95 | 29.5 |
| POCZ2 | 362±17 | 0.58±0.03 | 58±1.5 | 9.6%±0.25 | 72.5±3.67 | 80.5 |
| POCZ3 | 265±15 | 0.27±0.04 | 67±3.86 | 9.5%±0.42 | 106.9±3.81 | 118.7 |
| POCZ4 | 163.6±15 | 0.4±0.25 | 86±1.5 | 10.75%±0.2 | 209.3±4.28 | 232.5 |
| POCZ5 | 114±6.5 | 0.32±0.02 | 91±1.63 | 11.3%±0.125 | 683.76±2.47 | 759.73 |
| POCZ6 | 95.6±4.9 | 0.34±0.09 | 94.3±1.69 | 10.3%±0.11 | 1030.3±5.97 | 1144 |
| Pure drug | - | - | - | - | 0.9 | |

***In-vitro release study***

As POCZ6 has the smallest micelles size and the lowest PDI and high solubility factor when compared to the other formulae, and since the released profile is compared to that of pure POCZ powder, it was chosen as the optimal formula for release profile analysis. Figure (4) shows that POCZ6 had a 100% POCZ release after 70 minutes, but the pure drug only releases 23% after the same amount of time, the faster release of POCZ from POCZ6 might be due to the presence of TPGS in the micelles. TPGS is known to increase the ratio of the hydrophilic portion in the mixed micelles and facilitates entry of water into the core of micelles and forms more hydrophilic channel in the inner core part of nano-micelles [21]. According to statistical analysis by similarity factor (f2), it was shown that POCZ6 (f2 =17) with better release profile than pure POCZ.

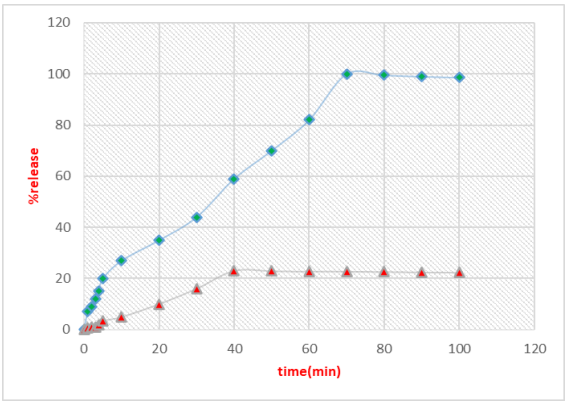



**Figure 4. in-vitro release profile of (a). POCZ6(■) (b). pure drug (▲)**

***Fourier transform infrared spectroscopy FTIR***

Various absorption peaks of functional group including: Carbonyl group stretching, Furan ring stretching, C-H bend alkane, CO-C stretch asymmetrical aryl alkyl ether, C-F aryl halide and C-H aromatic (out of plane) bending was found to be 1694 cm-1, 1452 cm-1, 1394 cm-1, 1271 cm-1, 1101 cm-1 and 734 cm-1 respectively. Hence, posaconazole nano-micelles POCZ6 showed similar absorption peaks which indicate its good compatibility with polymers. This declared that there was no remarkable chemical interaction between excipients or drug or confirms that the drug is in the stable nature during the formulation process.

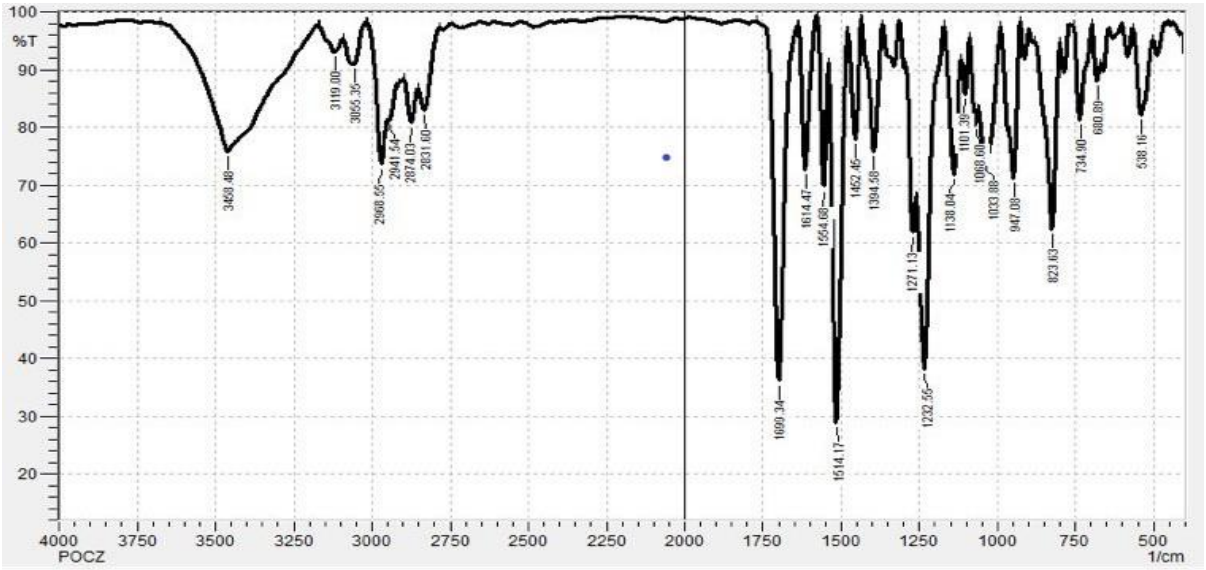



**Figure 5.FTIR Spectrum of Posaconazole**

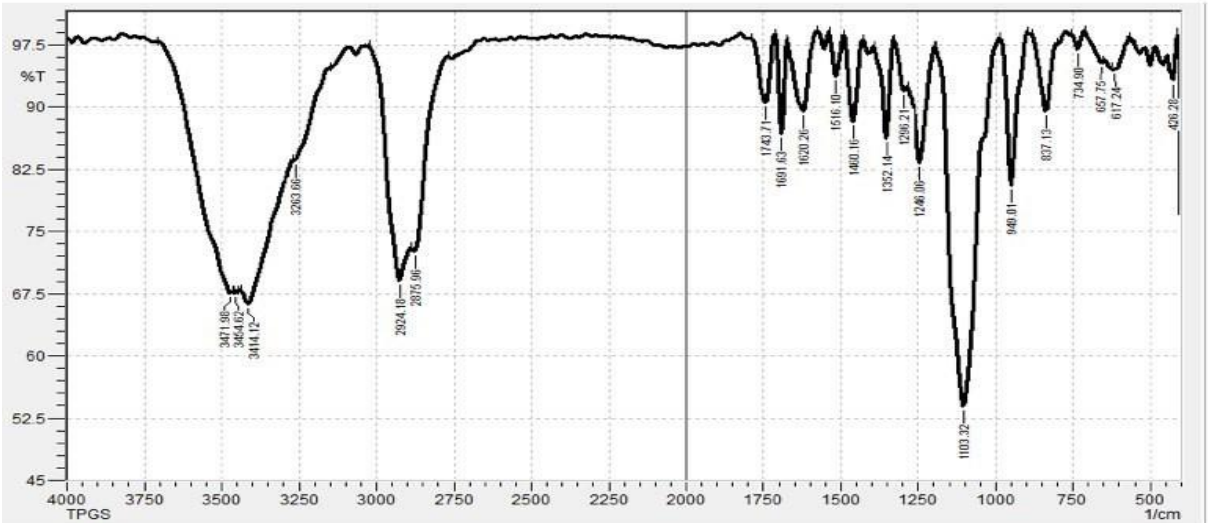



**Figure 6. FTIR spectrum of POCZ6**

***Field emission scanning electron microscopy (FESEM)***

FESEM image (7) shows the particle size in nanometer of selected formula POCZ6 nano-micelles and the shape of micelles is spherical that composed of the outer layer shell and the inner core that entrap POCZ.

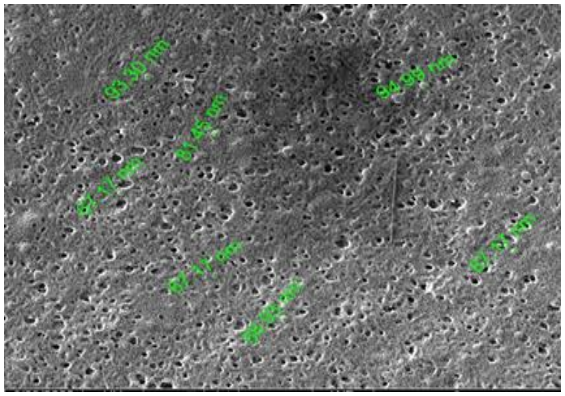


**Figure7. SEM of POCZ6**

# Conclusion

Depending on the obtained data from our present study, the study can conclude the following points: The posaconazole (POCZ) is suitable to be formulated as a nano-micelles with excellent entrapment efficiency, drug loading and best release profile in comparison with pure posaconazole (POCZ). FESEM studies showed an almost spherical particle shape with no particle's aggregation. While the FTIR studies of selected formula POCZ6 formulated as a nano-micelles showing compatibility between the drug and other formula excipients, and the drug was perfectly encapsulated within the nano-micelles.

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## Conflicts of Interest

No conflict

## Funding

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## Ethics Statements

No animal or human study

## Author Contribution

The authors contribute in practical procedures, biostatistics and writing of this study.

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