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Brimonidine-Soluplus Nanomicelles: Preparation and *in-vitro* evaluation

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Abstract

Brimonidine is an active pharmaceutical ingredient used to treat glaucoma as a topical eye drop. Ophthalmic topical preparations are associated with low ocular bioavailability due to several physiological and analytical barriers. Many approaches have been investigated to overcome this problem, for example, changing the dosage form by using ocular injections, altering the chemical formula of the medicines as a prodrug, or using different drug carrier systems like nanomaterials. This study aims to prepare nanomicelles as an ophthalmic drug carrier for topical application by using Soluplus® as a polymeric surfactant and enhancing the physical properties of these nanomicelles by studying different factors. Brimonidine-soluplus nanomicelles were prepared by the thin-film hydration method, and the best formula was prepared by another method (direct dissolution) to evaluate the preparation method as a variable factor. The physical properties of the prepared nanomicelles were analyzed using two factors, including brimonidine concentration and the ratio of the polymer to brimonidine concentration regarding their effect on particle size and entrapment efficiency using Zetasizer and amicon® ultra centrifugal filter units 10 KDa MWCO, respectively. The selected best formula had been characterized by Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR), Field Emission Scanning Electron Microscope (FESEM), and *in-vitro* release pattern compared with the free aqueous brimonidine suspension. The results showed that Soluplus® nanomicelles increases the intrinsic solubility of brimonidine compared to free form in water as an aqueous suspension by 2.17 folds for the selected best formula. However, soluplus® and brimonidine concentrations affect the physical appearance of the prepared nanomicelles and had a highly significant effect on the percentage of the entrapment efficiency but non on the polydispersity index. Furthermore, soluplus® concentration had a highly significant effect on the particle size, whereas brimonidine concentration did not. The method of nanomicelle preparation affect the physical appearance and had a highly significant effect on the percentage of the entrapment efficiency, in which the thin-film method was the best. The selected best formula contains 1.98mg/ml brimonidine with 59.4 mg/ml soluplus® had a particle size of (75.75 ± 1.13 nm), polydispersity index of (0.1243 ± 0.02) and percentage of entrapment efficiency (53.49 ± 0.58%) prepared by the thin-film hydration method and had a rapid *in-vitro* release rate (65.52% ± 0.26) within 15 minutes compared to the aqueous brimonidine suspension (23.88% ± 0.08). DSC, FTIR, and FESEM confirmed the formation of the brimonidine-soluplus- loaded nanomicelles. This study concludes the effectiveness of using a polymeric surfactant to prepare nanomicelles for brimonidine with enhanced physicochemical properties as an ophthalmic drug carrier system.

Keywords: Brimonidine, Nanomicelle, Ophthalmic, Soluplus, Thin-film hydration.

Introduction

Brimonidine Figure. 1, a lipophilic drug, was approved in 1966 by the FDA as a topical eye drop to reduce ocular hypertension, one of the glaucoma characteristics, thus lowering the risk of complications and the need for invasive treatments, such as surgical or laser procedures [(1)].

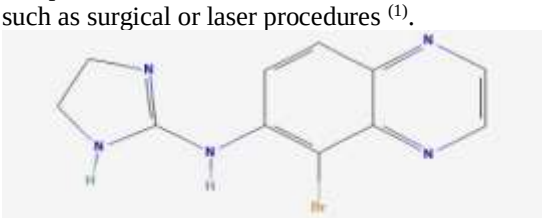

Figure 1. Brimonidine chemical structure [(2)].

The administration of medicines for treating ocular tissue diseases occurs via different routes, of which the topical route is the major. The topical drops are associated with many pros and cons in that despite the self-administration, easy application, and cost-effectiveness, it has poor patient adherence to the therapy regimen (31-67%) [(3)] and low ophthalmic bioavailability (up to 10%) [(4)] due to physiological and anatomical barriers [(5,6)]. Thus, to overcome this obstacle and increase ocular bioavailability, alternative routes of administration were used, such as intravitreal, periocular, and systemic injections, which all are invasive methods and are associated with the risk of adverse effects [(7)].

Nanotechnology deals with nanomaterials with a particle size range from 1-1000 nm, making it possible to design a topical ophthalmic liquid drug carrier system with enhanced properties, including site-specific targeting mainly for the retina and prolonged-release to overcome the ophthalmic barriers and increase ocular bioavailability, for example, sirolimus-poly(lactic-co-glycolic acid) nanoparticles, and prednisolone phosphate liposomes to overcome the ophthalmic barriers and increase ocular bioavailability [8,9]. Nanomaterials involve many types; for example, nanostructured lipid carriers [10], nanomicelles, nanosuspension, nanoemulsion, and liposomes [11]. Nanomicelles are a drug delivery system made from either amphiphilic surfactant or polymers [12] that are self-assembled into spherical colloidal dispersion upon contact with an aqueous solution with a hydrophobic core containing the dissolved hydrophobic drug and a hydrophilic corona towards the surrounding aqueous phase [13]. Soluplus® is an amphiphilic graft copolymer consisting of polyvinyl caprolactam-polyvinyl acetate as the hydrophobic part and polyethylene glycol as the hydrophilic part. Its amphiphilic properties and solubilizing activity make it a safe and superb polymer for loading lipophilic drugs in its hydrophobic nanomicelle core [14].This research aimed to prepare a soluplus nanomicelles colloidal dispersion system loaded with the lipophilic brimonidine particles within their cores and having an accepted physical property for the topical liquid ocular route of administration regarding their particle size, drug solubility, and entrapment efficiency.

Materials and Methods

Materials

Brimonidine (BR) crude powder was purchased from Anshi Pharmaceutical Co., Ltd, China, and Soluplus® (SO) from BASF SE, Germany. Methanol HPLC was purchased from Chem-Lab NV, Belgium. Amicon® Ultracentrifuge tube, 10kDa MWCO, was purchased from Sigma-Aldrich, USA. Dialysis Bag MD34-5M, Wide flat: 34 MM, Mw: 8000 - 14000 D, was purchased from MYM Biomedical Technology Company Limited, USA. All other chemicals and reagents obtained are of analytical grade.

Methods

preparation of brimonidine-soluplus nanomicelles

Two methods for nanomicelles preparation were used: thin-film hydration and direct dissolution. In the first one, different brimonidine and soluplus® concentrations were used to prepare a set of 7 formulas, Table 1, in which both of them dissolved in methanol with heat (55ºC) and stirring (300 rpm) (Premium Hotplate Stirrer, Witeg Labortechnik.GmbH). Then, the dissolved mixture was placed in a rotary-vacuum evaporator (Rotavapor® R-300a, Buchi, GmbH) to remove the organic solvent (at 50ºC, 100 rpm, and 244 mbar), then after leaving overnight for complete dryness, the brimonidine-soluplus® loaded nanomicelles were formed by hydration of the thin-film using (DDW) with stirring and heating [15]. The selected best formula prepared by the thin-film hydration method depending on the physical appearance, particle size, polydispersity index, and percentage of entrapment efficiency, was further prepared by the direct dissolution method (F8, and F9). This time, soluplus® nanomicelles colloidal dispersion was formed first by adding DDW (10 ml) to soluplus® crystalline powder (59.4 mg/ml). After that, brimonidine powder (1.98 mg/ml) was added to the prepared dispersion. Two techniques were used in the direct dissolution, the high-speed stirring and sonication techniques to load the drug into the nanomicelles hydrophobic core, once by stirring with high speed and heat (37.0 ±0.5ºC) and the other by sonication at 40Hz with heating (37.0 ±0.5ºC), respectively [14,16,17].

Table 1. Brimonidine-soluplus nanomicelles composition

Formula ID	Brimonidine mg/ml	Soluplus mg/ml	Drug-to-polymer ratio
F 1	1.32	13.2	1:10
F 2	1.32	26.4	1:20
F 3	1.32	39.6	1:30
F 4	1.32	52.8	1:40
F 5	1.32	59.4	1:45
F 6	1.98	59.4	1:30
F 7	2.64	79.2	1:22.5
F 8	1.98	59.4	1:30
F 9	1.98	59.4	1:30

Saturated solubility and solubility factor

The saturated solubility of brimonidine was studied in three different mediums, deionized distill water (DDW), different concentrations of soluplus® (0.5, 1.0, 1.5, and 2.0 mM) at 25°C, and phosphate buffer saline (PBS) pH 7.4 at 37.5ºC for 48 hours with 50 rpm using shaking water bath (Jeio Tech BS-11, 25Liter, Korea). After that, the samples were placed in a centrifuge (Centrifuge 5810 R, Eppendorf Company, Germany) at 13000 rpm for 1 hour at 10ºC to separate the excess undissolved brimonidine. Then, the supernatant was taken and

diluted it to a suitable dilution factor with methanol to measure the concentration of dissolved brimonidine using a UV-spectrophotometer (UV-VIS spectrophotometer UV-1900i, Shimadzu, Japan) at wavelength (λ) 257 nm. The solubility factor was determined using equation 1: [14,15]

$$Solubility\ Factor = \frac{Saturated\ solubility\ of\ brimonidine\ in\ blank\ micelle}{Saturated\ solubility\ of\ brimonidine\ in\ DDW}$$

Eq.1 [15]

Characterization of the prepared nanomicelles

Particle size determination

Particle size and polydispersity index (PDI) were determined by Malvern Zetasizer, UK, using the dynamic light scattering technique [18], using the native formula without dilution.

Entrapment efficiency percentage (%EE) determination

Soluplus-nanomicelles brimonidine %EE was determined by the indirect method using a pre-socked amicon® tube. Two milliliters of the prepared formula were placed in the amicon® tube and subjected to centrifuge at 6000 rpm for 15 minutes at room temperature. The amount of unentrapped free brimonidine was measured from the filter using a UV spectrophotometer. The %EE was calculated using equation 2: [19].

$$\%EE = \frac{BR\ total\ content\left(\frac{mg}{ml}\right) - BR\ content\ in\ the\ filterate\left(\frac{mg}{ml}\right)}{BR\ total\ content\left(\frac{mg}{ml}\right)} \times 100$$

Eq.2

***Thermal analysis by Differential Scanning Calorimetry (DSC) Analysis*:**

Crude brimonidine, soluplus, and the lyophilized powders of the selected best formula were analyzed thermally by the DSC analysis using (DSC-60, Shimadzu, Japan). The powdered form of the brimonidine-loaded soluplus nanomicelle was prepared by freeze-drying using 2ml of the prepared formula containing 2% mannitol as a cryoprotectant. The sample was placed in a glass vial and frozen up to -80C for about 15 minutes using liquid nitrogen. The frozen sample was partially closed with holed-plastic rubber and put on the lyophilizer (CHRIST-Alpha1-2 LD plus-Germany) pre-cooled shelf and started the "main drying process" at 0.2mbar (-36 C) for about 14 hours. A small amount (not more than 10 mg) of each was placed in an aluminum pan of the device and sealed. Then, the analysis ran at temperatures ranging from 25-300°C, with a heating rate of 10ºC/minute under N_2 gas flowed at 50ml/minute [20].

***Fourier Transform Infrared Spectroscopic (FTIR) Analysis*:**

FTIR analysis (FTIR-1800 Shimadzu, Japan) was done to determine any possible interaction between the drug and the polymer. The scanned samples include brimonidine and soluplus crystalline powders, their physical mixtures, and the liquid selected best formula. For FTIR scanning, the liquid samples were mixed with KBr solution on a glass plate to form a thin film after drying. The range for FTIR spectroscopic analysis was 4000 – 400 cm^{-1} [21].

***Field emission scanning electron microscopy (FE-SEM) Analysis*:**

FE-SEM (Inspect F50, FEI company, The Netherlands) was used to analyze the topography of brimonidine-soluplus loaded nanomicelles for the selected best formula. The liquid sample was dried first, then coated with conductive material (gold) to improve the image using 30 kV at 120000 magnifications [22].

***In-vitro release*:**

Using the dialysis bag method, 100 µl containing 0.198 mg of brimonidine, from both the selected best formula and the aqueous drug suspension (1.98mg brimonidine/ml), were placed in a pre-soaked dialysis bag (24 hours in advance with PBS pH 7.4) in which both bag ends were closed first and folded again to be closed with each other [23]. These packages were knotted separately, each in small weight, and each one of them was sunk in the receptor medium (50 ml phosphate buffer saline PBS pH 7.4) at 37.5±0.5 ºC with shaking at 50 rpm in the water bath shaker, keeping the sink condition for the drug [24,25]. At predetermined intervals, a 3 ml sample was taken and replaced with fresh PBS pH7.4 (37.5±0.5 ºC). These samples were analyzed for the amount of cumulative brimonidine released within the time using a UV-spectrophotometer. The release profile data for the selected best formula was analyzed using four kinetic release models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas, to determine the kinetic and the mechanism of drug release [23].

Statistical analysis

Triplicate measurements were performed for all the laboratory experiments and expressed the results as mean values ± standard errors (SE). The statistical significance of the variables was determined depending on the p-value using one-way analysis of variance (ANOVA) or student t-test, where p-value < 0.05 is statistically significant, and p-value > 0.05 is statistically non-significant.

Results and Discussion

Brimonidine solubility

Brimonidine saturated solubility in DDW was 0.461 mg/ml at 25±0.5°C, which means it is sparingly soluble in water, while in PBS pH 7.4 was 0.585±0.02 mg/ml at 37±0.5°C. The intrinsic solubility of brimonidine was increased proportionally with increasing soluplus concentration Table 2, which was similar to that published by Hadi BM [26]. This behavior might be explained by the presence of large numbers of (-OH) groups in its structure and the self-assembling to micelles at the nano-scale once it came in contact

with aqueous solution incorporating the drug in their hydrophobic cores that leads to an increase in the relative surface area and the hydrogen bonds formation with water [27,28].

Table 2. Effect of different soluplus concentrations on the intrinsic solubility of brimonidine

Soluplus concentration mg/ml	Brimonidine solubility mg/ml	Factor increment of solubility
0	0.461 ± 0.003	0
59	1.004 ± 0.014	2.17
118	1.287 ± 0.026	2.79
177	1.353 ± 0.032	2.93
236	1.692 ± 0.027	3.67

***Effect of soluplus concentration on the physical properties of brimonidine-loaded nanomicelles*:**

Brimonidine-soluplus nanomicelles were prepared by the thin-film hydration method, using 1.32mg/ml of brimonidine with different soluplus® concentrations Table 3. Soluplus® concentration affect the physical appearance and statistically had a highly significant effect on the particle size, and %EE of the nanomicelles, while there was no significant effect on the PDI. The lowest soluplus® concentration (F 1, 1.32mg/ml) caused brimonidine sedimentation with turbid appearance after 24 hours of preparation, and as the polymer concentration increased, the physical appearance became transparent, and the particle size together with %EE increased significantly; except for the last two concentrations, there were no significant differences. This effect can be related to the increment in the hydrophobic portion of the amphiphilic polymer as the polymer concentration increases, causing an increase in the hydrodynamic diameter of the nanomicelle and more brimonidine-loaded into the hydrophobic core [29].

Table 3. Effect of different soluplus concentrations on the particle size, polydispersity index (PDI), and %EE of brimonidine (1.32 mg/ml)-loaded nanomicelles prepared by thin-film hydration method

F ID	Soluplus concentration mg/ml	Physical appearance after 24 hours	Mean Particle size (nm) ± SE *** (P≤0.001)	Mean PDI ± SE (P≥0.05)	Mean % EE ± SE *** (P≤0.001)
F 1	13.2	Turbid	65.53 ± 0.63	0.0828 ± 0.06	31.15 ± 0.69
F 2	26.4	Clear	70.52 ± 1.03	0.1084 ± 0.02	32.18 ± 0.81
F 3	39.6	Clear	73.22 ± 1.83	0.1176 ± 0.02	37.05 ± 0.13
F 4	52.8	Clear	77.03 ± 1.08	0.1973 ± 0.01	47.13 ± 0.79
F 5	59.4	Clear	77.87 ± 1.11	0.1292 ± 0.01	47.45 ± 0.47

***Effect of brimonidine concentration on the physical properties of brimonidine-loaded nanomicelles*:**

The best formula (F 5), with the desired particle size, PDI, and highest %EE, was selected to study the effect of different drug concentrations on the physical properties of soluplus nanomicelles Table 4. Brimonidine concentration had a highly significant effect on the physical appearance and %EE, while none on the particle size and PDI. This effect could be due to the saturation of all the hydrophobic core of that soluplus concentration with brimonidine, and all the excess of the drug settled down [14,30].

Table 4. Effect of different brimonidine concentrations on the particle size and polydispersity index (PDI), and %EE of soluplus (59.4 mg/ml soluplus) nanomicelles prepared by thin-film hydration method

F ID	Brimonidine concentration mg/ml	Physical appearance after 24 hours	Mean Particle size (nm) ± SE (P≥0.05)	Mean PDI ± SE (P≥0.05)	Mean % EE ± SE *** (P≤0.001)
F 5	1.32	Clear	77.87 ± 1.11	0.1292 ± 0.01	47.45 ± 0.47
F 6	1.98	Clear	75.75 ± 1.13	0.1243 ± 0.02	53.49 ± 0.58
F 7	2.64	Tubid	76.35 ± 1.42	0.1464 ± 0.02	60.58 ± 0.16

***Effect of nanomicelles preparation method on the physical properties of brimonidine-loaded nanomicelles*:**

To study the effect of the preparation method on the previously analyzed physical properties, we selected formula F 6 since it had the highest %EE with the desired particle size and PDI ranges and prepared it by another method (direct dissolution). The method used to prepare brimonidine-loaded nanomicelles had a highly significant effect on the physical appearance and %EE of brimonidine-loaded nanomicelles with p-

value ≤ 0.001, as shown in Table 5, in which the thin-film hydration method was the best compared to direct dissolution method. This effect could be related to using the organic solvent (methanol) in thin-film hydration. The organic solvent had pronounced effects on the degree of solute-copolymer mixing and the extent of hydrophilic-hydrophobic extensions of the polymer, causing more drug loading in the hydrophobic core of the nanomicelles [31].

Table 5. Effect of the preparation method on the physical properties of brimonidine-loaded nanomicelles

F ID	Preparation method	Physical appearance after 24 hours	Mean % EE ± SE *** (P≤0.001)
F 6	Thin-film hydration	Clear	53.49 ± 0.58
F 8	Direct dissolution with stirring	Turbid	39.23 ± 0.53
F 9	Direct dissolution with sonication	Turbid	40.11 ± 0.44

In-vitro release

The best formula (F 6), with the desired physical properties, was compared to the aqueous brimonidine suspension for their *in-vitro* release behavior using PBS pH 7.4 at 37±0.5°C, keeping in mind to maintain the sink condition. Figure. 2, showed that the brimonidine-loaded soluplus nanomicelles had a fast cumulative release profile with a higher percentage of brimonidine released (65.52±0.37%) compared to its aqueous suspension (23.88±0.05) in about 43% within 15 minutes (highly significant effect with p-value ≤ 0.001). According to the Noyes-Whitney equation, this could be related to the 2.2 folds increment solubility factor of brimonidine by soluplus colloidal dispersion (59.4mg/ml) and the high relative surface area of the drug-loaded nanomicelles [32]. Four kinetic release models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) were used to compare the release kinetics of F 6. As shown in Table 6, F 6 follows Higuchi release kinetic with the highest coefficient of determination (R^2 = 0.9947), and the release mechanism (the n value parameter in the Korsmeyer-Peppas model) was controlled by Fickian diffusion since (n = 0.307) [33].

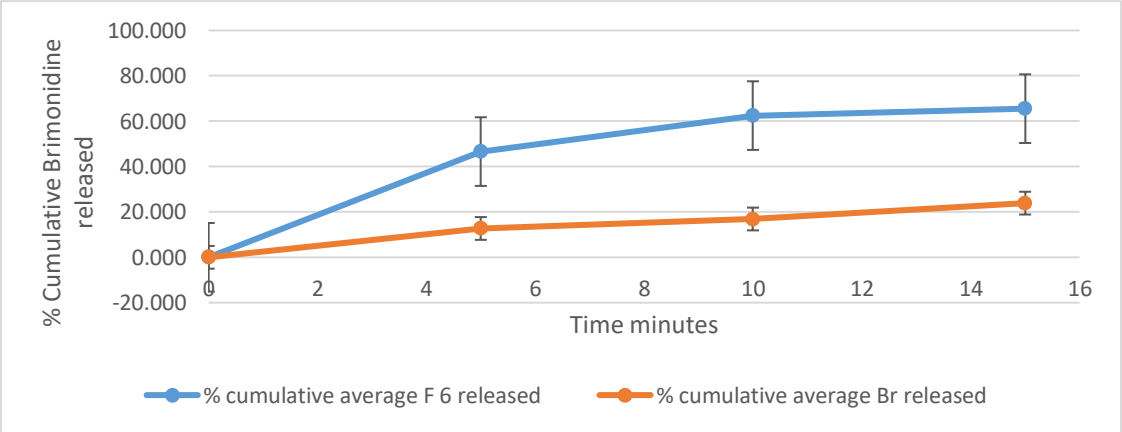

Figure 2. *In vitro* % cumulative release (mean ± SE, n=3) of F 6 and brimonidine aqueous suspension in PBS pH 7.4 at 37.5±0.5°C.

Table 6. *In-vitro* release kinetic models with R^2, n, and ß values for F 6

Kinetic Models	Zero-order	First-order	Higuchi	Korsemyer-Peppas	Weibull
F 6 (R2)	0.9325	0.9263	0.9706	0.9947	0.9961
n-parameter				0.307	
ß-parameter					0.494

Thermal Analysis

Brimonidine, soluplus®, mannitol, and the lyophilized F 6 (with 2%mannitol) powders were thermally analyzed using (DSC) as shown in Figure. 3. The results coincide with documented data for brimonidine crude and mannitol crystals regarding their melting points and the glass transition temperature (Tg) for soluplus® [34-37]. The sharp endothermic peak of brimonidine crystals was not present, and there was a shift from that of mannitol to a lower value, which indicates that all the brimonidine had been loaded, as an amorphous state in the hydrophobic core of the nanomicelles and there was no free crystalline drug in the colloidal dispersion system. For mannitol, the shifting of the peak indicates the formation of hydrated mannitol form due to the freeze-drying process [38].

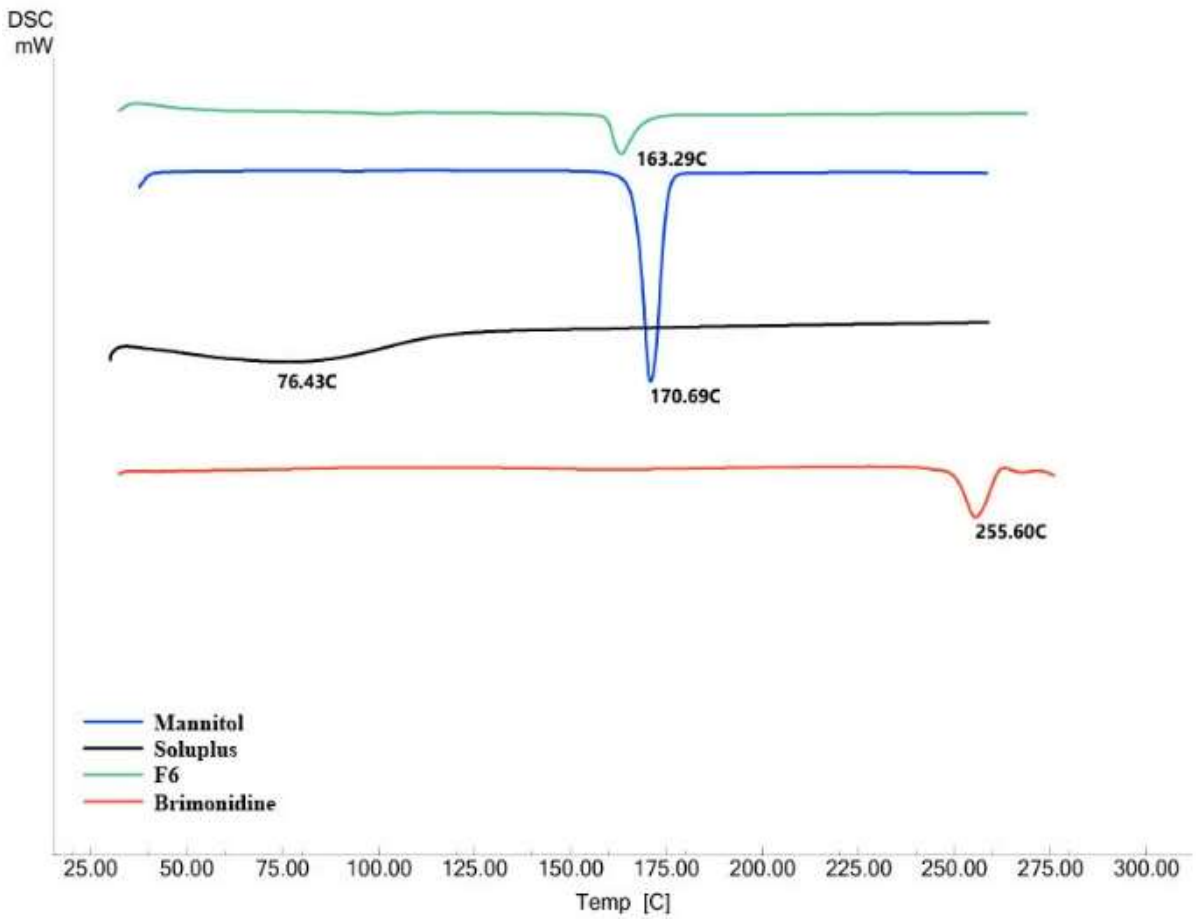

Figure 3. DSC thermogram showing the difference in thermal behaviors and melting points for mannitol, brimonidine crystalline powder, F6, and the transition glass temperature of soluplus.

***Fourier Transform Infrared Spectroscopy (FTIR) analysis*:**

The FTIR analysis was illustrated in Figure. 4. Brimonidine crude powder FTIR spectra showed the representative peaks that include the C-C stretching vibration of the benzene ring at 1481.13 cm^{-1}, the N-H bending vibration at 1589.34 cm^{-1}, the N=C and C=C stretching vibration at 1645.28 cm^{-1}, and the N-H stretching vibration at 3163.26 cm^{-1}, similar to what was found by Zhao Y et al [39]. For soluplus® FTIR spectra, the representative peaks were the -OH stretching vibration at 3477.66 cm^{-1}, the C=O stretching vibration of the ester group at 1741.72 cm^{-1}, and the C=O stretching vibration of the tertiary amide at 1631.78 cm^{-1}, close to that was published by Alwan RM [40]. The featured peaks of brimonidine and soluplus® were available in their physical mixture spectra also. For F 6 FTIR spectra, two characteristic intense peaks at 3441 cm^{-1} and 1741cm^{-1} were present in which they shifted in between the representative peaks of brimonidine (the -NH, and -N=C, -C=C groups) and of soluplus® (the -OH, and -C=O ester groups), which indicate the loading of brimonidine in the hydrophobic core of soluplus nanomicelles by both or one of hydrophobic interaction and hydrogen bonds interaction [41].

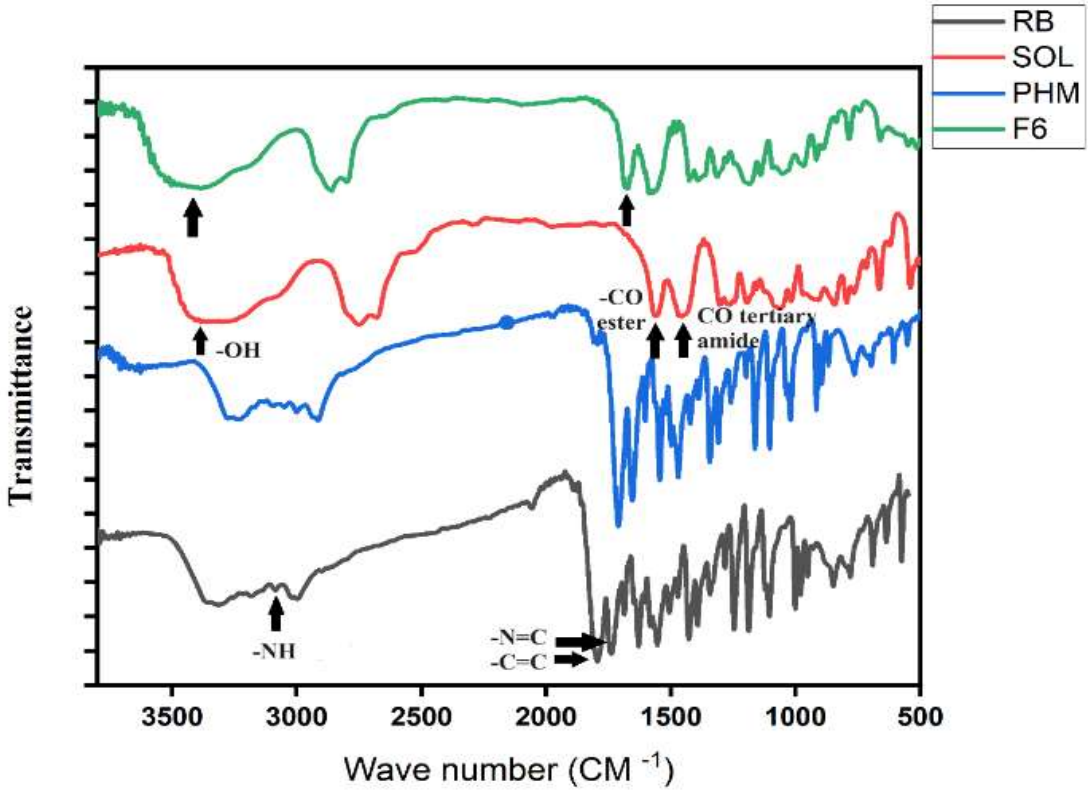

Figure 4. FTIR spectrum of brimonidine powder (BR), soluplus® powder (SOL), brimonidine/soluplus® physical mixture (PHM), and F 6.

Field emission scanning electron microscopy (FE-SEM)

The taken image Figure. 5, showed spherical particles with sizes ranging between 70.59 nm – 88.93 nm, which was close to the hydrodynamic diameters measured by the dynamic light scattering method that confirm the loading of the amorphous brimonidine inside the hydrophobic core of soluplus nanomicelles.

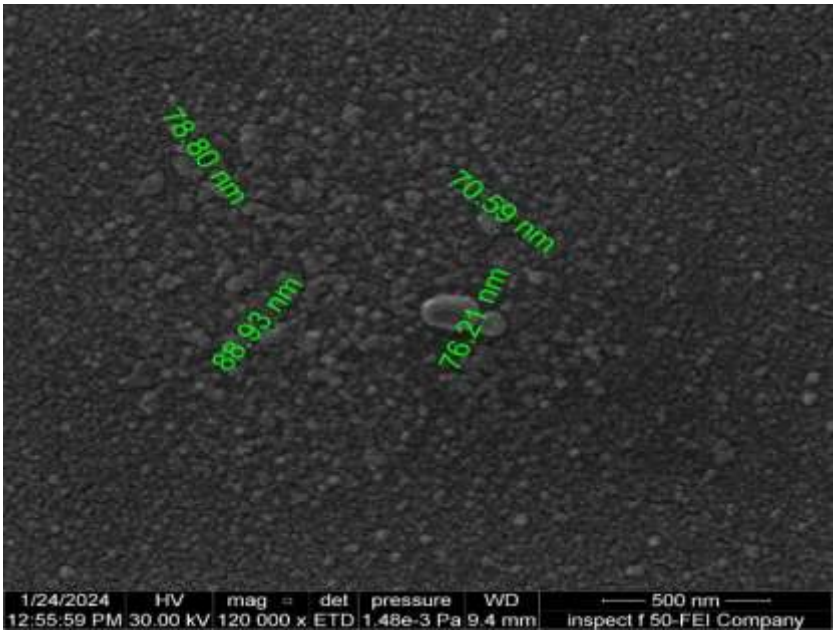

Figure 5. FESEM image of (F 6).

Conclusion

In conclusion, soluplus® was suitable for preparing polymeric nanomicelle drug carrier systems for lipophilic drugs like brimonidine. Soluplus nanomicelles enhance the intrinsic solubility of brimonidine and the in-vitro release behavior, making it a good choice as a topical ophthalmic drug carrier system for poorly soluble drugs, especially when a fast release is desirable.

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Conflicts of Interest

Both authors declared no conflicts of interest related to this work.

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Ethics Statements

Both authors assured that no animals were used for this study.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design, data collection, analysis, and interpretation of results were done by the first author, Noor N. Abdulla. Draft manuscript preparation, reviewing the results, and approving the final version of the manuscript was done by both authors, Noor N. Abdulla and Fatima J. Al-Gawahari.

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المذيلات النانونية للبريمونيدين: تحضير وتقييم خارج الجسم الحي

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الخلاصة

البريمونيدين هو المادة الصيدلانية الفعالة لعلاج الماء الازرق للعين كقطرة عينية موضعية. تتميز كافة المستحضرات الموضعية للعين بانخفاض التوافر الحيوي لها في الانسجة العينية بسبب العديد من العوائق الفسيولوجية التشريحية. وقد تم دراسة العديد من الأساليب للتغلب على هذه المشكلة، على سبيل المثال، تغيير شكل الجرعة باستخدام الحقن الموضعي في الانسجة العينية، أو تغيير الصيغة الكيميائية للأدوية كمقدم دوائي، أو استخدام أنظمة حاملة دوائية مختلفة مثل المواد النانوية. تهدف هذه الدراسة إلى تحضير المذيلات النانوية كحامل دوائي للإعطاء الموضع للعين للمحاليل الدوائية باستخدام مادة بوليمرية خافضة للتوتر السطحي (سولوبلس®) وتحسين خواصها الفيزيائية من خلال دراسة عوامل مختلفة. تم تحضير المذيلات النانوية بريمونيدين – سولوبلس بطريقتين، ترطيب الغشاء الرقيق والذوبان المباشر. تم تحليل الخواص الفيزيائية للمذيلات النانوية المحضرة باستخدام عاملين، هما تركيز البريمونيدين ونسبة البوليمر إلى البريمونيدين فيما يتعلق بتأثيرها على حجم المذيلات وكفاءة حجز الدواء باستخدام جهاز الزيتاسايزر و وحدات مرشح الطرد المركزي الفائق بحجم جزئي قطعي يساوي ١٠ كيلودالتون، على التوالي. تم اختيار أفضل صيغة مختارة و اجراء فحوصات اضافية عليها تتمثل بالمسح التفاضلي (DSC)، والمسح بمطيافية الاشعة تحت الحمراء باستخدام فورييه (FTIR)، والمجهر الإلكتروني الماسح ميداني الانبعاث (FESEM) ، ونمط تحرر الدواء في المختبر مقارنةً بالمعلق المائي للبريمونيدين. أظهرت النتائج أن مذيلات السولوبلس تزيد من قابلية الذوبان الجوهري للبريمونيدين مقارنة بذوبانيته لوحده بالماء على شكل معلق بمقدار ٢,١٧ مرة لأفضل تركيبة مختارة. ومع ذلك، كان هناك تأثير لتركيزالسولوبلس و البريموندين على المظهر الخارجي و بتأثير معنوي كبير للغاية لنسبة كفاءة حجز الدواء للمذيلات النانوية المحضرة في حين لم يكن لهما تأثيرعلى مؤشر تعدد التشتت. علاوة على ذلك، كان لتركيز السولوبلس تأثير معنوي كبير على حجم المذيلات، في حين لم يكن لتركيز البريمونيدين تأثير كبير. كما كان لطريقة تحضير المذيلات النانوية تأثير على المظهر الخارجي و بتأثير معنوي كبير للغاية لنسبة كفاءة حجز الدواء، حيث كانت طريقة الغشاء الرقيق هي الأفضل. تحتوي أفضل تركيبة مختارة على ١,٩٨ ملغم/مل من بريمونيدين مع ٥٩,٤ ملغم/مل من السولوبلس و بحجم جسيمي (٧٥,٧٥±١,١٣ نانومتر)، وبمؤشر تعدد التشتت قدره (٠,١٢٤٣±٠,٠٢) و نسبة كفاءة حجز الدواء مقدارها (53.49±0.58%) محضرة بواسطة ترطيب الغشاء الرقيق. كان لافضل تركيبة مختارة نسبة تحرر دواء في النختبر سريعة بلغت ٦٥,٥٢٪ ± ٠,٢٦ خلال ١٥ دقيقة مقارنة بالمعلق المائي للبريمونيدين والتي كانت ٢٣,٨٨٪ ± ٠,٠٨. أكدت نتائج فحوصات DSC و FTIRوFESEM على تكوين المذيلات النانوية للسولوبلس المحملة بالبريمونيدين. تستنتج هذه الدراسة فعالية استخدام مادة بوليمرية خافضة للتوتر السطحي مثل السولوبلس لتحضير المذيلات النانوية للبريمونيدين مع خصائص فيزيائية وكيميائية محسنة كنظام حامل للأدوية الموضعية للعين.

الكلمات المفتاحية: البريمونيدين, المذيلات النانوية, عيني, سولوبلس, ترطيب الغشاء الرقيق.