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Preparation and characterization of disintegrating film formulations containing bisoprolol fumarate for the treatment of hypertension

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ABSTRACT: Since oral administration is the most preferred route of drug administration, innovative and effective oral pharmaceutical dosage forms are being investigated. Among these new pharmaceutical forms, orally disintegrating films (ODFs) play an important role. This study aims to create optimum ODF formulations containing bisoprolol fumarate using solvent casting method. While pullulan and lycoat were used as polymers in the structure of the films, plasticizers such as polyethylene glycol 400 (PEG-400) and glycerin were used to provide flexibility. Characterization studies on the obtained films are determination of morphological characteristics, folding determination, thickness determination, determination of swelling behaviour, determination of disintegration time, in vitro release determination, mass uniformity determination, determination of content uniformity, tensile strength, elastic modulus and elongation percentage determinations. UV-Vis spectroscopy studies were performed to confirm bisoprolol fumarate. The complete disintegration time for the F-14 films with optimum characteristics was found to be 38 seconds on average in the petri dish method and 16 seconds on average using the dispersion time analyzer. These values revealed that pullulan polymer exhibited better film-forming capacity when used in close amounts with lycoate polymer. ODFs containing bisoprolol fumarate have provided an effective, safe, innovative and easy to use treatment for hypertension.

KEYWORDS: orally disintegrating films; bisoprolol fumarate; pullulan; lycoat

1. INTRODUCTION

One of the most important risk factors for cardiovascular disease is hypertension. One of the most commonly used drug classes in the treatment of hypertension is beta-blockers [1]. Bisoprolol fumarate in this therapeutic class is a cardioselective β1-adrenergic blocker. Bisoprolol fumarate is used for the prevention of myocardial infarction, heart failure, angina pectoris and mild to moderate secondary hypertension. [2, 3,4]. The daily dose of bisoprolol fumarate is 5-10 mg and can be increased up to 20 mg per day if necessary. Maintaining a constant plasma level of a cardiovascular drug is important for the desired therapeutic response. Therefore, more than one dose should be administered to maintain a constant plasma concentration of bisoprolol fumarate, which has a half-life of approximately 3-4 hours. After oral administration, bisoprolol fumarate is rapidly absorbed, although a very small amount undergoes first-pass metabolism in the liver, with an absolute bioavailability of approximately 80% after a 10 mg oral dose of bisoprolol fumarate [3,5, 6,7]. Compared to conventional drug formulations, ODFs have high bioavailability and rapid onset of action [8]. ODFs improve oral bioavailability by eliminating first-pass metabolism, allowing absorption through the oral mucosa [9].

Bisoprolol fumarate is a BCS class 1 drug with high solubility and low permeability. Highly water-soluble drugs are well suited for use in the production of orally disintegrating films (ODFs) [9,10]. ODFs were developed to be used without water in geriatric and pediatric patients with swallowing difficulties due to the difficulty of traditional drug administration routes. ODFs, a new dosage form, are placed on the tongue, come into contact with saliva and rapidly dissolve without the need for water, releasing the active substance and showing systemic effects [11].

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The aim of this study was to obtain innovative bisoprol fumarate-containing orally disintegrating films (ODFs) using Pullulan and Lycoat polymer combinations and to find the optimum formulation through characterization studies on these ODFs.

2. RESULTS AND DISCUSSION

In this study, a formulation containing bisoprolol fumarate was obtained and analyzed using solvent casting method. The morphological characteristics of these films were evaluated and the three films with the best characteristics were selected. Each film formulation was cut in 2x2 cm^2 dimensions and characterization studies were carried out. For the experiments conducted only with the texture analyzer, 2x8 cm^2 films were used for ease of measurement. In the characterization studies, n=3 parallels were taken from each petri dish.

2.1. Determination of morphology

Among the film formulations F1-F17 (Table 1), three formulations, F-2, F-8 and F-14, which showed the best characteristics in terms of transparency, elasticity and mechanical strength, were selected. There was no significant difference between the liquid forms of the optimum formulations when examined morphologically. F-14 formulation was morphologically more transparent in solid form than F-2 and F-8 formulations. The F-14 formulation without Metolose 90 SH-100 showed better elastic characteristics compared to the other optimum formulations used. Formulations with less amount of Cross-PVP have higher elasticity characteristics. This was observed more in the optimum F-2 and F-8 formulations.

2.2. Determination of disintegration time

In the study, the disintegration times of F-2, F-8 and F-14 formulations were determined. In the experiments, n=6 for each formulation were performed in parallel. According to the results obtained by Petri dish method, the disintegration times of F-2, F-8 and F-14 formulations were 56.83±1.77, 55.83±1.67 and 37±1.63 seconds, respectively. According to the results obtained with the method of disintegration time determination device, the disintegration times of F-2, F-8 and F-14 formulations were 18.67±1.49, 26.67±1.97 and 16.67±1.49 seconds, respectively. Based on the results obtained, the disintegration time was approximately 50% faster in the determinator method compared to the petri dish method. The difference in disintegration time between these methods resulted from the volume of buffer used and mobility.

2.3. Determination of folding

Folding endurance of F-2, F-8 and F-14 formulations were found to be 678±3.27, 585±8.83, and 541.67±4.99, respectively. The obtained folding endurance and plasticising properties were evaluated as good for all formulations.

2.4. Determination of swelling

In the experiments performed for swelling determination (n=3), the % swelling values of F-2, F-8 and F-14 formulations were found to be 93.75±6.46, 85.24±2.40 and 142.10±4.11, respectively. Accordingly, more swelling was observed in F-2 and F-14 formulations containing Sodium starch glycolate.

2.5. Determination of thickness

In the experiments performed for each of the optimum film formulations F-2, F-8 and F-14, the film thicknesses were found to be 0.0925±0.005, 0.0975±0.007 and 0.0508± 0.003 mm, respectively. (n=10).

2.6. Determination of mass uniformity

For the mass uniformity test, the weights of F-2, F-8 and F-14 formulations were 0.0523±0.002, 0.0516±0.002 and 0.0449±0.001 mg, respectively.

2.7. In vitro release study

The total release content of the optimum film formulations F-2, F-8 and F-14 was determined as 95,748, 97,683 and 93,659 at 45 minutes, respectively. Formulations with equal Lycoat and pullulan ratios (F-8 and F-14) were found to release more drug per unit time in vitro. In vitro release values of these film formulations are shown in Figure 1. In the study, n=3 parallel experiments were performed for each film formulation.

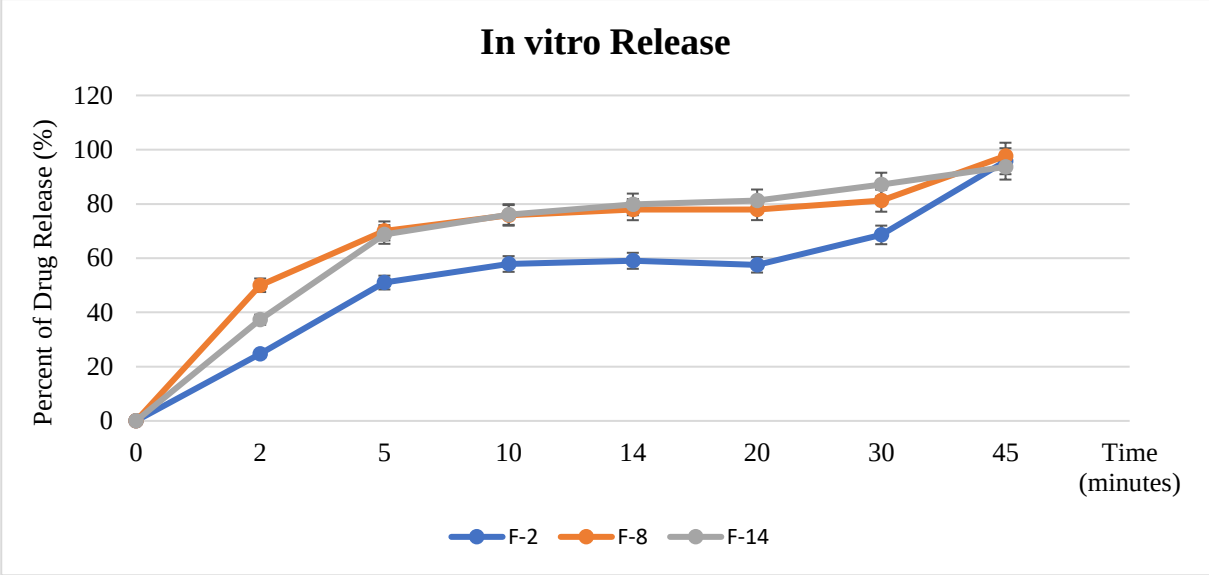

Figure 1. *In vitro* release of each formulation (n = 3, ± SD)

2.8. Uniformity of Content

Content uniformity experiments for each of formulations F-2, F-8 and F-14 were carried out in parallel n=6. Content uniformity was found to be 9.89 ± 0.05, 9.92 ± 0.04 and 9.97 ± 0.03 for formulations F-2, F-8 and F-14, respectively. Since there is no specification for the content uniformity of ODFs, the content uniformity of solid single-dose dosages was evaluated by considering pharmacopoeial standards for content uniformity. Accordingly, since the prepared ODFs did not deviate more than 10% from the specified content (10 mg), all prepared films were found to comply with pharmacopoeial requirements.

2.9. Validation of analysis method

The values obtained in the validation studies with bisoprol fumarate solutions prepared at different concentrations were analysed using UV-Visible spectrophotometry and a linear equation was established. The equation of the concentration and absorbance line was found to follow Beer's Lambert's law [12].

2.10. Determination of tensile strength, elastic modulus and elongation percentage

In the study, strength (MPa), young modulus (MPa/%) and elongation at break (%) values were found for F- 2, F-8 and F-14 formulations. Strength (MPa) values for F-2, F-8 and F-14 formulations were found to be 111.37±5.19, 50.755±5.25 and 212.19±6.97, respectively. Young modulus values for F-2, F-8 and F-14 formulations were found to be 2.19±0.40, 1.99±0.55 and 4.85±0.48, respectively. The elongation at break values for F-2, F-8 and F-14 formulations were 157.13±41.80, 50.05±11.82 and 256.32±80.14, respectively. The strength /strain graph for the F-14 formulation, which has the best strength, young modulus and elongation at break values among the formulations, is shown in Figure 3.

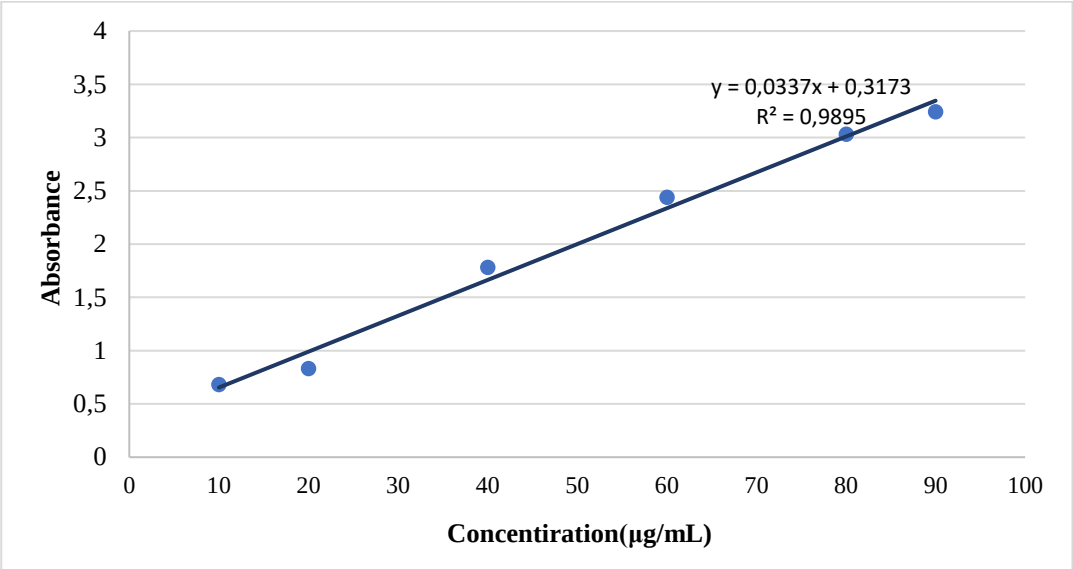

Figure 2. Standard curve chart of bisoprolol fumarate (λ=230 nm) (n=3)

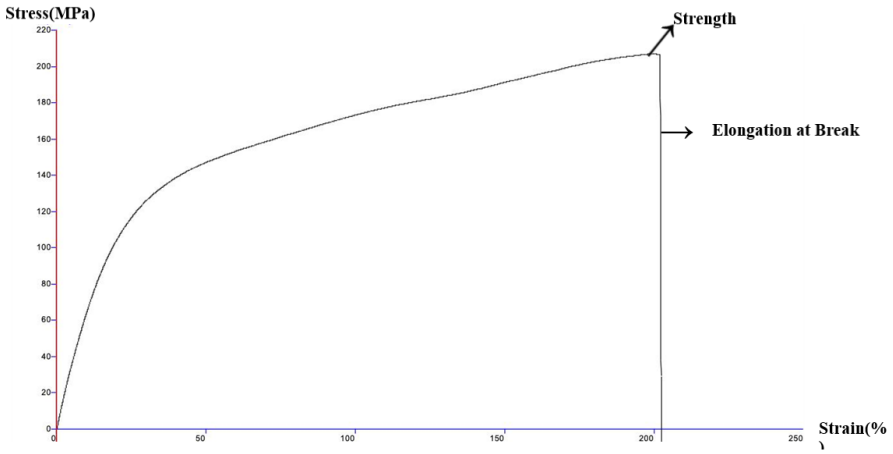

Figure 3. The stress/strain curve of the F-14 formulation is shown.

3. CONCLUSION

In this study, ODFs formulations containing bisoprolol fumarate using a combination of pullulan and lycoate polymers produced by solvent casting method were developed. With the combination of pullulan and lycoate polymers, transparent and elastic ODF formulations with good characteristics were obtained. Disintegrating agents (such as avicel, cross-linked PVP and Sodium starch glycolate) were added to the formulations in certain ratios to accelerate the pharmacological effects of ODFs containing pullulan and lycoate. ODF formulations provide ease of use without the need for water, chewing and swallowing. This has a favourable effect on treatment compliance in patients with hypertension and coronary heart disease. Even in very small amounts, bisoprolol fumarate undergoes first pass metabolism. This first pass effect is eliminated with ODF formulations containing bisoprolol fumarate. The results obtained in this study can be improved by supporting similar studies in the literature and by performing in vivo studies.

4. MATERIALS AND METHODS

4.1. Materials

Bisoprolol fumarate, Mehtaa API PVT.LTD, India; Pullulan, USP-NF Hayashibara NAGASE, Japan; Lycoat® RS 720 (E002R-E003R), Roquette, France; HPMC, Metolose® 90 SH 100, Shin-Etsu Chemical Co. Ltd., Japan; Sodium carboxymethyl cellulose (Na-CMC), Santa Farma Pharmaceutical Co. Ltd., Türkiye; Avicel® PH-101, NF FMC BioPolymer, USA; Cross-PVP, BASF Aktiengesellschaft, Germany; Na-starch glycolate, Bilim Pharmaceuticals Co. Ltd., Türkiye; PEG- 400, ABCR GmbH & Co. KG, Germany; Glycerine, Sigma Aldrich Biochemic. GmbH, Germany. The grade of all excipients were that of analytical reagents.

4.2. Methods

4.2.1 Preparation of orally disintegrating films

The method used in this study for the preparation of OTF formulations was the solvent casting method. In this method, water-soluble components were first prepared by mixing in a magnetic stirrer under the influence of heat [9,14]. API and other excipients were added to this mixture and a viscous solution was obtained. This solution was poured into a Petri dish and dried at room temperature to form films. [15,16]. Preformulations without bisoprolol fumarate were prepared using the solvent casting method described in this paper. The morphological characteristics of the preformulations were evaluated and F-2, F-8 and F-14 formulations were selected as optimum formulations. Then, 10 mg bisoprolol fumarate was added to these optimum formulations and characterization studies of ODFs were carried out. In the study, pullulan and lycoat were used as film forming polymers in the structure of ODFs. The preliminary formulations are shown in Table 1.

Table 1. ODF preformulations without bisoprolol fumarate

F	Lycoat (g)	Pullulan (g)	HPMC (g)	M 100 (g)	Na-CMC (g)	Avicel-101 (g)	Cross-PVP (g)	Na-SG (g)	PEG-400 (g)	GLI (g)	DW (mL)
F-1	0.30	0.10	-	0.10	0.10	-	0.05	-	0.30	0.10	15
F-2	0.10	0.30	-	0.10	0.10	-	0.05	-	0.30	0.10	15
F-3	0.20	0.15	0.10	0.10	0.10	0.05	-	-	0.20	0.10	15
F-4	0.15	0.15	-	0.20	-	0.10	-	0.10	0.30	0.10	15
F-5	0.20	0.20	-	0.10	-	0.10	-	0.10	0.05	0.05	15
F-6	0.25	0.25	-	0.10	-	0.15	0.10	-	0.10	-	15
F-7	0.10	0.10	0.10	0.10	-	0.10	0.10	-	0.10	-	15
F-8	0.10	0.10	0.10	0.10	-	-	0.05	-	0.20	0.10	15
F-9	0.15	0.20	-	-	0.10	0.10	-	-	0.30	0.10	15
F-10	0.20	0.15	-	-	0.10	-	0.05	-	0.20	0.15	15
F-11	0.25	0.10	0.15	-	-	0.10	0.05	-	0.20	0.10	15
F-12	0.15	0.15	0.10	-	-	0.10	0.05	-	0.25	0.15	15
F-13	0.15	0.15	0.15	-	-	-	-	-	0.10	0.10	15
F-14	0.15	0.15	0.15	-	0.10	-	-	-	0.10	0.10	15
F-15	0.15	0.15	0.10	-	0.10	0.05	-	-	0.10	0.10	15
F-16	0.15	0.15	0.10	-	0.10	0.05	0.05	-	0.10	0.10	15
F-17	0.15	0.15	0.10	-	0.10	0.05	0.05	0.05	0.10	0.10	15

F: Formulation, HPMC: Hydroxypropyl Methyl Cellulose, M: Metolose, Na-CMC: Sodium carboxymethyl cellulose, Cross PVP:Polyvinylpyrrolidone, Na-SG: Sodium starch glycolate, GLI: Glycerine, PEG:Polyethylene glycol, DW: Distilled water

4.2.2. Determination of disintegration time

The disintegration time was determined by two methods: petri dish method and disintegration time analyzer method. In the first method, the petri dish method, each of the 2x2 cm^2 films was placed in petri dishes containing 5 mL of phosphate buffer solution (pH 7.4) and the time of disintegration was measured with a stopwatch (n=6). In the other method, disintegration time determination device, films of the same size

were moved in phosphate buffer (pH 7.4) and disintegration was observed in a larger volume of solvent and this time was measured with a stopwatch. [17-19].

4.2.3. Determination of folding

The folding test was performed by foldinga 2x2cm² film formulation by hand multiple timesin the center and folding was continued until the films become detached. The folding endurance value was calculated after testing three samples for each ODF formulation [20].

4.2.4. Determination of swelling

During the swelling test, each 2x2cm² film was first weighed on an electronic balance. The weighed films were placed in petri dishes containing phosphate buffer solution and maximum swelling was observed and the swollen films were weighed again on an electronic balance. Swelling was calculated using the following formula [21,22].

$$\text{Swelling } \% = \frac{W1-W0}{W0} \times 100$$

W_1: Weight of the film after t time

W_0: Dry weight of the film

4.2.5. Determination of thickness

Thickness was measuredon four different edges of 2x2cm² films using an electronic micrometer and the average value was taken as the basis [23].

4.2.6. Mass uniformity

The mass uniformity test was performed by weighing each film of 2x2 cm² size separately on an electronic balance and observing the change in weight. 20 replicates were run for each formulation [24].

4.2.7. In vitro release study

During in vitro release studies, first, 2x2 cm² ODFs were placed in a beaker containing 100 mL phosphate buffer solution. This beaker was placed in a shaking water bath fixed at 37 ℃ and one mL of the dissolution medium was sampled at different time intervals (2, 4, 6, 8, 8, 10, 15 and 30 minutes). The same amount of buffer solution was added to the beaker to maintain the sink conditions. Samples taken at specific time intervals were measured by UV-visible spectrophotometry at 223 nm. In vitro release test was performed using a predetermined standard calibration curve equation of bisoprolol fumarate. The studies were performed in three parallels, protected from light and heat [25].

4.2.8. Uniformity of content

First, 2x2 cm² ODFs were placed in a beaker containing 100 mL phosphate buffer solution. Then, they were kept in a shaking water bath for 30 minutes and dilutions were made by taking 1 mL sample into a volumetric flask. Absorbance values were obtained by measurement with an UV-Vis spectroscopy. Content uniformity was calculated by placing the mean of the observed absorbance values (n = 6) in the equation of the standard calibration curve of Bisoprolol fumarate. The results of this study were evaluated in accordance with the European Pharmacopoeia (EP) standards for the content uniformity of solid single-dose dosages. Bisoprolol fumarate content in prepared ODFs should be in the range of 85-115% [26,27].

4.2.9. Determination of tensile strength, elastic modulus and elongation percentage

A texture analyzer was used to perform these tests. The films were cut in 4:1 ratios and fixed to the tensile grips of the texture analyzer A/MTG apparatus with tape. Measurement was then performed as a result of rupture and fragmentation [28, 29].

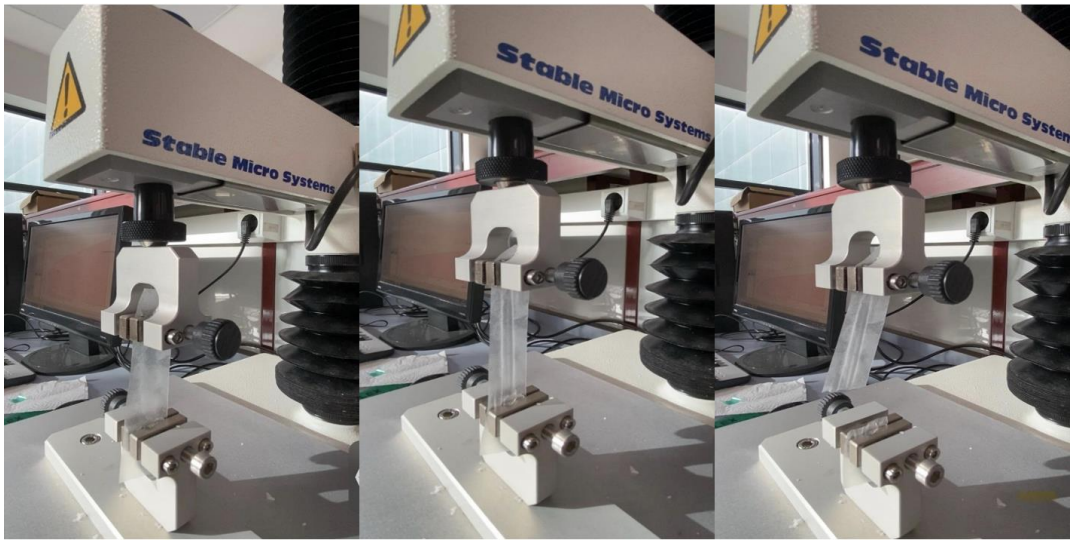

Figure 4. Placement of the F-14 formulation in the tensile grip, stress, elongation and rupture

4.2.10. Preparation of buffer

The pH 7.4 phosphate buffer solution used in the study was prepared according to EP. First, 0.2 M potassium dihydrogen phosphate was added to 250 mL distilled water and stirred with a magnetic stirrer until dissolved to obtain potassium dihydrogen phosphate solution. Then, 0.1 M sodium hydroxide was added to 393.4 mL distilled water and stirred until dissolved in the same way and sodium hydroxide solution was obtained. The prepared potassium dihydrogen phosphate solution was added to the sodium hydroxide solution and measured with a pH meter [30].

4.2.11. Validation of analysis method

Validation studies were carried out to show that the UV-spectrophotometry method applied in the analysis of Bisoprolol fumarate used in the structure of the prepared film formulations is accurate and reproducible under certain conditions. For this purpose, linearity, precision, accuracy, specificity and stability parameters were analyzed [31,32].

Initially, 10 mg Bisoprolol fumarate was weighed and dissolved in phosphate buffer solution in an ultrasonic bath. Then a stock solution was prepared by adding phosphate buffer solution to 100 ml. Dilutions were made from this stock solution and solutions were prepared at concentrations of 10, 20, 40, 60, 60, 80 and 90 µg/mL. To find the wavelength (λmax) of the maximum absorbance of the solutions at different concentrations, measurements were performed with a UV-visible spectrophotometry at a wavelength of 223 nm (n = 3). The standard calibration curve was obtained by calculating the linear equation and R^2 value of the values obtained [33,34].

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