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Original Article

Berberine-Loaded Solid Lipid Nanoparticles for Oral Administration Prepared by High-Shear Homogenization

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Abstract: Berberine (BBR) is a quaternary benzylisoquinoline alkaloid used for the local treatment of gastrointestinal tract diseases. Recently, a wide range of pharmacological properties of BBR have been reported, which include anticancer, metabolic regulation, cardiovascular protection, antihypertensive, antitumor, and neuroprotective effects. However, BBR has exhibited poor aqueous solubility and low permeability. Solid lipid nanoparticles were investigated for therapeutic improvement of BBR via oral administration. Therefore, this study aimed to prepare BBR-loaded solid lipid nanoparticles (BBR-SLNs) using the high-shear homogenization method. A lipid screen was performed, and formulation ingredients and processing parameters were evaluated. The characteristics of BBR-SLNs were evaluated, including particle size, particle size distribution, zeta potential, drug loading, and *in vitro* release profile. Specifically, the optimal BBR-SLNs had a reasonable size with a PDI value below 0.3, the absolute value of the zeta potential above 50 mV, and excellent entrapment efficiency (EE%) of nearly 95%. BBR-SLNs expressed a sustained release profile of BBR, especially in the initial period. The resulting BBR-SLNs could be considered as a potential drug delivery system to enhance BBR absorption in the human body.

Keywords: BBR, solid lipid nanoparticles, oral administration, high-shear homogenization.

1. Introduction

Berberine (BBR), a natural compound with strong pharmacological properties, has recently attracted significant attention. BBR ($C_{20}H_{18}NO_4$; 5,6-Dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium) is a benzyl tetra isoquinoline alkaloid that belongs to the

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protoBBR alkaloids. It is derived from plants such as goldthread and barberry, particularly from parts including stems, roots, bark, and rhizomes [1]. BBR is characterized by a distinctive yellow color and melting point of 145.1 – 146.7°C. This compound is soluble in hot water but has limited solubility in cold water or ethanol, and is insoluble in organic solvents like benzene, ether, and chloroform [2].

Traditionally, BBR has been used to treat diabetes and digestive disorders. Recent research has expanded its therapeutic potential, showing efficacy against various diseases. BBR acts as an anti-diarrheal by inhibiting intestinal smooth muscle movement and regulating K^+ influx in the intestinal mucosa. It exhibits anti-diabetic properties by activating AMPK pathways and is under investigation for its roles in anti-cancer, cardiovascular, psychotic, inflammatory, and immune-regulatory treatments [3].

Despite its benefits, the clinical application of BBR is hindered by poor oral absorption and low bioavailability. Several studies reveal that its absolute bioavailability in rats is only 0.37% at 240 mg/kg and 0.68% at 100 mg/kg doses [4]. In humans, only 0.5% of ingested BBR is absorbed in the small intestine, dropping to 0.35% after systemic circulation. Furthermore, approximately 56% of ingested BBR remains unabsorbed, with an additional 43.5% metabolized in the intestine, significantly limiting its therapeutic efficacy [2,5].

Over the past decade, lipid-based nanocarriers have gained significant interest as effective drug-delivery systems due to their low toxicity, high biocompatibility, and high drug-loading capacity [6]. These nanoparticles are particularly advantageous for enhancing the therapeutic potential of biopharmaceuticals with limitations such as poor water solubility or stability while offering alternatives to conventional drug delivery routes. Compared with other systems like liposomes and polymeric nanoparticles, lipid-based nanocarriers are biodegradable, non-toxic, and highly customizable [7].

Solid lipid nanoparticles (SLNs), introduced in the 1990s, have emerged as one of the most promising lipid-based carriers. Typically ranging in size from 150 to 300 nm, they can also be tailored to sizes under 100 nm or up to 1000 nm. SLNs consist of biodegradable lipids that remain solid at room and body temperatures, providing excellent matrices for encapsulating both hydrophobic and hydrophilic drugs. Their adaptability and customizable lipid components make them highly versatile [8]. SLNs rely on the interplay of lipids, surfactants, and active pharmaceutical ingredients. The choice of lipids and surfactants is crucial for particle stability, drug-loading capacity, and resistance to aggregation. This intricate engineering renders SLNs an effective and flexible tool for modern drug delivery, with immense potential in pharmaceutical applications [9-11]. It has been shown that SLN systems offer advantages over conventional formulations of bioactive compounds and plant extracts, including enhanced solubility and bioavailability, protection against toxicity, promotion of pharmacological activity and stability, improved macrophage tissue distribution, sustained delivery, and protection of drugs from physical and chemical degradation. Using SLN as a drug delivery system for BBR offers an attractive solution to the inherent difficulties associated with this natural compound [12]. SLNs were often fabricated by two major methods: hot and cold processes. Hence, in this study, BBR-loaded solid lipid nanoparticles (BBR-SLNs) were prepared using a facile hot method - hot-melting high-shear homogenization. By encapsulating BBR in SLNs, its solubility and stability can be improved, and its release can be controlled, leading to better therapeutic outcomes.

2. Materials and Methods

2.1. Materials

Glyceryl monostearate (GMS), stearic acid (SA), beeswax, Span 60, cetostearyl alcohol, soy

wax, Vaseline, lanolin, emulsifying wax, and sodium dodecyl sulfate (SDS) were obtained from Xilong Scientific (China). Poloxamer 188 and poloxamer 407 were from BASF. Compritol 888 and Texapon were gifted from Gattefosse. Berberine hydrochloride (BBR) met the requirements of active pharmaceutical ingredients.

2.2. Methods

2.2.1. Lipids and Surfactants Screening

The screening of lipids, surfactants, and combined excipients for SLN base was conducted to assess the solubility of BBR. An equal amount of BBR was added to the same amount of each ingredient (GMS, SA, cetostearyl alcohol, beeswax, soy wax, Vaseline, Compritol 888, lanolin, emulsifying wax). The mixture was heated until completely melted, maintaining a temperature approximately 5-10°C above its melting point, and continuously stirred for 1 hour. BBR solubility was assessed using visual scrutiny, focusing on the presence of a transparent substance with no observable crystal formations [13]. A similar process was applied for the examination of the effect of two types of surfactants, including Poloxamer 188, Poloxamer 407, and sorbitan monostearate, on the solubility of BBR.

2.2.2. BBR-SLNs Preparation

BBR-SLNs were prepared using the high-shear homogenization method. During the preparation of SLNs, a sequential approach involving two distinct phases was employed. In brief, accurately weighed solid lipids and BBR formed an oil phase; simultaneously, a surfactant was dissolved in water to create the aqueous phase. Both phases were heated in a water bath at 80°C for around 1 hour. After all the chemicals dissolved completely, the aqueous phase was slowly poured into the oil phase. Subsequently, the ultrasonic homogenization process was executed utilizing a high–shear ultrasonic homogenizer (WiseTis Homogenizer). The homogenization period was investigated in the range of 5 to 20 minutes, and the high shear speeds were between 10,000 and 20,000 rpm. Besides, the combination of lipid base, surfactant ratio, and hydrophilic-lipophilic balance (HLB) was also altered in the fabrication process.

2.2.3. Physical Characteristics of BBR-SLNs

The BBR-SLNs formulation underwent characterization for particle size, polydispersity index (PDI), and zeta potential (ζ) using dynamic light scattering with the Nano Partica SZ-100V2 Series (Horiba Ltd, Japan). The average size (Z-average) and PDI were determined by laser diffraction. Zeta potential (ζ) was measured to evaluate the disruption of electronic information of small nanoparticles when subjected to an electric field. All samples were serially diluted before starting the measurements.

2.2.4. BBR-SLN Morphology

The visualization of BBR-SLNs was investigated by transmission electron microscopy (TEM) (JEOL Inc, Jem–1400 Flash).

2.2.5. Quantification of BBR

A high-performance liquid chromatography (HPLC) system was used to quantify BBR in a solid lipid nano dispersion system [14]. The ChromElute ODS-BP-C18 (5 µm) column (4.6x150 mm) separation used a flow rate of 1 mL/min and an injection volume of 20 µL was completed at 30°C. The mobile phase consisted of 25 mM potassium dihydrogen phosphate and 5.9 mM SDS in acetonitrile:water (1:1). The UV detector was set at 345 nm. An established standard stock solution series produced the calibration curve.

2.2.6. Entrapment Efficiency (EE%) and Loading Capacity (LC%)

The entrapment efficiency and drug loading capacity were measured by an indirect method – ultrafiltration. BBR-SLNs were added to the filter tube (Mw cut off at 10.000 Da, 500 uL) to separate unentrapped drugs from drug-loaded particles by using the centrifuge 5425 R (Eppendorf, Germany) at 10000g in 10 mins. The concentrations of free BBR in the filtrates were quantified by HPLC. Entrapment

efficiency and drug loading capacity were calculated based on the following equation:

$$EE\ (\%) = \frac{W_i - W_u}{W_i} \times 100\%;$$

$$LC\ (\%) = \frac{W_i - W_u}{W_{l.p.}} \times 100\%.$$

W_i here is the initial amount of BBR added to the SLN formulation, W_u is the amount of free drug in the supernatant, and $W_{l.p.}$ is the total amount of lipids.

2.2.7. In vitro Release

The release of BBR was tested with a Dissolution Tester PT-DT70 (Pharma Test, Germany) using a stirring paddle, with a rotating speed of 50 rpm. Samples were put in a 14,000 Da dialysis bag, including BBR and BBR-SLNs at the same quantity of 10 mg BBR. The dissolution medium was 900 mL of distilled water with a dissolution medium at approximately 37.5°C. All test samples were placed in the dialysis bag, put into the dissolution test cup, and the machine was operated. Samples were collected at the following time intervals: 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours and then quantified by HPLC.

2.2.7. Statistical Analysis

All the results are statistically processed with the support of Microsoft Excel software 2019. Results are presented as mean ± standard deviation (X ± SD). Each experiment was repeated 3 times.

3. Results and Discussion

3.1. Lipids and Surfactant Screening

Based on the visual observations, GMS, beeswax, and SA were selected as solid lipids resulting from the higher solubility of BBR in these lipids compared to others, as clearly shown in Figure 1.

Through a comprehensive examination of BBR solubility in two distinct surfactants, it was observed that Poloxamer 407 exhibited superior solubility compared to Poloxamer 188 and sorbitan monostearate. Consequently, Poloxamer 407 was chosen for inclusion in the water phase, and further exploration of SLN formulation is required.

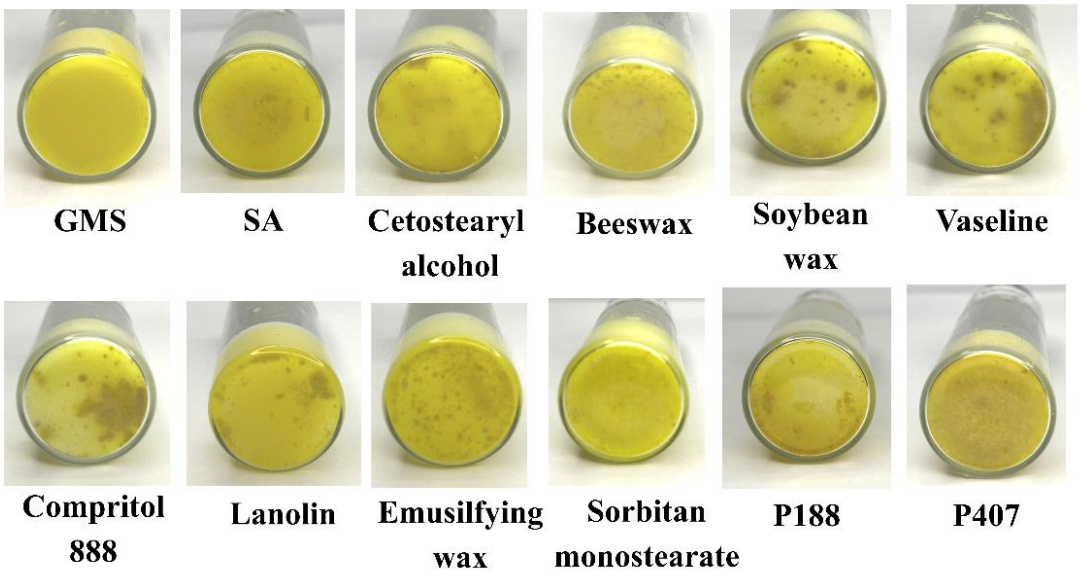

Figure 1. The screening results of solid lipids and surfactants (partly adapted from [14]).

3.2. Effect of High-shear Homogenization Parameters on BBR-SLNs Physical Properties

The high-shear homogenization duration was carried out from 5 to 20 minutes. The formulation used to optimize the fabrication process was 1% (w/v) solid lipid, 0.2% (w/v) Poloxamer 407, and a BBR loading of 5% relative to the total lipid weight. As shown in Table 1, increasing the SLN formation time from 5 minutes to 10 minutes resulted in a significant effect on the particle size and PDI of BBR-SLNs, with a smaller size at 10 minute-duration (158.43 ± 2.76 nm) compared to 5 minute-duration (162.30 ± 5.36 nm), and a reduction in PDI to 0.21 ± 0.06. at 10 minutes, from 0.32 ± 0.03 at 5 minutes. However, continuously raising the shearing time from 10 minutes to 20 minutes almost induced no change in the size or PDI of BBR-SLNs. Additionally, the zeta potential of BBR-SLNs after 10 min homogenization resulted in the highest absolute value, -49.30 ± 1.91 mV, compared with the others in the range of 40 and 45 mV. Therefore, 10 minutes was the chosen homogenization duration for the preparation of BBR-SLNs.

Table 1. BBR-SLNs physical properties at various homogenization durations (n=3)

Duration (minute)	Particle size (nm)	PDI	Zeta potential (mV)
5	162.30 ± 5.36	0.32 ± 0.03	-40.93 ± 2.40
10	158.43 ± 2.76	0.21 ± 0.06	-49.30 ± 1.91
15	156.28 ± 0.90	0.23 ± 0.02	-43.80 ± 0.72
20	157.30 ± 4.12	0.21 ± 0.07	-45.07 ± 1.92

Regarding homogenization speed, at higher speeds of 15,000 rpm and 20,000 rpm, there was black dust in the samples, which may have been caused by the friction between the stir blade and excipients. Hence, 10,000 rpm was chosen for further preparation steps of BBR-SLNs.

3.3. Effect of Lipid Composition on BBR-SLNs Physical Properties

3.3.1. Effect of Lipid Types on BBR-SLNs Physical Properties

After lipid screening, three selected lipids, GMS, SA, and beeswax, went through further investigation to choose a combination of lipid bases. Following the optimized high-shear homogenization process, for single lipids, SA showed the largest particle size and PDI, followed by beeswax, with the particle size approximately 800 nm for SA and over 600 nm for beeswax, and PDI values were 0.5 and 0.4, respectively. GMS displayed the lowest particle size and PDI, at approximately 160 nm (Table 2). When SA or Beeswax was combined with GMS at a 1:1 ratio, the resulting BBR-SLNs were reduced by a factor of four (below 150 nm) compared to those formed by using SA alone, and by a factor of three (225 nm) compared to those formed by using beeswax alone. BBR-SLNs with lipid bases of GMS and SA even had the smallest particle size among all samples, as well as the lowest PDI (above 0.25). Therefore, GMS and SA were chosen for the lipid base of BBR-SLNs.

Table 2. BBR-SLNs physical properties at various lipid types (n=3)

Samples	Particle size (nm)	PDI	Zeta potential (mV)
100% GMS	160.54 ± 10.28	0.33 ± 0.02	-39.77 ± 0.91
100% SA	755.13 ± 37.24	0.52 ± 0.02	-33.46 ± 1.53
100% Beeswax	626.80 ± 30.16	0.43 ± 0.01	-36.07 ± 0.66
50% GMS + 50% SA	148.45 ± 1.31	0.27 ± 0.05	-41.86 ± 0.90
50% GMS + 50% Beeswax	225.77 ± 2.52	0.37 ± 0.03	-39.07 ± 1.04

3.3.2. Effect of Lipid Combination Ratio on BBR-SLNs Physical Properties

Glyceryl monostearate is a lipid with a less ordered crystalline lattice, which exhibits emulsifying properties (HLB ~ 3.8) and improves the stability and drug-loading capacity of the nanoparticles. Stearic acid is a free fatty acid that can act as a co-emulsifier and modify the lipid matrix properties [15]. The ratios of GMS and SA in the lipid base were also investigated. Although there are minor differences between the physical properties of BBR-SLNs at various ratios, the ratio 7:1 of GMS:SA was chosen for further study based on the lowest particle size and PDI, and the highest zeta potential as shown in Table 3. The lower PDI indicated a narrower BBR-SLNs size distribution, and the higher absolute value of zeta potential ensured more stable nanocarriers via electrostatic repulsion [16].

Table 3. BBR-SLNs physical properties at different ratios of GMS and SA (n=3)

GMS : SA ratios	Particle size (nm)	PDI	Zeta potential (mV)
9 : 1	137.98 ± 1.96	0.29 ± 0.02	-55.47 ± 2.34
7 : 1	135.03 ± 1.01	0.26 ± 0.01	-56.05 ± 1.06
5 : 1	136.40 ± 1.71	0.28 ± 0.02	-51.83 ± 1.05
3 : 1	138.43 ± 1.55	0.29 ± 0.03	-51.63 ± 2.46
1 : 1	148.45 ± 1.31	0.27 ± 0.05	-41.86 ± 0.90

3.4. Effect of Surfactant on BBR-SLNs Physical Properties

The most suitable lipid base was GMS:SA at the ratio of 7:1. Surfactants with HLB values between 13 and 30 are often used to stabilize SLN dispersions because the dispersion is an oil-in-water emulsion. The formulations were fixed with 1% lipid (w/v) and 0.2% (w/v) surfactant, with three investigated types: Poloxamer 407, Poloxamer 188, and Texapon OC-N (sodium lauryl sulfate). Poloxamer 407, a polyoxyethylene polymer, is widely recognized as a surfactant for its exceptional properties. This compound boasts an HLB value of approximately 22 and is characterized by its excellent water solubility, solution clarity, etc [17]. In this research, Poloxamer 407 had the greatest effect in reducing the size and PDI of BBR-SLNs, with particle size above 130 nm and PDI value above 0.25 (Figure 2). This could be explained by the lowest HLB of Poloxamer 407 among the three surfactants, which enabled better interactions with the lipid base in BBR-SLNs, resulting in the formation of nanoparticles of a smaller size. The morphology of BBR-SLNs can be considered as a round shape, shown in the TEM image (Figure 3).

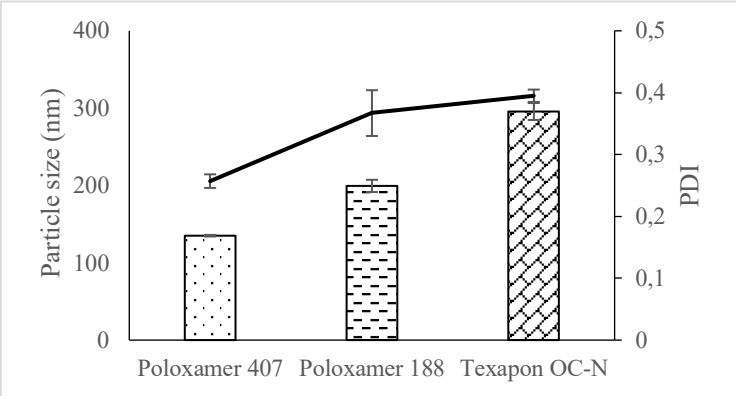

Figure 2. The particle size and PDI values of BBR-SLNs with different surfactants.

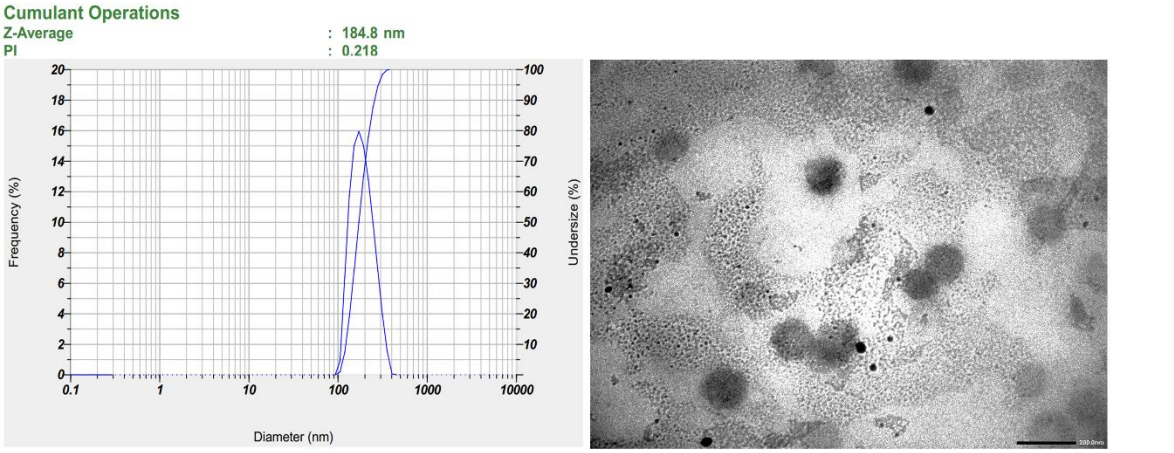

Figure 3. The particle size, PDI value, and TEM images of representative BBR-SLN.

3.5. Quantification of BBR

To construct a standard curve for BBR quantification, standard solutions at concentrations of 5, 10, 25, 50, and 100 µg/mL were prepared. The obtained result showed that the retention time of BBR was about 9 minutes. The peaks on the chromatogram were balanced, sharp, clearly separated, and had high purity. The concentration of berberin (µg/mL) was proportional to the peak area (mAu.min) according to the equation y = 1.0451x + 0.0784 with coefficient $R^2 = 1$ (Figure 4).

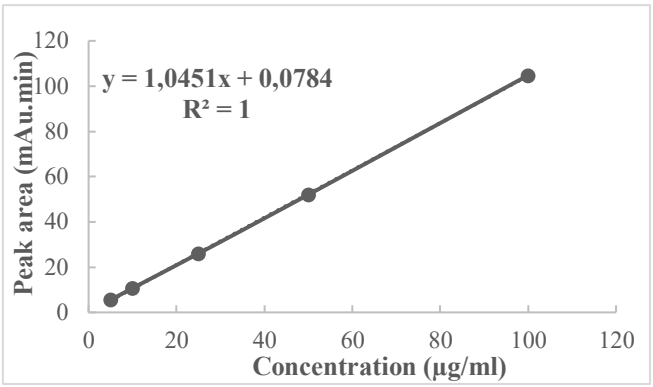

Figure 4. The correlation between the concentration of BBR (µg/mL) and peak area (mAu.min).

3.6. Entrapment Efficiency and Loading Capacity of BBR in SLNs

The optimal SLNs have an excellent entrapment efficiency (EE%) of nearly 95% and a loading capacity value of almost 4% with added BBR at 5% (w/w) compared with the lipid base. These high values showed that the bulk of BBR was efficiently encapsulated in the SLNs, provided that SLNs are the potential nanocarrier for BBR.

3.7. Drug Release of BBR-SLNs

The drug release of optimal BBR-SLNs was evaluated. BBR released through the dialysis bag was about 42% after 30 minutes, up to nearly 90% after just 4 hours, and almost wholly 100%

after 24 hours (Figure 5). The BBR-SLNs expressed/demonstrated sustained controlled release compared to the standard BBR. The dissolution percentage of BBR from BBR-SLNs was approximately 65% after 4 hours, and nearly 70% after 24 hours. BBR-SLNs shared the same release pattern as previous studies, which also used SLNs to deliver BBR [14, 18]. Poloxamer 407 could enhance dispersion, reduce aggregation, and promote BBR dissolution in the surrounding medium, thus preventing BBR precipitation and contributing to the controlled release profile observed in BBR-SLNs.

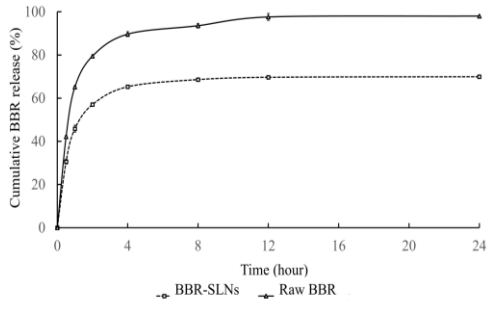

Figure 5. The drug release profile of the optimal BBR-SLNs in distilled water.

4. Conclusion

In lipid screening, BBR showed higher solubility in GMS, SA, and beeswax. P407 was the most effective surfactant for delivering BBR in lipid-based systems. The suitable lipid combination for BBR-SLNs was GMS and SA at the ratio of 7:1, at 1% (w/v) of total sample volume, and Poloxamer 407 at 0.2% (w/v). BBR was loaded at the ratio of 5% (w/w) of the lipid base, which resulted in a reasonable size of BBR-SLNs (above 130 nm) and could be considered a homogeneous system (PDI approximately 0.25) with high entrapment efficiency (95%). BBR-SLNs exhibited extended release in an *in vitro* release study, with 70% of the drug released at 24 hours for oral administration. Hence, the formulated SLNs in this study could serve as a potential nano-vehicle for oral delivery of BBR.

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