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Original Research Article

Evaluation of Gentamicin-Entrapped Solid Lipid Microparticles Formulated with a Biodegradable Homolipid from *Capra hircus*

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Abstract

Purpose: *To formulate solidified reverse micellar solutions (SRMS)-based solid lipid microparticles (SLMs) using homolipid from Capra hircus, and evaluate its suitability for the delivery of gentamicin.*
Methods: *SLMs were formulated by melt-emulsification using SRMS (15 % w/w Phospholipon® 90G in 35 % w/w Capra hircus), PEG 4000 and gentamicin (1.0, 2.0 and 3.0 % w/w), and characterized with respect to size, morphology, encapsulation efficiency (EE) and pH-dependent stability. In vitro release of gentamicin from the SLMs was performed in phosphate buffer (pH 7.4) while bioevaluation was carried out using clinical isolates of Pseudomonas aeruginosa and Staphylococcus aureus.*
Results: *Stable and discrete SLMs of size range 1.47 ± 0.02 to 3.55 ± 0.09 µm were obtained. The SLMs showed a biphasic pattern of drug release and exhibited time-dependent and capacity-limited bioactivity. Overall, SLMs containing 2 % w/w SRMS, 3 % w/w gentamicin and PEG 4000 entrapped the highest amount of drug, released 99 % of drug and gave the highest inhibitory zone diameter (IZD) against the organisms within 420 min, while plain gentamicin gave the least.*
Conclusion: *SRMS-based SLMs prepared with homolipid from Capra hircus offers a suitable delivery system for gentamicin.*

Keywords: *Solid lipid microparticles, Gentamicin, Capra hircus, Phospholipon® 90 G, Solidified reverse micellar solution*

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INTRODUCTION

Sustained-release formulations offer numerous advantages compared to conventional dosage forms [1,2]. The proven safety and efficacy of lipid-based carriers make them potential alternative drug carrier materials to polymers as well as attractive candidates for preparing lipid-based formulations. These formulations allow for controlled/sustained drug delivery, among other benefits [3-5]. Solidified reverse micellar delivery systems (SRMDS) are lipid-based biodegradable matrix drug delivery systems [6], and have been widely investigated as potential drug delivery systems for drugs which encounter penetration and absorption problems [7,8]. Gentamicin, an aminoglycoside antibiotic used in the control of severe Gram-positive and Gram-negative microbial infections, is limited by poor absorption, low bioavailability and toxicity [9-11]. By tactical

engineering of lipid drug delivery systems (LBDDS) such as solidified reverse micellar solution-based solid lipid microparticles (SRMS-based SLMs), these problems could be surmounted. Researchers have used this novel technology to increase the overall efficacy while minimizing toxicity of gentamicin [4,5,12-17]. Homolipids and heterolipids have gained renewed interests as excipients for LBDDS [15]. Homolipids are esters of fatty acids with various alcohols. Previous studies on LBDDS using a homolipid from goat fat (*Capra hircus*) and containing either hydrophilic or lipophilic drugs demonstrated positive results [16,17]. Similarly, Phospholipon® 90 G (P90G) has been shown to be a good excipient in the formulation of SRMS-based SLMs [18].

Consequently, the objectives of this study were to formulate SRMS (lipid matrix) consisting of P90G and *Capra hircus*, and SRMS-based SLMs containing gentamicin using melt-emulsification technique and evaluate the *in vitro* dissolution and bioactivity of gentamicin from such a delivery system.

EXPERIMENTAL

Materials

Gentamicin pure sample (JUHEL Pharmaceutical Limited, Awka, Nigeria), goat fat (a biodegradable homolipid was obtained from Capra hircus and purified in our laboratory), Phospholipon® 90G (Phospholipid GmbH, Köln, Nattermann, Germany), poloxamer 188 (Sigma Aldrich, Spain), polyethylene glycol 4000 (Acros Organics, USA), monobasic potassium phosphate, sodium hydroxide and concentrated hydrochloric acid (BDH, England) and distilled water (Lion water, UNN, Nigeria).

Extraction and purification of homolipid from *Capra hircus*

The homolipid was extracted from the adipose tissue of *Capra hircus* by wet rendering following standard procedures [16,17].

Preparation of lipid matrix (SRMS) and solid lipid microparticles (SLMs)

Lipid matrix consisting of mixture of 35 % w/w goat fat (homolipid) and 15 % w/w Phospholipon® 90G (P90G) was prepared by fusion method [13]. Briefly, the goat fat and P90G were weighed using electronic balance (Mettler H8, Switzerland), placed into a crucible, melted together at 75 ^{o}C on a thermo-regulated water bath shaker (Heto, Denmark) and stirred thoroughly. Thereafter, the mixture was allowed to cool and solidify at room temperature to obtain the lipid matrix (SRMS).

For the preparation of the SLMs, the melt-emulsification technique [19] was adopted. In each case, the SRMS was melted at 75 ^{o}C, and the aqueous phase containing PEG-4000 and poloxamer 188 at the same temperature was added to the SRMS with gentle stirring with a magnetic stirrer (SR 1 UM 52188, Remi Equip., India), and the mixture was further dispersed with a mixer (T 25 digital Ultra-Turrax®; IKA, Staufen, Germany) at 8000 rpm for 5 min. The SLMs suspension obtained after cooling at room temperature was then lyophilized using a freeze-dryer (Amsco GT3, Germany).

Table 1: Composition of the SLMs formulation

Batch	PEG 4000 (g)	Poloxamer 188 (g)	Gentamicin (%w/w)	Lipid base (15%w/w P90G in 35%w/w GF) (g)
A_1	1.0	2.0	1.00	4.0
A_2	2.0	2.0	1.00	3.0
A_3	3.0	2.0	1.00	2.0
B_1	1.0	2.0	2.00	4.0
B_2	2.0	2.0	2.00	3.0
B_3	3.0	2.0	2.00	2.0
C_1	1.0	2.0	3.00	4.0
C_2	2.0	2.0	3.00	3.0
C_3	3.0	2.0	3.00	2.0
D_1	1.0	2.0	-	4.0
D_2	2.0	2.0	-	3.0
D_3	3.0	2.0	-	2.0

Note: *Batches A_1–A_3, B_1–B_3 and C_1-C_3 are gentamicin-loaded SLMs while batches D_1–D_3 are unloaded (zero-drug) SLMs; P90G = Phospholipon® 90G, GF = goat fat; each formulation was made up to 100 %w/w with distilled water*

Particle size analysis and morphological characterization of SLMs

The above procedure was repeated using PEG and gentamicin (1.0, 2.0 and 3.0 % w/w) and lipid matrix (4.0, 3.0 and 2.0 % w/w), to obtained gentamicin-loaded SLMs (batches A1–A3, B1–B3 and C1-C3). The unloaded SLMs (D1–D3) were also prepared. The formulation compositions are shown in Table 1.

The particle size and morphology of the SLMs were determined by computerized image analysis. Briefly, approximately 5.0 mg of the SLMs from each batch was dispersed in distilled water and smeared on a slide (Marinfield, Germany) using a glass rod. It was then covered with a cover slip and viewed with a photomicroscope (Hund®, Weltzlar, Germany) attached with a digital camera at a magnification of 1000x. With the aid of the software in the photomicroscope, the particle morphologies were observed and photomicrographs taken. The sizes of the particles were measured and average taken.

Determination of encapsulation efficiency (EE) and Loading capacity (LC)

Approximately 0.5 % w/v dispersion of the SLMs in distilled water was prepared, allowed to equilibrate for 48 h at room temperature, shaken and filtered. The filtrate was adequately analyzed for gentamicin content spectrophotometrically (Unico 2102 PC UV/Vis Spectrophotometer, USA) at 203 nm. The amount of drug encapsulated in the SLMs was calculated with reference to a standard Beer's plot for gentamicin to obtain EE using Eq 1 [13].

$$EE\ (\%) = (Da/Dt)100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where Da and Dt are actual and theoretical drug contents, respectively.

LC expresses the ratio between the entrapped active pharmaceutical ingredient (API) and total weight of the lipids [18], and was computed as in Eq 2.

$$LC = [W_a/W_l] \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

where W_l is the weight of lipid added in the formulation and W_a is the amount of API entrapped by the lipid.

Time-resolved pH-dependent stability studies

The pH of dispersions of the SLMs from each batch was determined using a pH meter (Suntex TS - 2, Taiwan) after one week, 1 and 3 months of storage.

***In vitro* drug release studies**

Phosphate bufferred saline (PBS, pH 7.4) and the USP XXII rotating paddle apparatus (Erweka, Germany) were employed for this release study. The dissolution medium consisted of 500 mL of freshly prepared PBS maintained at 37 ± 1 ^{o}C by means of a thermostatically controlled water bath. The polycarbonate dialysis membrane used was pre-treated by soaking it in PBS for 24 h prior to the commencement of each release experiment. In each case, 300 mg of the formulated SLMs was placed in the dialysis membrane containing 5 mL of the PBS, securely tied with a thermo-resistant thread and then immersed in PBS under agitation provided by the paddle at 100 rpm. At 60 min intervals, 10 ml portions of PBS were withdrawn and replaced with equal volume of PBS to maintain sink condition, filtered and analysed spectrophotometrically at 341 nm. The amount of drug released at each time interval was determined with reference to the standard Beer's plot for gentamicin in PBS. This test was replicated for all the batches, gentamicin pure sample and commercial gentamicin injection.

Antimicrobial studies

The antimicrobial activity of the SLMs was tested against clinical isolates of *Staphylococcus aureus* and *Pseudomonas aeruginosa* by agar diffusion technique [12] using samples withdrawn during the *in vitro* drug release studies. Molten nutrient agar was inoculated with 0.1 ml of *Staphylococcus aureus* broth culture. It was mixed thoroughly, poured into sterile petri dishes and rotated for even distribution of the organism. The agar plates were allowed to set and a sterile cork borer was used to bore three cups in the seeded agar medium. Using a sterile syringe, a definite volume withdrawn from the receptor compartment of the diffusion apparatus at pre-determined time intervals was used to fill the holes. The plates were allowed to stand at room temperature before incubating at 37 ± 1 °C for 24 h. The diameter of each inhibition zone was measured and the average determined [5]. The procedure above was repeated for *Pseudomonas aeruginosa*.

Statistical analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± SD. ANOVA and Student's t-test were performed on the data sets generated using SPSS. Differences were considered significant at $p < 0.05$.

RESULTS

Table 2 shows the particle sizes and time-resolved pH values of the SLMs. The results indicate that gentamicin-loaded SLMs and unloaded SLMs had a mean particle size (n = 30) range of 1.49 ± 0.05 to 3.55 ± 0.09 and 1.47 ± 0.02 to 1.51 ± 0.07 µm, respectively. It also shows that, after three months of storage, drug-loaded SLMs and unloaded SLMs showed mean pH range of 3.27 ± 0.11 to 3.29 ± 0.08 and 4.23 ± 0.09 to 6.18 ± 1.97, respectively. The photomicrographs (pictures not shown) showed that the SLMs were discrete and had a greenish and spherical appearance. The EE of the SLMs was in the range of 57.20 ± 0.96 to 94.60 ± 1.89 %. EE (Table 2) increased with increase in the concentration of gentamicin for all batches. So, batches C1-C3 gave the highest EE while batches A1-A3 gave the least. Table 2 also shows that maximum LC of 62.00, 64.30 and 70.80 g of gentamicin per 100 g of lipid were obtained for batches C1-C3 respectively containing 3 % w/w gentamicin.

The release profiles of gentamicin from the SLMs in PBS are depicted in Fig. 1. A characteristic feature of the release profile of gentamicin from the SLMs is the biphasic pattern of release. Drug release from the SLMs followed the order: C1-C3 > B1-B3 > A1-A3. The in vitro release profiles indicate very significant release of gentamicin from the SLMs. In batch A formulations, sub-batch A3 gave a maximum release of 90 % while sub-batch A1 gave the least (maximum release, 68 %). Similarly, in batch B formulations, sub-batch B3 released the highest amount (i.e., 94 %) of the drug while sub-batch B1 released the least amount (75 % of the drug). Furthermore, in batch C formulations, sub-batch C3 gave a maximum release of 99 % while sub-batch C1 released 81 % of the encapsulated drug. Commercial gentamicin injection (G1) and gentamicin pure sample (G2) gave 63 % and 60 % drug release, respectively. The results of the bioactivity recorded as inhibition zone diameter (IZD) (Tables 3 and 4) indicate that gentamicin-loaded SLMs produced very significant IZD against Gram positive organism (*S. aureus*) and Gram negative organism (*P. aeruginosa*). The formulations recorded increasing IZDs against the organisms with time. Moreover, gentamicin-loaded SLMs gave greater IZDs than the plain gentamicin as well as commercial gentamicin injection against the organisms. Overall, sub-batch C3 containing the highest PEG-4000 and drug gave the greatest IZD against Staph aureus (27.49 ± 2.38 µm) and Ps. aeruginosa (29.40 ± 3.07 µm) compared with other SLMs.

Table 2: Some physical parameters of the SLMs

Batch	Particle size(µm)[a,b]	pH [a,c]			EE (%)[a,c]	LC (g API/100 lipid) [c]
		1 week	1 month	3 months		
A_1	1.49 ± 0.05	4.20 ± 0.05	4.25 ± 0.30	4.24 ± 0.04	57.20 ± 0.96	27.00
A_2	1.56 ± 0.08	4.31 ± 0.12	4.30 ± 0.08	4.29 ± 0.05	61.77 ± 0.88	32.20
A_3	1.53 ± 0.07	4.21 ± 0.17	4.27 ± 0.02	4.23 ± 0.09	65.10 ± 1.73	40.60
B_1	2.53 ± 0.15	5.49 ± 0.11	5.46 ± 0.07	5.47 ± 0.25	76.34 ± 1.14	44.00
B_2	2.70 ± 0.04	5.50 ± 0.02	5.49 ± 0.10	5.48 ± 0.22	80.96 ± 1.22	51.70
B_3	2.54 ± 0.12	5.46 ± 0.17	5.48 ± 0.09	5.45 ± 0.03	88.20 ± 1.99	59.50
C_1	3.55 ± 0.09	6.10 ± 2.45	6.13 ± 2.45	6.11 ± 2.45	90.55 ± 1.58	62.00
C_2	3.50 ± 0.13	6.15 ± 0.82	6.12 ± 0.82	6.13 ± 0.82	92.75 ± 1.65	64.30
C_3	3.52 ± 0.06	6.17 ± 1.97	6.20 ± 1.97	6.18 ± 1.97	94.60 ± 1.89	70.80
D_1	1.47 ± 0.02	3.27 ± 0.12	3.30 ± 0.05	3.28± 0.07	-	-
D_2	1.51 ± 0.07	3.28 ± 0.04	3.27± 0.12	3.29± 0.08	-	-
D_3	1.50 ± 0.03	3.31 ± 0.03	3.30 ± 0.02	3.27± 0.11	-	-

[a]Mean ± SD, [b]n = 30, [c]n = 3; Batches A_1–A_3, B_1–B_3 and C_1-C_3 are gentamicin-loaded SLMs while batches D_1–D_3 are unloaded (zero-drug) SLMs; EE = encapsulation efficiency, LC = loading capacity

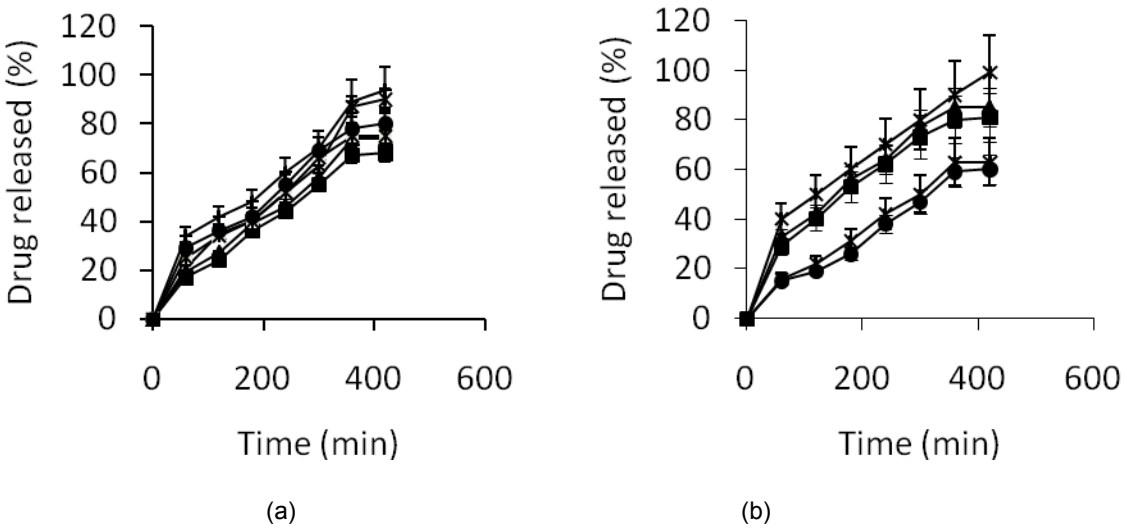

Fig. 1: *In vitro* release profile of gentamicin from (**a**) A_1-A_3 and B_1-B_3 SLMs (**b**) C_1-C_3 SLMs, $G_1$and G_2 in PBS, pH 7.4 (n = 3). ***Key***: A_1, C_1 (■); A_2, C_2 (▲); A_3, C_3 (×); G_1, B_1 (Ж); G_2, B_2 (●); B_3 (+). A_1-A_3, B_1-B_3 and C_1-C_3 contain 1.0, 2.0 and 3.0 %w/w of gentamicin respectively while G_1 and G_2 are commercial gentamicin injection and plain gentamicin, respectively

Table 3: Susceptibility of *Staphylococcus aureus* to gentamicin in the SLMs

Batch	IZD (mm)[a,b]						
	Time (min)						
	60	***120***	***180***	***240***	***300***	***360***	***420***
A_1	2.04±0.19	3.89±0.12	5.47±0.11	6.78±0.54	8.15±0.96	10.37±1.45	11.72±1.69
A_2	2.95±0.43	4.07±0.35	6.55±0.32	7.83±0.09	9.74±0.85	11.91±1.73	13.53±1.04
A_3	3.68±0.81	5.97±0.06	7.66±0.94	9.34±0.87	11.52±1.06	13.81±1.75	16.56±1.50
B_1	2.96±0.09	4.37±0.08	7.23±0.19	10.19±1.04	13.62±1.53	16.89±1.44	17.32±1.09
B_2	4.02±0.50	5.98±0.17	8.67±0.25	11.87±1.23	14.63±1.09	17.95±1.18	18.64±1.33
B_3	4.95±0.67	6.62±0.88	9.03±0.72	12.83±0.98	17.95±1.82	22.56±2.07	24.35±1.98
C_1	2.99±0.45	4.59±1.67	7.43±2.20	10.96±1.79	13.82±3.10	17.19±2.48	20.22±3.93
C_2	4.03±0.78	7.29±1.09	11.80±1.33	15.24±2.05	18.07±2.41	21.26±0.99	23.87±1.56
C_3	5.00±0.82	8.57±1.46	12.23±1.00	16.04±1.72	19.68±2.15	23.80±2.75	27.49±2.38
G_1	2.02±0.98	2.46±0.74	3.71±0.19	5.64±0.43	7.98±0.95	9.16±0.79	11.87±1.47
G_2	1.98±0.62	2.28±0.39	3.59±0.97	4.77±0.56	5.14±0.79	7.81±0.35	9.77±0.72

[a]Mean±SD, [b]n=3, A_1-A_3, B_1-B_3 and C_1-$C_3$are SLMs containing 1.0, 2.0 and 3.0 % w/w of gentamicin respectively; G_1 and G_2 are commercial gentamicin injection and plain gentamicin, respectively

Table 4: Susceptibility of *Pseudomonas aeruginosa* to gentamicin in the SLMs

Batch	***IZD (mm)[a,b]***						
	Time (min)						
	60	120	180	240	300	360	420
A_1	2.18±0.07	4.09±0.02	6.00±0.17	8.13±0.70	10.25±1.96	12.87±1.04	13.72±0.99
A_2	3.00±0.21	5.32±0.45	7.19±0.06	9.08±0.14	11.28±1.77	13.64±2.05	15.00±2.87
A_3	4.13±0.94	6.83±0.17	8.08±0.74	10.43±1.25	12.93±0.82	14.48±1.90	17.30±1.56
B_1	3.63±0.87	5.82±0.59	8.53±0.62	11.95±0.89	14.27±2.08	17.14±3.00	18.63±1.75
B_2	4.46±0.90	6.37±0.67	9.19±0.83	12.44±2.00	15.94±3.01	18.86±1.98	19.46±2.46
B_3	5.03±0.76	8.16±0.45	10.62±0.78	13.95±0.83	18.32±0.56	23.18±2.14	25.53±1.93
C_1	3.03±0.94	6.18±1.02	9.75±2.31	12.46±1.98	16.72±3.06	19.09±2.84	22.87±3.00
C_2	4.59±0.23	7.73±0.94	10.10±1.90	13.89±2.09	17.64±2.52	21.47±1.88	24.59±2.22
C_3	5.40±0.19	8.28±0.08	11.98±1.04	14.76±1.22	19.99±1.97	24.00±2.55	29.40±3.07
G_1	2.98±0.07	3.64±0.71	4.99±0.01	6.05±0.33	8.19±0.15	10.19±1.07	12.47±1.88
G_2	2.00±0.16	3.19±0.05	4.07±0.09	5.38±0.66	6.77±0.90	8.15±0.03	10.98±2.07

[a]Mean±SD, [b]n=3, A_1-A_3, B_1-B_3 and C_1-$C_3$are SLMs containing 1.0, 2.0 and 3.0 % w/w of gentamicin respectively; G_1 and G_2 are commercial gentamicin injection and plain gentamicin, respectively

DISCUSSION

The physicochemical properties of the SLMs showed that high drug loading resulted in large particle sizes, consistent with earlier reports [12,13,19]. The stability tests were carried out to determine the pH stability of the SLMs when stored at different time intervals. There was an insignificant change in the pH of the SLMs over a period of three months, implying that there was little or no degradation of the drug and/or the excipients used in the formulations within this period of time.

EE results showed that the lipid contents improved EE of gentamicin in the SLMs. The values of LC showed improved solubility of gentamicin in the lipid matrices. In addition, the incorporation of P90G in SLMs led to the formation of structured lipid matrices, which invariably enhanced gentamicin entrapment in the core of the SLMs. Furthermore, PEG-4000 being a hydrophilic surfactant improved the solubilization of the drug within the core lipids [5,18].

The percentage drug released is highly dependent on the compositions of the SLMs. The rapid release of gentamicin from the SLMs was possibly due to a burst effect caused by the leaching out of the unentrapped drug adhering to the surface of the SLMs after the initial rapid hydration and swelling. Burst release resulting in biphasic release pattern may be utilized in dosage form design [15-17]. Perhaps, there was a lot of peripheral attachment of the drug as a result of expulsion or drug migration due to solvent drag during lyophilization. Advantageously, this would lead to a high initial blood concentration of the drug and a gradual release of the remaining drug. The high and rapid release of gentamicin from the SLMs, in addition to the burst effect, may also be related to high rate of hydration and swelling of the SLMs in the medium, which might be attributed to the lipophilicity imparted on the drug by the excipients used in preparing the SLMs [6,8]. The subsequent slow release phase could be a consequence of the decreasing residual amount of drug in the SLMs and the build-up of drug concentration in the dissolution medium in the course of time [19].

The microbiological test was performed to establish that gentamicin did not lose activity during formulation. Additionally, the test was performed using samples withdrawn from the in vitro studies to show an increasing IZD over time during the drug release study. Gentamicin-loaded SLMs produced very significant IZDs against the organisms. Gentamicin is active against *S. aureus* [2] and *P. aeruginosa* [1]. It was observed that the greater the amount of gentamicin loaded into the SLMs, the greater the IZD produced, in agreement with earlier reports [5, 12]. The formulations thus exhibited capacity-limited antimicrobial activity. Similarly, the antibacterial activity of the formulations was concentation and time-dependent, manifested by an increasing IZD against the organisms with time. High IZDs recorded against the organisms within 60 min of the study especially with batches C1-C3 was an indication that these formulations would have exhibited the fastest release of the entrapped drug, hence the fast antibacterial activities; whereas time-dependent increases in IZDs within 420 min implies that the SLMs had potentials for sustained drug release. Moreover, all batches of the gentamicin-loaded SLMs gave greater IZDs than plain gentamicin and commercial gentamicin injection against the organisms. Overall, batch C3 gave the greatest IZD against the organisms. This formulation would be a useful alternative for enhanced delivery of gentamicin in the treatment of infections caused by gentamicin-susceptible micro-organisms, thus encouraging further development of this formulation.

CONCLUSION

The design and preparation of SRMS-based SLMs is a relatively new field of research that seeks to exploit the attractive properties of lipid carriers to improve the delivery of therapeutic molecules. The present study shows that gentamicin-loaded SRMS-based SLMs can be successfully prepared by melt-mulsification using PEG 4000, P90G and a homolipid from *Capra hircus*. Further studies should seek to evaluate the pharmacokinetics of these formulations in experimental animals.

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