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Research Article

Preliminary investigation of Ciprofloxacin-loaded microparticles for the treatment of bone diseases using coconut oil and shea butter

Olufunke Dorothy Akin-Ajani*, Tomisin Awe, Kehinde Ademola Adediran

Department of Pharmaceutics & Industrial Pharmacy, University of Ibadan, Ibadan, Nigeria.

*Correspondence: oakinajani@yahoo.com; od.akin-ajani@ui.edu.ng

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Abstract

Conventional drug delivery systems have several limitations, including poor bioavailability and an inability to effectively transport antibiotics to the needed site of infection in the bone. A formulation of ciprofloxacin-loaded microparticles derived from coconut oil and shea butter was developed to enable a selective and targeted distribution of the broad-spectrum antibiotic. Solid microparticles (SM), a mixture of solid and liquid lipid (coconut oil), solid-liquid microparticles (SLM), or coconut oil alone; liquid microparticles (LM), loaded with ciprofloxacin using the hot homogenization technique, were formulated. Evaluation of the microparticulate formulations included testing for particle size, the efficacy of entrapment, antibacterial activity, and in vitro drug release. The size of the microparticles that were loaded with ciprofloxacin ranked SM (5.25 ± 2.50 - 5.56 ± 2.01 µm) < SLM (7.94 ± 3.89 - 7.98 ± 2.00 µm) < LM (15.5 ± 1.50 - 20.29 ± 10.75 µm). The microparticulate formulations had an entrapment efficiency of 43.26% and 63.34% for the antibiotic ciprofloxacin. When tested against *Staphylococcus aureus*, all formulations exhibited good antibacterial activity; however, the microparticles generated from coconut oil and shea butter exhibited more significant antibacterial activity (zone of inhibition 24.0 ± 0.8 - 39.5 ± 9.2 mm), in comparison to the other formulations. LM had the fastest ciprofloxacin release (t_{50} = 5.5 min), but the microparticles formed from shea butter had a higher cumulative release (t_{50} = 12.7 min) compared to that from the mixture ($p>0.05$). These findings were obtained from in vitro drug release studies. The Korsmeyer-Peppas model could account for every formulation using the Fickian Case I transport mechanism. Because of their increased antibacterial activity, size, ability to entrap drugs, and in vitro drug release, the ciprofloxacin-loaded microparticles made from cold-pressed coconut oil combined with shea butter have the potential to provide a more effective treatment for bone diseases.

Keywords: bone disease; ciprofloxacin; coconut oil; microparticles; shea butter

Introduction

Diseases of the bone, particularly infections such as periprosthetic joint infection, osteomyelitis, and acute management of open fractures, are challenging to treat [1,2]. Periprosthetic joint infection is a severe consequence that can be life-threatening and necessitates high-dose antibiotics [3,4]. Meanwhile, osteomyelitis is a disorder in which the bone cells or marrow get infected, destroying bone tissue unless antibiotics are administered [5]. The degree of infection is influenced by various variables, including the patient's health, the state of the surrounding soft tissues, and how long the infection has been present in the joint [6]. *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (S. aureus) and *Staphylococcus epidermidis* are the bacteria that cause these illnesses. The fact that these bacteria reside packed together in a highly moist extracellular matrix ("slime") connected to a surface complicates matters [7]. As a result, bacteria in biofilms are far more resistant to antimicrobial drugs acting in their development phase than free microorganisms [7,8].

In order to ensure efficient drug delivery at the point of action, numerous innovative cell-specific targeting methods have been created in recent years. They include the utilisation of drug ligands,

boosting drug stability, enhancing drug solubility, and limiting degradation to enable pharmaceuticals to reach their targets before being removed from circulation [9].

Currently, antibiotic-loaded PMMA (polymethyl methacrylate) beads or calcium sulphate-loaded beads are used to treat periprosthetic joint infection, osteomyelitis, and the acute management of open fractures. The antibiotic is released by surface bleaching rather than desorption in the former, resulting in relatively low local drug concentrations and swiftly being released within 2 days. In certain situations, preventing the antibiotic from being entirely released [10]. A second surgery is also required to remove the cement beads in single-stage operations. Furthermore, only antibiotics that are heat stable can be used with PMMA. Calcium sulphate, on the other hand, is biodegradable and so preferred, although it has the potential to produce inflammation, wound drainage, and heterotopic ossification when exposed to synovial fluid. Microparticles (MPs) are formulated to protect the drug core from the environment, eliminate incompatibilities, mask unpleasant taste, modify drug release, improve bioavailability and minimize the side effects [11].

On the other hand, drug-loaded microparticles act as reservoirs that release the active ingredient over an extended period and maintain effective drug concentrations. This reduces the frequency of administration of the formulation and improves patient acceptance and compliance with medication. Side effects are also reduced. The size and shape of the microparticles also improve the delivery of the incorporated drug to the specific target site (reduced dosage quantities since the medicine would be delivered at the same site). If designed as a bioadhesive, it ensures that the drug remains localized at the application site long enough to be absorbed without being quickly eliminated; thus, bioavailability is improved [12]. Such delivery systems may also increase drug stability and permeability through biological layers.

Bone cement that is loaded with antibiotics is incredibly expensive, making it out of reach for many people. In addition, the proportion of gentamycin-resistant microorganisms (mixed flora) among those responsible for chronic osteomyelitis in our healthcare facilities is extremely low. The vast majority of these microbes are susceptible to commonly used antibiotics [13]. Hence, it is essential to develop systems of drug administration that are tailored specifically to bones.

Ciprofloxacin, a fluoroquinolone antibiotic with a pH of 3.7, is highly stable to heat and has a half-life of 4-6 h, with a narrow absorption window [14]. Ciprofloxacin has a wide range of therapeutic effects, including urinary tract infections, pneumonia, skin and soft tissue infection, and bone and joint infections, to mention a few [15]. It inhibits the bacterial DNA-separating enzymes DNA gyrase, type II topoisomerase, and topoisomerase IV [16]. This prevents DNA replication and bacterial cell division. It is an excellent option for controlled delivery because it works equally well against Gram-positive and Gram-negative bacteria and mycoplasma [17,18]. The fact that ciprofloxacin has activity against mycoplasma, which is usually resistant to most antibiotics, shows it to be a promising candidate for this microparticulate formulation.

Coconut oil is an edible oil derived from the mature, harvested *Cocos nucifera* plant in the Arecaceae family. There are many reasons coconut oil is eaten worldwide, and some of its health advantages have been scientifically proven [19]. Shea butter is also edible and obtained from the tree's seeds, *Vitellaria paradoxa*, family Sapotaceae. It has been used in the food, cosmetic, paint and pharmaceutical industries [20]. In order to synthesize ciprofloxacin-loaded microparticles using coconut oil and shea butter, the purpose of the study was to carry out a preliminary evaluation of the microparticles generated, with the goal of delivering the antibiotic to the bone site at a rate that can be controlled.

Materials and method

Materials

Ciprofloxacin was a gift from Bond Chemicals Nig. Ltd., Soy lecithin (Merck, GmbH), Coconut oil (cold-pressed and hot-pressed, Healthwise Food & Farm Resources, Ibadan, Nigeria), Shea butter (obtained from a local market in Ibadan, Nigeria), Tween 80 (BDH Chemical Ltd Poole, England).

Pre-formulation studies

In order to prepare the microparticulate formulations, a slight modification was made to the hot homogenization method described by Soutoa [21] and Narala and Veerabrama [22]. This modification involved the use of varying concentrations of the surfactants in order to achieve a stable formulation while simultaneously maintaining the concentration of oils and medication. Stable microparticles were eventually formed with the formulations prepared with cold-pressed coconut oil by using the surfactants soy lecithin (0.6%) and Tween 80 (2.0%). On the other hand, stable microparticles were formed with the formulations prepared with hot-pressed coconut oil by using egg lecithin (1.2%) and Tween 80 (4.5%).

Preparation of ciprofloxacin-loaded microparticles

Microparticles loaded with ciprofloxacin were produced using a hot homogenization method. At a temperature above the lipid's melting point, microparticles were generated. Microparticles were produced utilizing solid lipid (shea butter), SM, a blend of solid and liquid lipid (coconut oil), SLM, or coconut oil by itself, LM. Shea butter, ciprofloxacin (Table 1), and a lipophilic surfactant were mixed at 70ºC in a water bath. The hydrophilic surfactant was heated with distilled water in a separate beaker. After bringing the aqueous and lipid phases to the same temperature, the aqueous phase was injected gently into the lipid phase and magnetically stirred at 700 rpm for 10 min. The hot dispersion was then homogenized for 5 min at 7200 rpm using an Ultra-Turax T18 homogenizer (Janke and Kunkel, Staufen, Germany). The SLM was made similarly to the SM, with the exception that 50% of the solid lipid was substituted with cold- or hot-pressed coconut oil. The LM was also produced in an identical fashion, utilizing simply cold- or hot-pressed coconut oil.

Table 1. The formula for the ciprofloxacin-loaded SM, SLM and LM using cold and hot-pressed coconut oil.

Ingredient	**Concentration (% w/w)**					
	Cold pressed			**Hot pressed**		
	SM_c	**SLM_c**	**LM_c**	**SM_h**	**SLM_h**	**LM_h**
Shea Butter	7.250	3.625	-	7.250	3.625	-
Coconut Oil	-	3.625	7.250	-	3.625	7.250
Soy Lecithin	0.600	0.600	0.600	-	-	-
Egg Lecithin	-	-	-	-	1.200	1.200
Tween 80	2.000	2.000	2.000	4.500	4.500	4.500
Ciprofloxacin	0.100	0.100	0.100	0.100	0.100	0.100
Water to	100.0	100.0	100.0	100.0	100.0	100.0

SM = Solid microparticle; SLM = Solid liquid microparticle; LM = Liquid microparticle; c = cold pressed coconut oil; h = hot pressed coconut oil

Determination of particle size of microparticles

The microparticles' size and shape were determined using a scanning electron microscope (VEGA3 TESCAN, Germany) and an accelerating voltage of 15 kV.

Determination of the drug entrapment efficiency of the microparticles

After centrifuging a set amount of the microparticles at 4200 rpm for 15 min at 20°C and filtering the supernatant through a micro millipore (45 μm) filter, the amount of ciprofloxacin incorporated into the microparticles was measured by spectrophotometrically at 276 nm using a UV spectrophotometer (Spectrum lab 752s UV-VIS spectrophotometer, China). The amount of medication that was found to be encapsulated in the microparticles was calculated by using the following equation:

$$\%\ \text{drug entrapment efficiency} = \frac{\text{analyzed weight of the drug in microparticles}}{\text{Theoretical weight of drug} - \text{loaded microparticles}} \times 100$$

Determination of in vitro drug release of the microparticles and release kinetics

Drug release studies were carried out *in vitro* using the dialysis bag method [22]. Before the release investigations, a 5 cm dialysis membrane (Edu-lab 008 MWCO 12000 - 14000 g/mol) was soaked in distilled water for 30 min. The release media was 0.01N hydrochloric acid. The temperature was maintained at 37°C while the dialysis membrane was suspended in the release medium. Samples (10

ml) were taken out of the release medium and replaced with new ones at intervals of 15 min. The samples were collected, appropriately diluted, and examined with a UV-visible spectrophotometer at 276 nm. Drug release kinetics was investigated by putting the release data into different equations, such as zero order, first order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. The ideal model was chosen using values for the correlation coefficients. The drug release kinetic parameters were calculated using the DD Solver software programme (Microsoft Excel add-in, Excel, 2016).

In vitro antibacterial studies of the microparticulate formulations

The antibacterial activity of ciprofloxacin-loaded microparticles was determined using the cup plate method. Using a sterile swab, the *Staphylococcus aureus* isolate suspension was streaked onto a sterile petri dish containing nutrient agar. A sterile cork borer was employed to bore wells in the nutrient agar plate. The control solution (gentamicin 1mg/ml), SM, SLM, and LM were all poured into the wells separately. The inhibition zones around the wells were measured after 24 h at 37°C [23].

Results and Discussion

Particle size of the microparticles

Particle size is one of the physicochemical features of particulate systems that is critical to the stability and bioavailability of any integrated medication [24,25]. Particulate systems' physical stability, surface area, and drug dissolving rate are determined by particle size. The particle sizes of the ciprofloxacin-loaded microparticles are shown in Table 2, and the SEM image is presented in Figure 1. The rank order for particle sizes of the microparticles produced was SM < SLM < LM. The SEM showed the SMs as the smallest while the LMs had the largest sizes. The microparticles produced from the cold-pressed coconut oil had a more comprehensive range of sizes and larger particle sizes than those produced from the hot-pressed oil. It has been demonstrated that various parameters, including the physicochemical qualities of the drug [26], influence the size distribution.

Table 2. Particle size, entrapment efficiency, and zones of inhibition of ciprofloxacin-loaded microparticles.

Oil Type	Formulation Code	Particle Size (μm)	Entrapment Efficiency (%)	Zone of Inhibition (mm)
Cold-pressed	SM_c	5.56 ± 2.01	52.00 ± 0.10	38.0 ± 9.90
	SLM_c	7.94 ± 3.89	48.95 ± 0.05	39.5 ± 9.20
	LM_c	20.29 ± 10.75	55.40 ± 0.10	20.0 ± 0.00
Hot-pressed	SM_h	5.25 ± 2.5	56.67 ± 0.04	38.0 ± 0.80
	SLM_h	7.98 ± 2.00	63.3 ± 0.04	24.0 ± 0.80
	LM_h	15.58 ± 1.50	43.3 ± 0.04	-
Control				22.0 ± 0.00

(mean ± sd, n = 3)

SM = Solid microparticle; SLM = Solid liquid microparticle; LM = Liquid microparticle; c = cold pressed coconut oil; h = hot pressed coconut oil

According to the results of the SEM analysis, not a single one of the microparticles had a spherical shape. This is most likely due to the fact that they all incorporated drugs. Nnamani et al. [25] conducted a study in which they found that the drug's incorporation changed the microparticles' morphology from spherical to somewhat spherical and irregularly shaped.

Drug entrapment efficiency of the microparticles

Drug entrapment efficiency measures how well a drug is ingrained in a particulate system and is an essential factor in determining the drug loading of microparticles [27]. The drug entrapment efficiency of the microparticulate preparations is presented in Table 2. The SM had a good entrapment of the drug; however, the SLM produced using hot-pressed coconut oil had the highest entrapment of ciprofloxacin, while the LM prepared from hot-pressed coconut oil exhibited the least entrapment, thus showing no clear trend. Microparticles with high drug content allow for the administration of fewer microparticles [28].

In vitro drug release of the microparticles and release kinetics

The percentage of medications released significantly depends on the microparticulate system's makeup [29]. Release from the particle surface, diffusion through the polymer, and release due to polymeric erosion are the three mechanisms that mediate drug release from particulate systems. These three mechanisms often occur in different ways. In cases of surface release, ingested medicines disintegrate instantly upon contact with the release media, resulting in a burst effect [27,30].

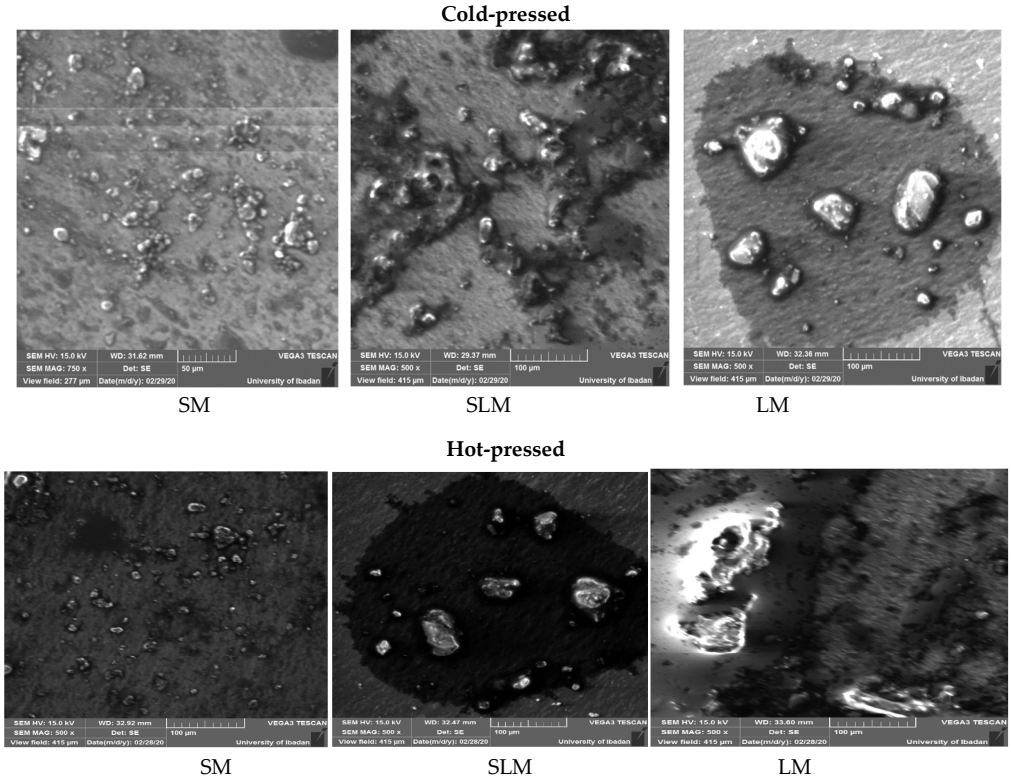

Figure 1. Scanning electron micrograph of ciprofloxacin-loaded microparticles (cold and hot pressed) (magnification: x500).

The plots of % ciprofloxacin released per time are shown in Figure 2. The microparticulate preparations made from cold-pressed coconut oil had a higher and faster release of ciprofloxacin, with the LM even exhibiting burst release. This burst release could have been caused by free medication adhering to the surface of the microparticles following the initial rapid hydration and swelling. As the temperature of the water phase dropped, the drug's solubility in the water phase may have continuously decreased as it partitioned between the liquid oil phase and the aqueous phase during particle production using the hot homogenization method. As a result, the drug concentrates on the microparticles' outer crust in a vicious cycle of re-partitioning and recrystallization. This amount of drug would be discharged in a burst from the particle's surface and outer wall [25,31]. The preparations made from hot-pressed coconut oil gave a lower and slower release of ciprofloxacin (t_{30} = 12-54 min). Thus, showing potential for prolonged release and suggesting effective entrapment [32]. On fitting the data into various release kinetic models, the highest correlation coefficient values were found for the Korsmeyer-Peppas model (Table 3). Drug release from all microparticle formulations fit the same model with similar regression coefficients, $r^2 \geq 0.996$ and diffusion constant, $n<0.45$ (0.155-0.270), indicating a Fickian (Case I) diffusion release mechanism [25,33]. This implies that the drug release mechanism is diffusion controlled.

Antibacterial properties of the microparticulate formulations

The antibacterial activity of the microparticulate formulations was evaluated against *Staphylococcus aureus*, the prevalent microorganism responsible for bone infections. All the formulations had activity against *S. aureus*, as shown by their inhibition zones in Table 2. This showed that ciprofloxacin retained

its activity even in the formulation. Only LM prepared from hot-pressed coconut oil had no detectable activity against *S. aureus*. The ranking of the antibacterial activity of the microparticulate formulations was of the order SLMc > SM > SLMh > LMc. The ciprofloxacin-loaded microparticulate formulation prepared from the shea butter and cold-pressed coconut oil had the highest activity against *S. aureus*. This may have resulted from the cold-pressed oil having undamaged lauric and capric acid, which confer antimicrobial properties on the oil [34-36] alternatively because the phospholipid profile and fatty acid composition of soy and egg lecithin vary [37]. Antimicrobial lipids have been acknowledged to have antibacterial properties ever since Dr Robert Koch et al. demonstrated in the late 1880s that fatty acids, a significant class of antimicrobial lipids, prevented the proliferation of the bacterium *Bacillus anthracis*, which causes anthrax [38]. Soy lecithin contains much more unsaturated fatty acids than egg lecithin [37]. As a result, this could have a synergistic antibacterial impact with coconut oil. Additionally, Parsons et al. looked at how pervious S. aureus was after being exposed to palmitoleate. This ideal toxic fatty acid causes the cytoplasmic membrane to rupture and causes solutes and low-molecular-weight proteins to leak into the medium [39].

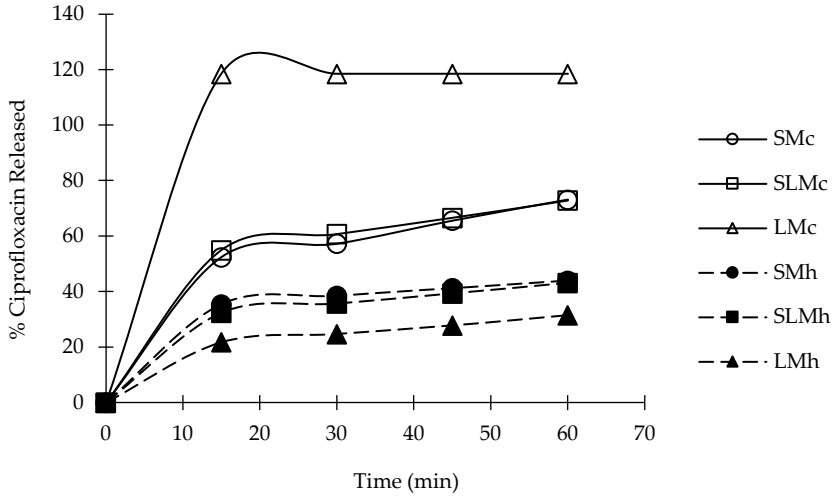

Figure 2. In-vitro drug release profile for the different Microparticulate formulations.

Table 3. Correlation coefficients of the release kinetic mathematical models for the microparticles.

Formulation code	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	
					r^2	n
SM_c	0.604	0.870	0.937	0.807	0.996	0.249
SLM_c	0.536	0.849	0.913	0.774	0.998	0.205
LM_c	0.167	-	0.722	-	-	-
SM_h	0.453	0.643	0.878	0.586	0.999	0.155
SLM_h	0.544	0.704	0.916	0.656	0.998	0.209
LM_h	0.632	0.727	0.948	0.697	0.997	0.270

SM = Solid microparticle; SLM = Solid liquid microparticle; LM = Liquid microparticle; c = cold pressed coconut oil; h = hot pressed coconut oil

Since numerous host-derived lipid groups found on mucosal surfaces, in saliva, and on the skin have recently been identified as antimicrobial molecules that function in both specific and selective inborn immune activities, with evidence that the bacterial membrane is the target, local delivery of ciprofloxacin using lipid-based microparticles can be an effective method to reduce antibacterial resistance in bone infections and to target the biofilm bacteria [40].

Conclusion

Ciprofloxacin-loaded microparticles prepared from hot-pressed coconut oil showed prolonged release and higher drug entrapment efficiency. In contrast, those prepared from cold-pressed coconut oil showed more excellent zone of inhibition and thus higher antibacterial activity, particularly in

combination with shea butter. Drug release from all the microparticulate formulations fitted the Korsmeyer-Peppas model with a Fickian (Case I) diffusion release mechanism. Thus, based on size, drug entrapment effectiveness, in vitro drug release, and antibacterial activity, the ciprofloxacin-loaded microparticles made from cold-pressed coconut oil could provide better therapy for bone diseases.

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Authors contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

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