

Effect of hydroxyapatite on the physicochemical characteristics of a gentamicin-loaded monoolein gel intended to treat chronic osteomyelitis

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ABSTRACT

Many works have demonstrated the real potential of gentamicin-monoolein-water formulations as bioresorbable and sustained-release implants for the local treatment of the chronic osteomyelitis. In order to improve the efficacy of this type of implant, the incorporation of hydroxyapatite, a well-known osteointegrator material, is thought to be an interesting approach. Five formulations incorporating 0, 2.5, 5, 10, and 20% of hydroxyapatite were examined with regard to their physicochemical and *in vitro* drug release characteristics. The rheological, thermal (differential scanning calorimetric and thermogravimetric diffraction analysis), X-ray diffraction, and dissolution studies have showed that the presence of hydroxyapatite does not dramatically disturb the cubic liquid crystalline structure of the monoolein-water gel and their ability to progressively release the antibiotic. Implant 20% that was capable to release gentamicin sulfate over a period of four weeks without marked burst effect could be used as a more suitable biodegradable delivery system for the local management of chronic osteomyelitis.

Key words: Drug release, implants, *in vitro* characterization, liquid crystalline, osteointegrator material

INTRODUCTION

Osteomyelitis is an infection of the bone and its marrow mainly caused by pyrogenic microorganisms like *Staphylococcus aureus*. It is characterized by a progressive inflammatory destruction and a new apposition of bone.^[1]

In order to maximize the efficacy of chronic osteomyelitis antibiotherapy while reducing antibiotic systemic toxicity

as well as time and costs of hospitalizations, a local, bioresorbable, sustained-release and sterile implant consisting of monoolein-water-gentamicin sulfate has been developed and fully characterized *in vitro*, with regard to its physicochemical and *in vitro* drug release.^[2]

This type of formulation is indeed known as solid-like, skin- and mucoadhesive and cubic phase gel.^[3-5] It is also able to enhance the chemical stability for antibiotic drugs like cefazolin and cefuroxime.^[6] These properties, which are interesting for the local administration of the drug in the curretted bone cavities, are not observed with the biodegradable polymeric systems already investigated by some authors.^[7-11]

The *in vitro* characterization has permitted to select an implant formulation consisting of 80-15-5% w/w monoolein-water-gentamicin sulfate as more formulation with a view to the management of chronic osteomyelitis. It was indeed capable to progressively release the antibiotic for a period of 3 weeks without burst effect.^[2] Furthermore, the biocompatibility and the absence of genotoxicity by *in vitro* assessment, the good biocompatibility and the absence of sub-chronic toxicity in mice, and the apyrogenicity by *in vitro* endotoxin test of the

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implant have been demonstrated.^[12-14] Finally, the preliminary clinical assessment of the tolerance and efficacy has been conducted with success on nineteen patients.^[15]

Based on these results, it has been thought that the incorporation of hydroxyapatite (calcium phosphate) could improve the biological performance of the monoolein-water-gentamicin sulfate implant. Hydroxyapatite is an insoluble powder and presents a physicochemical structure closed to that of the biological apatite, the mineral part of the bone. Being an osteoconductor, slowly absorbed, biocompatible, biodegradable, and bioactive material, hydroxyapatite could therefore promote the reconstruction and the reparation of the bone.^[16-17] Such an approach has also been investigated on non-adhesive films, microspheres, or implants prepared from polymers like poly (methyl methacrylic acids), poly (caprolactone), poly (lactic acid), and poly (lactic glycolic acid).^[18,19]

The aim of this work was to investigate *in vitro* the influence of the incorporation of hydroxyapatite on the physicochemical and drug release properties of monoolein-water-gentamicin implant intended to treat chronic osteomyelitis.

MATERIALS AND METHODS

The various implants were prepared and physicochemically characterized by assay of gentamicin sulfate, rheological studies, differential scanning calorimetric (DSC), thermogravimetric (TGA), X-ray diffraction (XRD) analysis, and dissolution testing, according to the description of Quédrago *et al.*^[2]

Preparation of the Implants

Five formulations of gentamicin implants incorporating hydroxyapatite, referred to as Implant 0%, 2.5%, 5%, 10%, and 20% [Table 1], weighing 100 g each, were prepared as follows: gentamicin sulfate (Yantsai Justware Pharmaceutical co, LTD, China) and monoolein (Danisco Pharma, Denmark) were separately dissolved in a volume of 50 ml deionized water and 50 ml of ethyl alcohol/Ethyl ether 97.1/2.9 v/v (Stella, Liège, Belgium), respectively. These solutions and hydroxyapatite (fluoroapatite Unsintered, Supelco INC, USA) were placed together in a 500-ml glass flask that was then mounted on a Büchi rotary evaporator R-205 (Switzerland). The mixture was then evaporated at 50°C, under magnetic stirring (60 to 150 rotations per minute [rpm]) and pressures ranging from -0.60 to -0.80

bar, until the desired quantity of final product (100 g) was obtained. The products were immediately conditioned in brown glass flask and kept in a refrigerator (2-8°C). Blank implant, containing 2.5% of hydroxyapatite but without gentamicin sulfate, was also prepared in the same way.

Assay of Gentamicin Sulfate

Gentamicin contents in the implants were determined in triplicate as follows: about 500 mg of sample was accurately weighed, introduced in a 100 ml volumetric flask, and manually dissolved with 20 ml methanol. After completion to the required volume with distilled water and stirring at 500 rpm for 2 hours with a magnetic stirrer, the solution was decanted and the supernatant was filtered twice through membrane filters (Durapore, pore size 0.45 µm). Ten ml of this filtered solution were put in 25-ml volumetric flasks and 800 µl of O-phthaldialdehyde reagent was then added. This reagent, the pH of which was adjusted to 10.4 with 45% w/v potassium hydroxide aqueous solution, was obtained by adding 400 mg of 1,2-phthalic dicarboxaldehyde (Acros organics, Belgium), 2 ml of methanol, and 800 µl of mercaptoacetic acid 98% (Acros organics, Belgium) to 38 ml of sodium borate buffer.

The volumes were then completed with methanol to 25 ml, the flasks were manually stirred, and then placed in a thermostated bath set at 60°C for 15 minutes. After cooling at room temperature for 25 minutes, absorbencies of the solutions were measured at 325 nm, using a UV/vis spectrophotometer (PU 8620 UV/VIS/NIR Philips, England). Solutions prepared in the same way with the correspondent blank implants were used as blanks. A calibration curve (absorbencies *vs* concentrations), established using 10, 25, 50, 75, and 100 µg/ml gentamicin sulfate solutions, was finally used for calculating the drug content (% w/w) in the implants.

Rheological Studies

These were performed in triplicate with a digital Brookfield Model LVDV-E viscosimeter (Brookfield engineering Laboratory, USA) mounted with an adaptor for small sample volumes and a n° 8 spindle. About 8 ml of each sample previously liquefied at 40°C were introduced into the external cylinder of the viscosimeter and the temperature was maintained at 37°C, using an Ecoline RE 106 thermostat (Germany). At each speed of the spindle (varying from 0.3 to 100.0 rpm and then from 100.0 to 0.3 rpm), the viscosity (mPa.s) was recorded after five rotations of the spindle. The sample rheograms were then plotted, after converting

Table 1: Theoretical, qualitative and quantitative (% w/w) compositions of the various implants

Formulation	Implant 0%	Blank implant	Implant 2.5%	Implant 5%	Implant 10%	Implant 20%
Gentamicin sulfate	5.0	0.0	4.9	4.750	4.5	4.0
Deionized water	15.0	19.5	14.6	14.3	13.5	12.0
Glycerol monooleate	80.0	78.0	78.0	76.0	72.0	64.0
Hydroxyapatite	0	2.5	2.5	5.0	10.0	20.0

the viscosity and the spindle speed values into shear stress (mPa) and shear rate (s^{-1}), respectively.

Thermal Analysis

The thermal properties were investigated using DSC and TGA.

DSC was carried out using a DSC 7 equipped with a Controller TAC-7/DX, Intercooler-2-cooling, and Pyris software (Perkin Elmer Instruments, USA). The instrument, calibrated with indium and cyclohexane, was continuously purged with nitrogen at 20 ml/minute. Five to ten mg samples were placed in perforated aluminium-sealed 50- μ l pans and were thermally scanned, according to the following cycle of temperatures: equilibration at -10°C for 5 minutes, heating from -10°C to 45°C at a rate of $2^{\circ}\text{C}/\text{minute}$, cooling from 45°C to -10°C at $40^{\circ}\text{C}/\text{minute}$, and heating from -10°C to 45°C at $2^{\circ}\text{C}/\text{minute}$.

For TGA, an analytic balance TGA MTB 10-8 (Setaram, France) equipped with two ovens was used. Samples of about 10 mg were loaded on quartz pans suspended from the analytic balance and continuously purged with dry air in order to avoid atmospheric moisture uptake. They were then heated from 20°C to 350°C at $2^{\circ}\text{C}/\text{minute}$ and the weight loss was recorded, using the Dasilab software.

X-ray Diffraction

XRD patterns of each sample (implants, monoolein, or gentamicin sulfate) were recorded at 20°C , using a Siemens Diffractometer D5000 (Germany) with $\text{Cu K}\alpha$ radiation of wavelength of 1.5418 \AA . Standard runs using a 40 kV voltage, a 40 mA current, and a scanning rate of $0.02^{\circ}\text{C}/\text{minute}$ over a 2θ (scattering angle) range of $5 - 50^{\circ}$ were used.

In vitro Dissolution Testing

In vitro dissolution studies were conducted in triplicate at $37.0 \pm 0.5^{\circ}\text{C}$, using the USP XXIV (2000) n°2 (paddle) apparatus. The dissolution medias consisted of 500 ml of pH 7.0 acetate-phosphate buffer-containing Polysorbate 20 (Federa, Belgium). The paddle was positioned to 3.5 cm from the bottom of the dissolution vessel and its speed was set to 60 rpm. Topical dissolution cells (Distek, Netherlands) were filled with weighed quantities of implants (about 1.6 g) and then put into the vessels. A standard vessel, containing about 80 mg of gentamicin sulfate and 1.6 g of blank implant, was also mounted in parallel in order to take into account the decrease of gentamicin sulfate concentration in the media due to its interactions with the free fatty acids released from monoolein.

After 3, 6, 24, 48, 96, 168, 240, 336, 480, 552, and 624 hours of the test, 15 ml of the dissolution media were withdrawn from each vessel and immediately replaced with the dissolution medium maintained at 37°C . After filtering

through membrane filters (Durapore, pore size $0.45 \mu\text{m}$) and appropriate dilution of the withdrawal solutions, ten ml were used for assaying gentamicin sulfate. The percentages of drug released in the dissolution media were calculated and then corrected by the values obtained from the standard vessel. Finally, the mean cumulative were plotted as a function of time and the standard deviations were represented on graphs by error bars.

At the end of the dissolution tests (26th day), the gentamicin sulfate contents in the implants remaining in the topical dissolution cells were also determined as follow: each cell was disassembled, immersed in a vial containing 50 ml of methanol, and soaked to dissolve all the residual implants. The cell was then withdrawn and the methanol solution was stirred with a magnetic plate for 15 minutes at 200 rpm, diluted with 100 ml distilled water, and stirred for 20 minutes. The resulting solution was then introduced in 250 ml volumetric flask, adjusted to the volume, homogenized, and filtered through membrane filters. The filtrate was finally used to assay gentamicin sulfate as described above.

Statistical Analysis

Data are expressed as means \pm Standard Deviation ($m \pm \text{SD}$). Student's *t* paired and One-way ANOVA tests were used to compare two and more than two means, respectively. Criterion for statistical significance was $P < 0.05$. Statistical analysis was carried out using GraphPad PRISM version 2.01 software (GraphPad software Inc., USA).

RESULTS AND DISCUSSION

All the monoolein implants prepared were viscous gels and become in contact with water, more solid and adhesive to the fingers. Table 2 shows the results of some properties determined from the different implants. Implant 0%, of which the preparation required about two hours, was a translucent gel without visible particles. In contrary, formulations incorporating hydroxyapatite were prepared in less than one hour and were more and more whiteness and trouble when the hydroxyapatite content were increased from 2.5% to 20% wt/wt. The gentamicin sulfate contents found in the various formulations were closed to the theoretical values [Table 1] attesting the absence of its degradation or lost during the manufacturing process.

The viscous and adhesive properties of the implants and the absence of lost or degradation of gentamicin sulfate during the manufacturing process have been previously observed on a monoolein-water gel similar to Implant 0%, by Ouédraogo *et al.*^[2]

Formulations containing hydroxyapatite display a negative thixotropic behavior at 37°C . Indeed, the shear stress increased with the increasing of the shear rate and

the “up” rheograms [Figure 1] were significantly lower than the “down” ones (not shown). However, Implant 0% displays a pseudoplastic behavior like the monoolein-water gels examined by other authors.^[12,20] Moreover, higher the hydroxyapatite content, higher is the viscosity of the implant [Table 1]. Some variations of the viscosity of monoolein-water gels by water or active compound contents have also been reported.^[12,21] The rheological behavior of the implants incorporating hydroxyapatite is probably due to the tightening of the internal structure of the monoolein-water gel by this insoluble powder.

The examination of DSC curves (not shown) obtained during the first heating has revealed two endothermic peaks for Implant 0%, corresponding to the melting points of monoolein-gentamicin sulfate aqueous solution mixture and non-hydrated monoolein, respectively.^[2] On the other hand, the presence of hydroxyapatite modified the thermal behavior of the implants, because only the first endothermic peak appears. However, the thermogram profiles and the melting points of the implants have not been modified by the hydroxyapatite content. The endothermic peak of formulation containing hydroxyapatite occurred at 16°C, except that of the blank implant (9.2°C). The lower melting point of this later is probably due to its relative higher water content (19.5% w/w), as observed on other monoolein-water gels by Chang and Bodmeier.^[22]

The results of the TGA have shown three stages of weight loss for the implants [Figure 2]. As discussed by Ouédraogo *et al.*, these three stages correspond to the evaporation of free water (30°C and 110°C), the evaporation of water from hydrated monoolein (110°C to 210°C), and the degradation of gentamicin sulfate and monoolein (210°C to 350°C), respectively.^[2] The cumulative weight losses of the various implants due to the evaporation [Table 2], calculated at the inflexion points (210-220°C) of the TGA thermograms, are close to their theoretical contents of water [Table 1].

The XRD patterns of all the implants [Figure 3] display two peaks in the range from 2 to 20°, as shown with implants without hydroxyapatite by Ouédraogo *et al.*^[2] Therefore, the presence of hydroxyapatite does not destroy the liquid crystal structure of the monoolein implants. However, other peaks of which the intensities increased with the hydroxyapatite content in the implant appeared in the range from 25 to 50°.

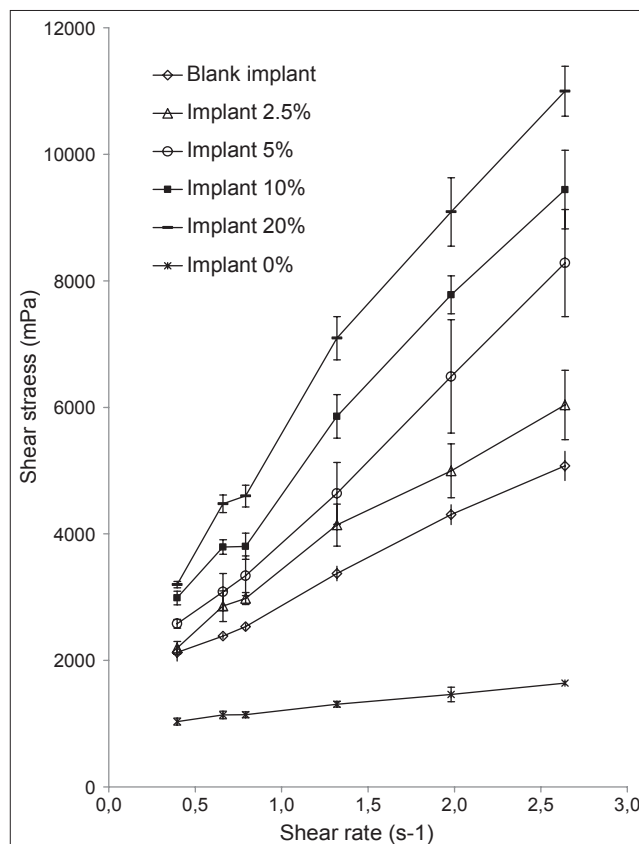


Figure 1: Up rheograms of the blank implant and the various gentamicin implants incorporating hydroxyapatite (implants 0, 2.5, 5, 10, and 20%).

Table 2: Values of some characteristics of the various implants

Formulation	Implant 0%	Blank implant	Implant 2.5%	Implant 5%	Implant 10%	Implant 20%
Time of preparation (minutes)	130	45	50	45	45	50
Gentamicin sulfate content (% wt/wt, m ± SD, n = 3)	103 ± 2	-	106 ± 1	109 ± 1	96 ± 2	98 ± 2
Water content (% w/w, m ± SD, n = 3)	15%	19%	12%	13%	14%	11%
Viscosity at a shear rate of 2 s ⁻¹ (mPa.s, m ± SD, n = 3)	1564 ± 44	2174 ± 79	2523 ± 215	3277 ± 452	3929 ± 151	4591 ± 273
Expected drug content in the residual implant at the 26 th day of the dissolution test (% w/w, m ± SD, n = 3)	1.1 ± 0.6	-	29.4 ± 0.6	18.9 ± 1.0	10.0 ± 3.2	2.0 ± 1.7
Drug content determined in the residual implant at the 26 th day of the dissolution test (% w/w, m ± SD, n = 3)	0.6 ± 0.4	-	8.4 ± 0.6	9.5 ± 0.5	9.4 ± 0.5	1.3 ± 0.7

Wt = weight; m = mean; SD = standard deviation

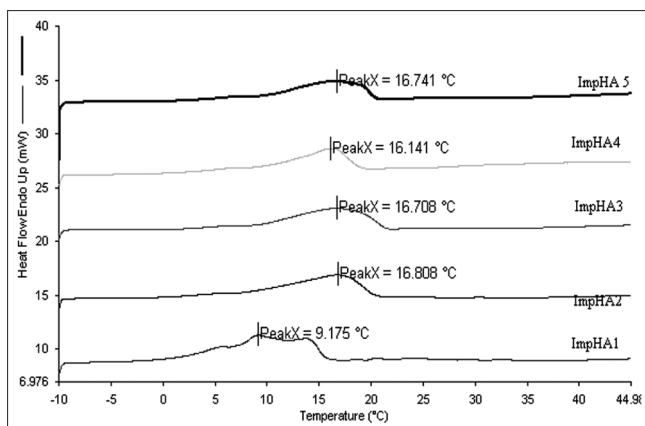


Figure 2: Differential scanning calorimetry (DSC) heating curves recorded during the first heating for implants 0% (ImpHA1), 2.5% (ImpHA2), 5% (ImpHA3), 10% (ImpHA4), and 20% (ImpHA5)

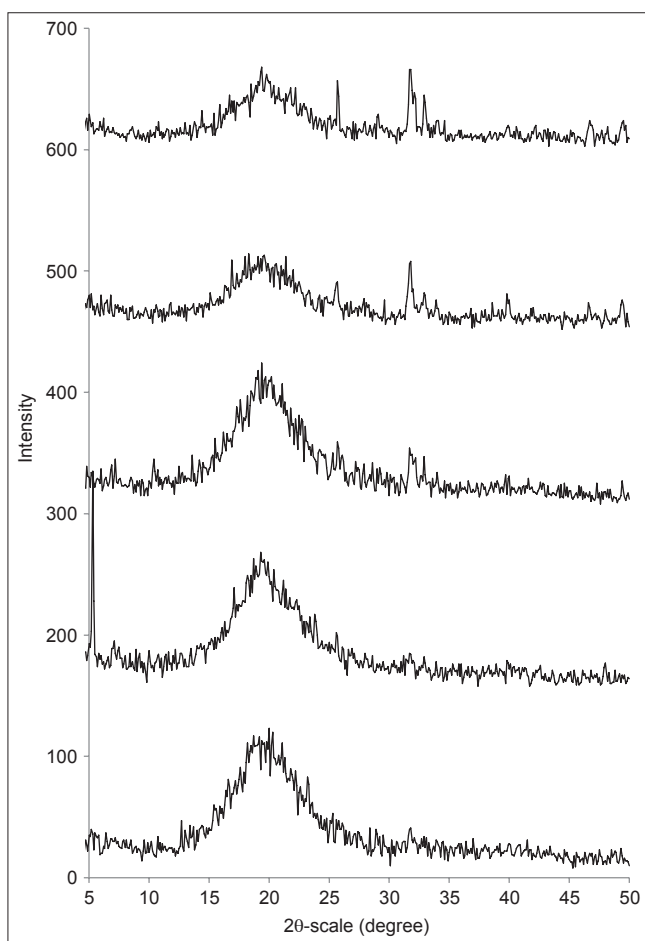


Figure 3: X-ray diffraction spectra of implants 0%, 2.5%, 5%, 10%, and 20%, from the bottom to the top of the graph

The release of gentamicin sulfate from all the implants was progressive and sustained [Figure 4], as already observed from various monoolein-water crystalline cubic phase gels. [2,23,24] It also depended on the hydroxyapatite content of the implants. It was higher than 50% and 60 % after seven days (168 hours) and 20 days (480 hours), respectively.

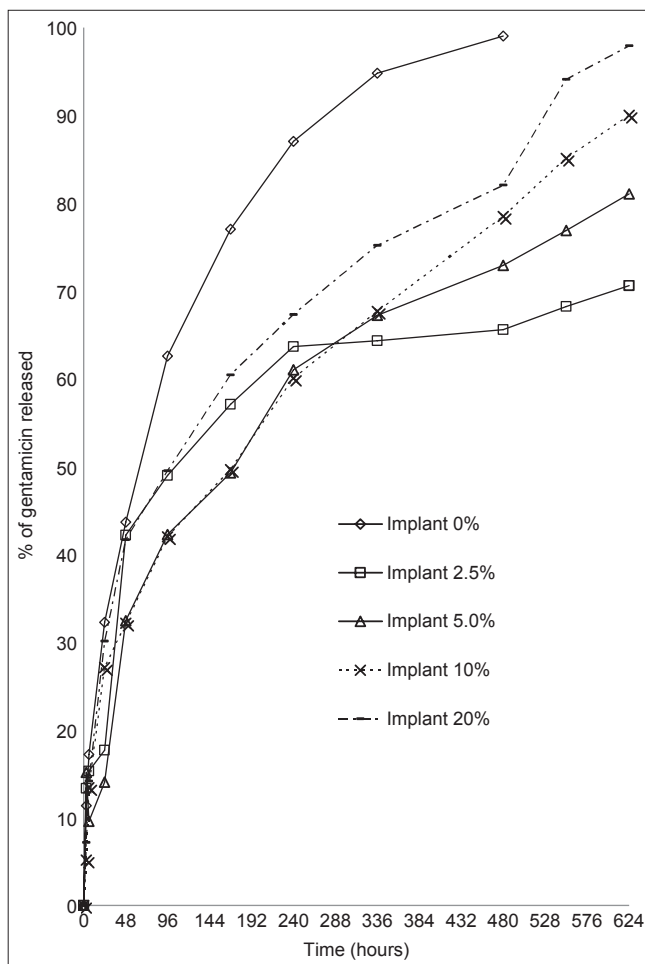


Figure 4: *In vitro* release profiles of gentamicin sulfate from Implants 0%, 2.5%, 5%, 10%, and 20%

The drug release from Implant 0 was faster than that from implants with hydroxyapatite. For these ones, however, lower the hydroxyapatite content, slower is the gentamicin sulfate release.

Among the implants incorporating hydroxyapatite, Implant 20% seems to be more promising. Indeed, its higher amount of hydroxyapatite could progressively induce the reconstruction of the curretted bone. It is also a bioadhesive gel, capable to sustain the release of gentamicin sulfate for three weeks without marked burst effects, like 80-15-5% w/w monoolein-water-gentamicin sulfate formulation for which the chronic osteomyelitis treatment potential has been demonstrated with success. [2,12-15] Some poly (L-lactic acid) and poly (L-lactic glycolic acid) implants incorporating hydroxyapatite are also able to release about 95% of their gentamicin sulfate content within four weeks. [18] However, these biodegradable polymeric systems present marked burst effects and are not bioadhesive.

The plots of the percentages of gentamicin sulfate released from the various implants as a function of the square root of time were linear, with a regression coefficient (r^2) varying from

0.90 to 0.98 (not shown). Therefore, their drug release profile is typical of a matrix-type delivery system, which means that it follows a fickian diffusion.^[25] A similar release mechanism of pseudoephedrine, bupivacaine, and gentamicin from monoolein cubic phase gels has also been reported.^[2,22,26,27]

Finally, during the dissolution test, fragments of Implants 2.5% and 5% were found in the dissolution media. This observation explains the significant differences between waited and determined values of gentamicin sulfate contents in the residual implants observed at the 26th day of the test [Table 2]. Therefore, the drug release from Implants 2.5% and 5% results in a combination of diffusion and erosion mechanisms.

CONCLUSION

The *in vitro* characterization of gentamicin-monoolein-water formulation containing increasing amount of hydroxyapatite has showed that the presence of this osteointegrable material does not destroy the liquid crystalline structure and the good physicochemical and drug release properties of the implants. Implant 20% that contains high content of hydroxyapatite as bone reconstruction material and capable to release gentamicin sulfate over a period of four weeks without marked burst effects could be used as a suitable biodegradable delivery system for the local management of chronic osteomyelitis.

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