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Development and evaluation of wound healing hydrogels based on a quinolone, hydroxypropyl methylcellulose and biodegradable microfibres

Chukwuma O. Agubata [a,*], Chiadikaobi Okereke [a], Ifeanyi T. Nzekwe [b], Remigius I. Onoja [c], Nicholas C. Obitte [a,d]

[a] Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka, Enugu State, Nigeria
[b] Department of Pharmaceutics and Pharmaceutical Technology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria
[c] Department of Veterinary Pathology and Microbiology, University of Nigeria, Nsukka, Enugu State, Nigeria
[d] Universitaet Greifswald, Institut fuer Pharmazie, Biopharmazie & Pharmazeutische Technologie, Felix-Hausdorff-Straße 3, C_DAT, 17489, Greifswald, Germany

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ABSTRACT

Ofloxacin is a synthetic antibiotic of the fluoroquinolone class, with activity against gram-positive and gram-negative bacteria. Wound healing involves a complex interaction of cells and processes which can be improved using appropriate wound- dressing materials. The aim of the present study was to develop and evaluate wound healing hydrogels containing hydroxypropyl methylcellulose (HPMC), ofloxacin and biodegradable microfibres from surgical sutures. The hydrogels were formulated by air-drying mixtures of dilute dispersions of micronized sutures (polyglycolic acid, Vicryl® and catgut), ofloxacin and HPMC gel. The prepared hydrogels were evaluated for gel fraction, swelling capacity, breaking elongation, particle size and morphology, and chemical interactions. Furthermore, *in vivo* wound healing activities were studied in rats using excision wound model and histological examination. The percentage gel fraction was ≥50% in all the batches, the percentage swelling ratio was within the range of 531.8–1700% and the percentage breaking elongation was found to be in the range of 70–120%. The chemical interaction studies using Fourier Transform Infra Red (FTIR) spectroscopy showed that there was no interaction between the drug and excipients used. Ofloxacin-loaded hydrogels containing dilute microfibres of the sutures showed 95% wound size reduction after fourteen days. These formulations also caused high collagen deposition after twenty one days of wounding, with minimal scar formation. Ofloxacin hydrogels containing HPMC and micronized suture fibres can be applied for effective wound healing.

1. Introduction

A wound can occur as defect or break in the skin, resulting from physical, chemical, thermal damage or as a result of the presence of an underlying medical or physiological condition. Wound healing is a necessary response to tissue injury. It involves sequential steps of inflammation and tissue repair, which are complex physiological processes of epithelialization, formation of granulation tissues and tissue remodeling (Evans, 1980). These complex processes of cellular and biochemical interactions involve various cells such as keratinocytes, fibroblasts and endothelial cells. The wound healing phases and their biophysiological functions are expected to occur in the proper sequence, at specific times, and progress for a specific duration at an optimal intensity (Mathieu et al., 2006). Energy, carbohydrate, protein, fat, vitamin, and mineral metabolism all can affect the healing process (Arnold and Barbul, 2006).

Wound dressings are expected to maintain a moist environment around the wound and absorb the exudates from the wound surface (Turner, 1979). Hydrogels swell upon hydration without dissolving and can provide the necessary trapped moisture for effective wound healing. Hydroxypropyl methylcellulose (Hypromellose) exhibits a thermal gelation property in an aqueous solution. When the gel solution heats up to a critical temperature, the solution congeals into a non-flowable but semi-flexible mass.

Hydrogels with large water content are highly biocompatible and possess mechanical properties similar to those of soft tissues and this allow the incorporation of cells and bioactive molecules during the gelling (Drury and Mooney, 2003; Nguyen and West, 2002). However, although cells do not readily attach to highly hydrophilic surfaces like hydrogels, the bulk or surface chemistry of hydrogels can be easily modified with extracellular matrix (ECM) domains, which promote cell adhesion (Seliktar, 2005).

The incorporation of biodegradable suture materials in hydrogels may provide domains that could promote cell adhesion, tissue regeneration and wound healing. A form of biodegradable scaffold may be created. Bio-composite formulations have been developed with synergistic wound healing outcomes (Perumal et al., 2014). Furthermore, in order to prevent contamination of wound, an *anti*-infective agent would be necessary. Ofloxacin is a synthetic antibiotic of the fluoroquinolone class. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by

* Corresponding author.
E-mail address: chukwuma.agubata@unn.edu.ng (C.O. Agubata).

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Table 1
Gel fraction and swelling index of ofloxacin-based hydrogels.

Batch	Suture used	Concentration of suture Material in gel (mg%)	% Gel fraction	% Swelling Ratio
*C*1	Catgut	0.64	75	1200
C2	Catgut	1.28	75	1233.3
C3	Catgut	1.92	75	900
*P*1	Polyglycolic acid	0.64	91	1700
P2	Polyglycolic acid	1.28	84.8	531.8
*P*3	Polyglycolic acid	1.92	88.9	584.6
V1	Vicryl® (PGLA)	0.64	66.7	828.6
V2	Vicryl® (PGLA)	1.28	50	971.4
V3	Vicryl® (PGLA)	1.92	50	1320

inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV (Drlica and Zhao, 1997).

The aim of this research is to investigate the application of micronized suture materials and quinolones as components of HPMC-based hydrogels for wound healing.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (Qualifine chemicals, India), Ofloxacin (a gift from Pauco pharmaceuticals, Nigeria), Catgut (Huaiyin, China) Vicryl® (Huaian, Jiangsu, China), Polyglycolic acid (fabricado, Mexico).

2.2. Preparation of hydrogels

A 10 cm size (23 mg) of polyglycolic acid (PGA) suture was dispersed in 10 ml of phosphate buffer (pH 7.4) in a beaker, allowed to soften for 30 min and thereafter made up to 300 ml with the buffer solution. The dispersed PGA material was micronized by using a mixer blade set at 250 rpm for 10 min. A 10 ml, 20 ml, 30 ml volume of micronized suture dispersions were, respectively, withdrawn from the beaker and mixed with 300 mg of ofloxacin dispersed in 20 ml of water (1.5% *w*/*v* ofloxacin suspension). In another beaker, 5 g quantity of HPMC was dispersed in 60 ml of water and heated while stirring. Furthermore, initial dispersions containing ofloxacin and microfibres of the suture material were each mixed with the HPMC gel, with continuous stirring to ensure homogeneity. These mixtures were each made up to 120 ml with phosphate buffer (pH 7.4) and poured into moulds (9 cm diameter and 1.2 cm height). The gels were air-dried at room temperature.

This procedure was also carried out using Vicryl® (polyglactin 910) suture and catgut suture, respectively. Vicryl® is composed of *co*-polymers of 90% glycolide and 10% *L*-lactide (polyglyc*o*lide-co-lactide or PGLA). The concentration of HPMC and ofloxacin were kept constant while varying the concentrations of the suture microfibres *via* dilutions.

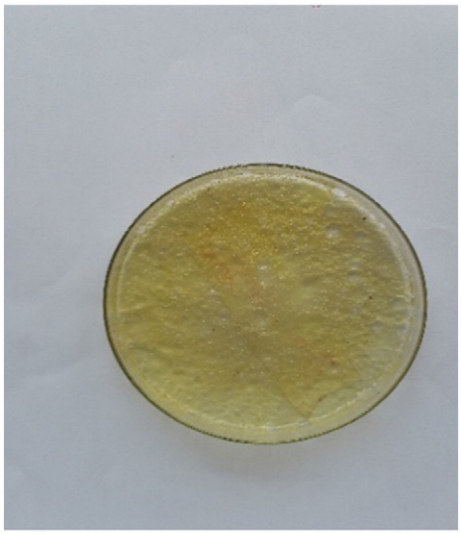

Fig. 1. Image of sample hydrogel containing HPMC, ofloxacin and polyglycolic acid microfibres in a mould of 9 cm diameter and 1.2 cm height.

Highly diluted, micronized suture dispersions were used to avoid excessive scarring.

2.3. Evaluation of the hydrogels

2.3.1. Determination of gel fraction

A piece of each formulated hydrogel sample (1 × 1 cm) was dried for 6 h at 50 °C under vacuum and weighed (W_o). Subsequently, each piece was soaked in 10 ml of distilled water in petri dish for 24 h until a constant weight was observed after the gel was taken out of the petri dish to remove the soluble part. The gels were dried again at 50 °C for 6 h under vacuum and weighed (W_e). The gel fraction percentage was calculated using Eq. (1).

$$\textit{Gel fraction } \% = \frac{W_e}{W_o} \times 100 \tag{1}$$

Where W_o and W_e are the weights of hydrogel sample dried for 6 h at 50 °C before and after soaking, respectively.

2.3.2. Determination of swelling ratio (SR%)

Pieces of hydrogel samples (1 × 1 cm) were dried at 60 °C for 12 h and weighed (W_a). The cut pieces were soaked in phosphate buffer solution (pH 7.4) at 37 °C for 10 min, withdrawn and weighed (W_s). The swelling ratio was calculated using Eq. (2):

$$SR\% = \frac{W_s}{W_a} \times 100 \tag{2}$$

Table 2
Breaking elongation data of hydrogels.

Batch	Suture used	Concentration of suture Material in gel (mg%)	Initial length (cm)	Final length (cm)	% elongation
*C*1	Catgut	0.64	1.0	1.7	70
C2	Catgut	1.28	1.0	1.9	90
C3	Catgut	1.92	1.0	2.0	100
*P*1	Polyglycolic acid	0.64	1.0	2.2	120
P2	Polyglycolic acid	1.28	1.0	2.0	100
*P*3	Polyglycolic acid	1.92	1.0	2.2	120
V1	Vicryl® (PGLA)	0.64	1.0	1.9	90
V2	Vicryl® (PGLA)	1.28	1.0	1.8	80
V3	Vicryl® (PGLA)	1.92	1.0	2.1	110