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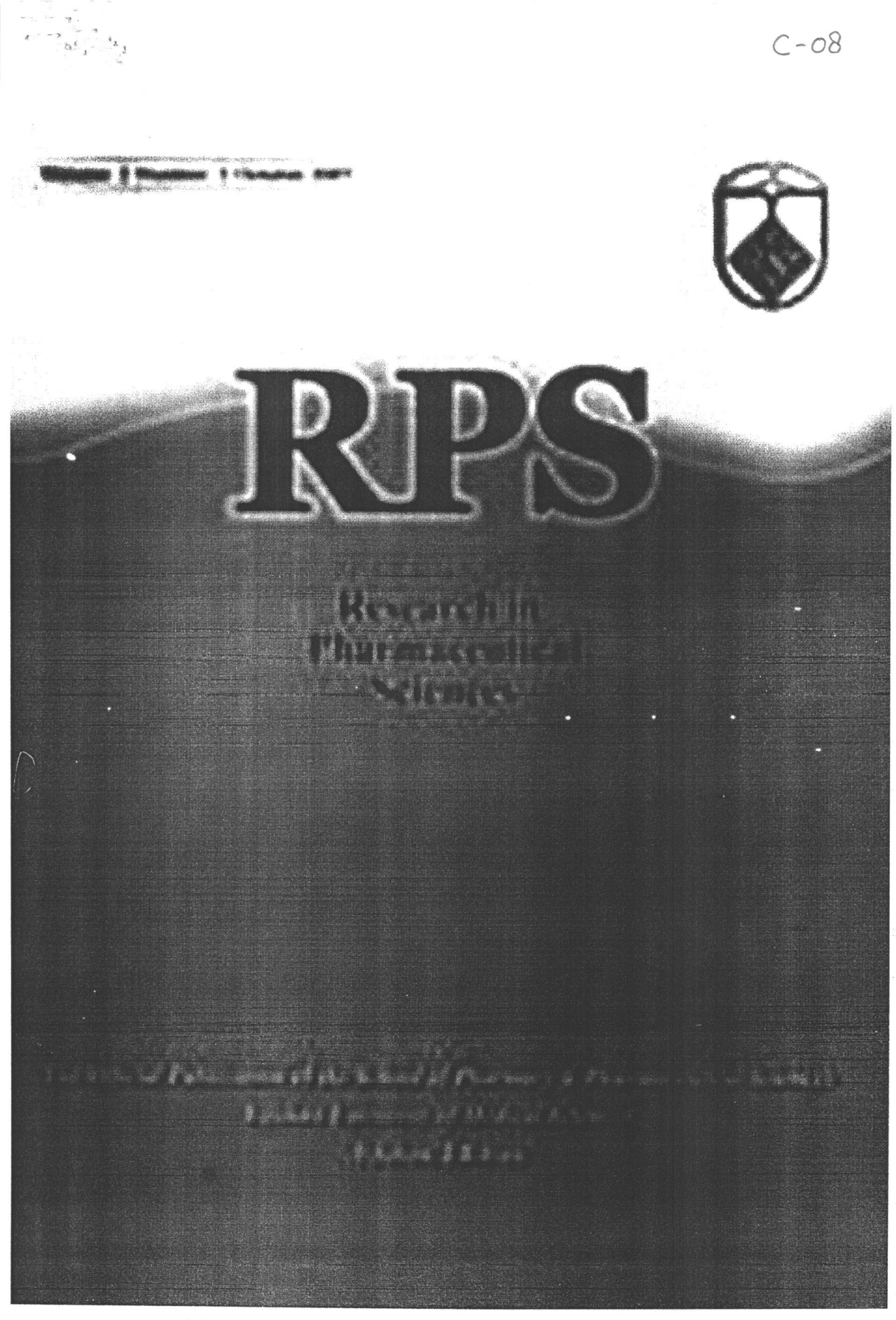

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Original Article

The effect of two different crosslinkers on *in vitro* characteristics of ciprofloxacin-loaded chitosan implants

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Abstract

The objective of this study was to determine and evaluate a controlled release implant of ciprofloxacin using bovine hydroxyapatite (BHA)-chitosan composite and glutaraldehyde or genipin as crosslinking agents. Ciprofloxacin implants were prepared using BHA, chitosan, ciprofloxacin at 30:60:10 and using three different concentrations of glutaraldehyde or genipin (0.3, 0.5, or 0.7%) as crosslinkers. Implants were formed as mini-tablet with 4.0 mm diameter weighing 100 mg using compression method. Further, the prepared ciprofloxacin implants were characterized for porosity, density, water absorption capacity, swelling, degradation, compressive strength, compatibility (Fourier transforms-infrared spectroscopy (FT-IR)), morphology (scanning electron microscope (SEM)), X-ray diffraction (X-RD), and *in vitro* drug release. The addition of glutaraldehyde or genipin as crosslinkers in ciprofloxacin implant showed controlled release profile of ciprofloxacin over a time period of 30 days. SEM photomicrograph revealed low porosity of the implant after crosslinking with glutaraldehyde or genipin. The FTIR study confirmed the formation of covalent imine bonds between chitosan and glutaraldehyde. Moreover, the addition of glutaraldehyde or genipin as crosslinkers caused a decrease in the mechanical strength of the implant. Increased concentration of glutaraldehyde or genipin reduced the crystallinity of BHA and chitosan, which were confirmed by X-RD studies. The results obtained from this study indicated that glutaraldehyde or genipin had the potential effect to retard ciprofloxacin release from BHA-chitosan-ciprofloxacin implant for 30 days.

Keywords: Ciprofloxacin implant; Crosslinker; Glutaraldehyde; Genipin

INTRODUCTION

Bones are essential parts of human body which have an important role in supporting the physiological functions of the body (1). Complications of bone disease and bone disorder caused by traumatic accidents may result in the presence of bone defect. The healing process of bone damage or bone fracture is determined by the level of trauma and soft tissue damage (2). Some cases of bone damage or bone injury cannot be naturally repaired and healed (1). Therefore, clinical rehabilitation to overcome bone defect is expected to rise along with population growth (3).

Rehabilitation of bone defects is associated with the risk of infection. The number of complications varied from 1% in the case of total joint replacement to 23% in the case of bone fracture (4). The cause of infection complication is the entry of the bacteria into the bone tissue through the defects. The infection occurs because of a less sterile surgical process, bacteria adhering to the implant, bacteria in human skin, open wounds, and circulatory patients suffering from infection elsewhere (3,5). The occurrence of bacterial infections can be treated by administering antibiotics. However, tissue devascularization in the case of bone defect limits the delivery of the antibiotic to the target site. This condition leads to the lower antibiotic concentration in the target tissues and consequently the antibiotic is not able to penetrate into the bacteria biofilm layer. This may lead to the bacterial resistance in the target tissue (6).

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To overcome these problems, antibiotics can be delivered locally by using specific drug delivery systems.

The purpose of such drug delivery systems is to provide adequate drug concentration at a specific location ensuring drug release profile for a longer period (7). Local drug delivery systems have several advantages such as minimizing systemic adverse effects, using smaller quantity of drugs with greater efficiency, avoiding multiple drug therapy, reducing risk of toxicity and ease of the delivery of the drug to target site (8). In addition, administering antibiotics locally also cause high antibiotic concentration in target tissue (3).

The release of antibiotic on the target tissue is expected to take place continuously for a specific period and the concentration is higher than minimum inhibitory concentration (MIC). Controlled release system also can enhance the bioavailability of antibiotic in the target tissue. This system is designed to release the drug in the target tissue with appropriate rate during specific period (3).

The combination of bovine hydroxyapatite (BHA) as inorganic material and chitosan as organic material could construct implants with porous structure and adequate mechanical strength to support bone formation. But, previous study revealed that drug release from hydroxyapatite-chitosan composite was so fast.

In this study, chitosan as organic material and BHA as inorganic material were used to increase mechanical strength and bone bioactivity of the implant (3) and also to control the release rate of ciprofloxacin as the antibiotic. Glutaraldehyde (8) and genipin (9) were used as crosslinkers.

MATERIALS AND METHODS

Materials

Following materials were used in the present study. Ciprofloxacin (Shangyu Jingxin Pharmaceutical Co. Ltd,); BHA (Tissue Bank RSUD DR Soetomo Surabaya, Indonesia); chitosan (Biotech, Indonesia); glutaraldehyde 25% (Merck Millipore, Germany); Genipin (Challenge Bioproduct Co. Ltd., Taiwan). Glacial acetic acid, KBr IR (for spectroscopy), Na_2HPO_4, K_2HPO_4, KH_2PO_4, and NaCl (Merck, Germany). Deionized water was used throughout the study.

Preparation of homogeneous chitosan powder

Homogenous chitosan powder was obtained by dissolving chitosan flakes in acetic acid solution (1%, v/v). The solution was stirred at 400 rpm on a mechanical stirrer for 24 h to obtain chitosan solution with 2% w/v concentration. 1 M NaOH solution was added into chitosan solution until the pH reached neutral (pH, 7). After the addition of NaOH solution into chitosan solution, a chitosan gel was obtained. Chitosan gel was dried at 40 °C for 24 h. the dried chitosan gel was sieved by 1 mm sieve to produce homogeneous chitosan powder.

Formulation of ciprofloxacin-loaded bovine hydroxyapatite-chitosan implant

The implant was prepared using direct compression method. Ciprofloxacin was dissolved in distilled water; BHA was added gradually and mixed until homogenized with ciprofloxacin. Chitosan powder was added to ciprofloxacin-BHA blend and mixed well. Distilled water was added gradually with continuous stirring until a wet mass formed. Wet mass were sieved through a 1-mm sieve and dried overnight (24 h) at 40 °C to obtain dried granules. Dried granules were immersed in glutaraldehyde or genipin solution at various concentrations (0.3, 0.5, or 0.7%) for 24 h until the color was changed. The composition of various formulations is given in Table 1.

Granules were washed with distilled water to remove the residual glutaraldehyde or genipin. At the final stage, granules were washed with phosphate buffer saline (PBS) at pH 7.40. To ensure the absence of glutaraldehyde residues, the rinsed solution tested with Schiff reagents. Granules were dried in an oven at 40 °C for 24 h. Dried granules (100 mg) were weighed out, pressed using tablet press machine with 4.0 mm diameter and the compression pressure set to 2 tons.

Table 1. The composition of implant formulations.

Formulation	Cyprofloxacin (%)	Composite (%)		Crosslinkers (%)	
		BHA	Chitosan	Glutaraldehyde	Genipin
F3	10	30	60	-	-
F3-0.3% GA	10	30	60	0.3	-
F3-0.5% GA	10	30	60	0.5	-
F3-0.7% GA	10	30	60	0.7	-
F3-0.3% GE	10	30	60	-	0.3
F3-0.5% GE	10	30	60	-	0.5
F3-0.7% GE	10	30	60	-	0.7

(GE), genipine; (GA), glutaraldehyde; (BHA), bovine hydroxyapatite.

Evaluation of implants

Density test

The density of the implant was calculated from the weight of the implant (in the dry state) divided by volume of the implant through the equation below.

$$\text{Density} = \frac{W}{\text{Implant volume}} \quad (1)$$

where, W is the weight of the implant. Implant volume was calculated by multiplying the implant thickness by implant surface area. An implant was cylindrical with 4.0 mm diameter and 0.525 mm thickness.

Porosity test

The implant was weighed in the dry state and placed in 5 mL water. The implant was taken out from the water after 1 min and placed on a filter paper to remove the excess water on the surface of the implant. The implant was weighed again (10). The porosity of the implant was calculated using equation 2.

$$\text{Porosity (\%)} = \frac{W_w - W_i}{\text{Implant volume}} \quad (2)$$

where, W_w is the wet weight of the implant and W_i is the initial weight of the implant.

Water absorption capacity and swelling ratio

The implant was weighed in dry state and immersed in 5 mL PBS, pH 7.4 for 1 min at 37 ± 0.5 °C.

The implant was withdrawn and gently blotted with filter paper to remove the excess water and weighed again (11). The percentage of water absorption capacity and swelling ratio of the implant was calculated using equations 3 and 4.

$$\text{Swelling ratio} = \frac{W_w - W_i}{W_i} \times 100 \quad (3)$$

$$\text{Water absorption capacity} = \frac{W_w - W_i}{W_w} \times 100 \quad (4)$$

where, W_i is the weight of implant in the dry state and W_w is the weight of the implant after immersion process in PBS, pH 7.40.

Hardness test

The implant was pressed by load cell compression machine 5 mm/min by autograph E-10 instrument. The hardness of the implant obtained from the force (F, in newton unit) which was displayed at the instrument was divided by contact surface area of the implant (in mm unit) (10).

Degredation test

Implant was immersed in 5 mL PBS, pH 7.4 at 37 ± 0.5 °C. Visual inspection was done to observe the changing of implant structure which was caused by erosion and degradation (12).

Evaluation of implant morphology

Morphology of the implants was observed using a scanning electron microscope (SEM). The samples were fitted to aluminum stubs with conductive paint and were sputter-coated with gold. The differences between implant morphology before and after crosslinking process were observed using specific magnification.

Drug content

The implant was placed in a mortar and milled, then transferred into an Erlenmeyer flask. 100 mL HCL 0.1 N was added into Erlenmeyer flask contained milled implant and stirred for 24 h at 400 rpm until a suspension was obtained. The suspension was filtrated and the filtrate was diluted to determine ciprofloxacin concentration. The absorbance of this solution was observed using a spectrophotometer at three wavelengths of 260, 270, or 280 nm. (Δ), absorbance which was obtained from the observation

extrapolated in standard curve equation to obtain ciprofloxacin HCL concentration. Determination of ciprofloxacin content in the implant was done in triplicate (10)

In vitro drug release study

The implant was placed in a vial containing 5 mL of PBS, pH 7.4. The vial was placed on a shelf and incubated in water bath at 37 ± 0.5 °C. Sampling was conducted by pipetting of 1 mL of elution fluids at 1, 3, 5, 7, 9, 12, 14, 16, 18, 20, 22, and 24 h on first day and every 24 h for 30 days and replaced with fresh buffer to maintain sink condition. The sample solution was filtered with Millipore membrane (ø = 0.45 μm). Appropriate dilution was prepared using PBS, pH 7.4. The absorbance of the solution was analyzed using UV spectrophotometer at three wavelengths of 260, 270, and 280 nm. Cumulative percent of drug release was found at each time interval. The release of ciprofloxacin HCL from the implants was assayed in triplicate (10).

Characterization of the implant

Fourier transforms infrared spectroscopy

A sample of the implant was combined with KBr and pressed into a tablet. The solid tablet was analyzed using Fourier transform-infrared (FT-IR) spectroscopy in the wave number range 4000-400 cm^{-1}.

X-ray diffraction study

The X-ray diffraction (X-RD) study was carried out to determine the crystal phases of the implant using monochromatic CuKα radiation (40 KV, 30 MA). X-RD peaks of the implants were compared to the diffraction peaks of pure materials (ciprofloxacin HCL, BHA, and chitosan) in 2θ scan range of 5-50 °.

Data analysis

The results of implant evaluation including density, porosity, swelling ratio, water uptake, hardness were statistically analyzed using one way analysis of variance (ANOVA) with 95% confidences interval.

RESULTS

Physical characteristics of the implants

Physical characteristics including density, porosity, water absorption capacity, swelling ratios, and hardness of the glutaraldehyde or genipin crosslinked implants are shown in Fig. 1. The content of ciprofloxacin HCL in implants is also shown in Table 2.

Degradation test

Degradation test of implants crosslinked with glutaraldehyde or genipin was done by visual observation. The result showed formulations containing 0.7% of crosslinkers had lowest degradation time. In contrast, formulations containing 0.3% of crosslinker showed longest degradation time.

Implant morphology

SEM micrograph of the implants crosslinked with glutaraldehyde or genipin is presented in Fig. 2. Based on the micrograph, it could be seen that there was small pores in the structure. These pores facilitate the release of ciprofloxacin from the implants.

In vitro drug release study

The *in vitro* release profiles of ciprofloxacin from prepared implants in PBS, pH 7.40 are illustrated in Fig 3. The release profile of ciprofloxacin HCL from the implants showed that ciprofloxacin release was at a therapeutic level of ciprofloxacin for osteomyelitis (2-50 μg/mL) (13). This condition could be kept for 30 days.

Fourirer transform infrared spectroscopy

The infrared spectrum of ciprofloxacin, BHA, chitosan, implants BHA-chitosan-ciprofloxacin before the crosslinking process and implants BHA-chitosan-ciprofloxacin after crosslinking process with three different concentrations of glutaraldehyde and genipin can be seen in Fig. 4.

Table 2. Drug content of implant formulations

Formulations	Drug content (%)
F3, 0.3% GA	96.04 ± 7.11
F3, 0.5% GA	84.80 ± 10.3
F3, 0.7% GA	87.31 ± 3.40
F3, 0.3% GE	92.81 ± 7.96
F3, 0.5% GE	95.30 ± 1.07
F3, 0.7% GE	92.81 ± 2.41

Each data represents the mean ± SD of three determinations. (GA), glutaraldehyde and (GP), genipin.

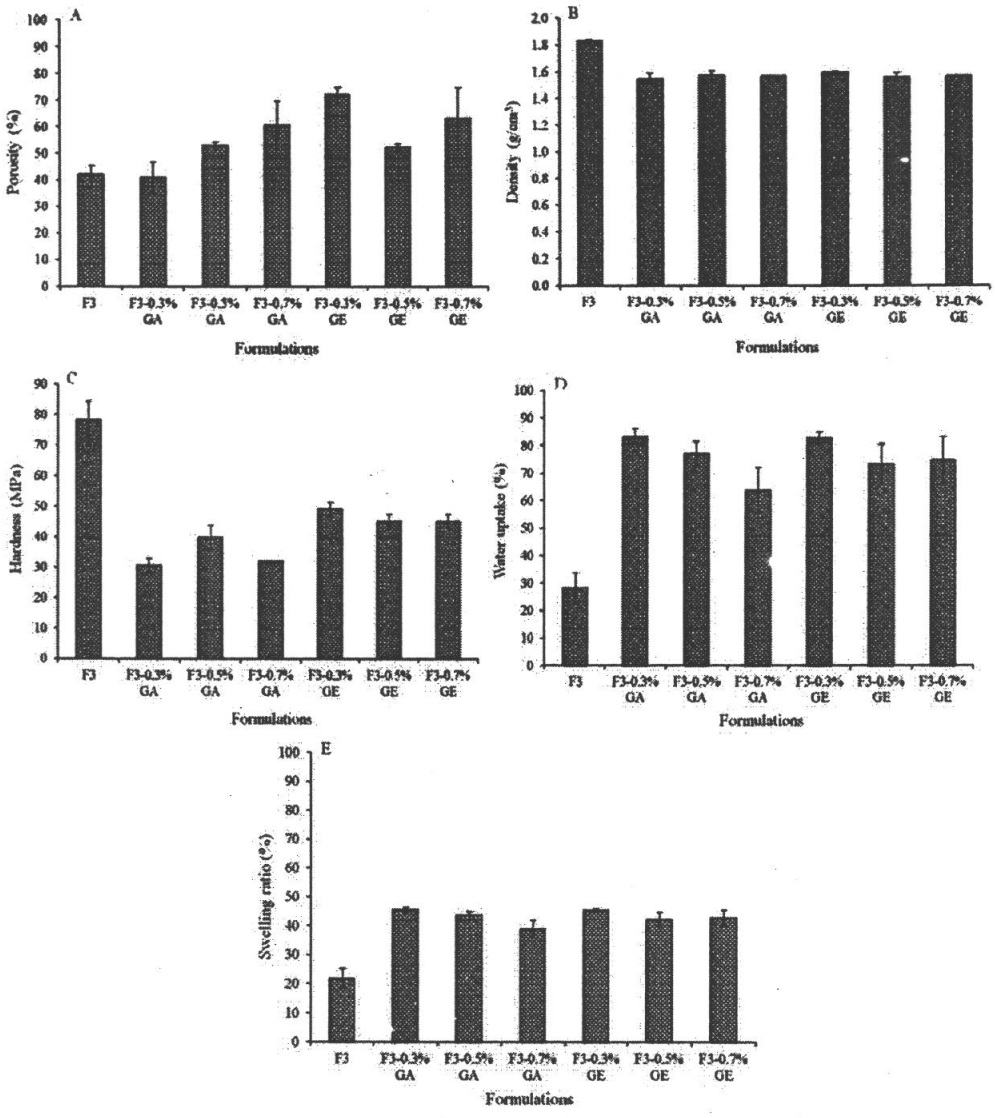

Fig. 1. Porosity (g/cm3), density (%), hardness (MPa), water uptake (%), and swelling ratios (%) of implants with crosslinker glutaraldehyde (GA) and crosslinker genipin (GE). Each column represents the mean ± SD of three determinations.

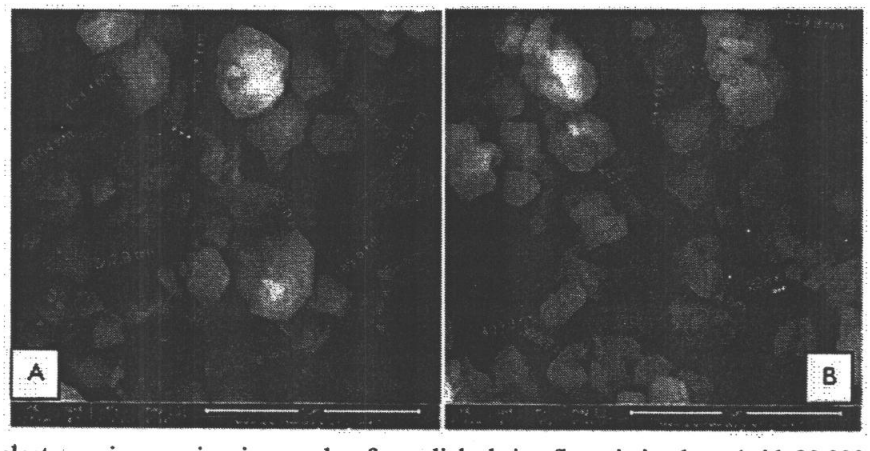

Fig. 2. Scanning electron microscopic micrographs of crosslinked ciprofloxacin implants (with 30.000 × magnification). (A) bovine hydroxyapatite-chitosan-ciprofloxacin (30:60:10) with 0.7% glutaraldehyde, (B) bovine hydroxyapatite-chitosan-ciprofloxacin (30:60:10) with 0.7% genipin. The green lines inside the images show the pore size of the implants.

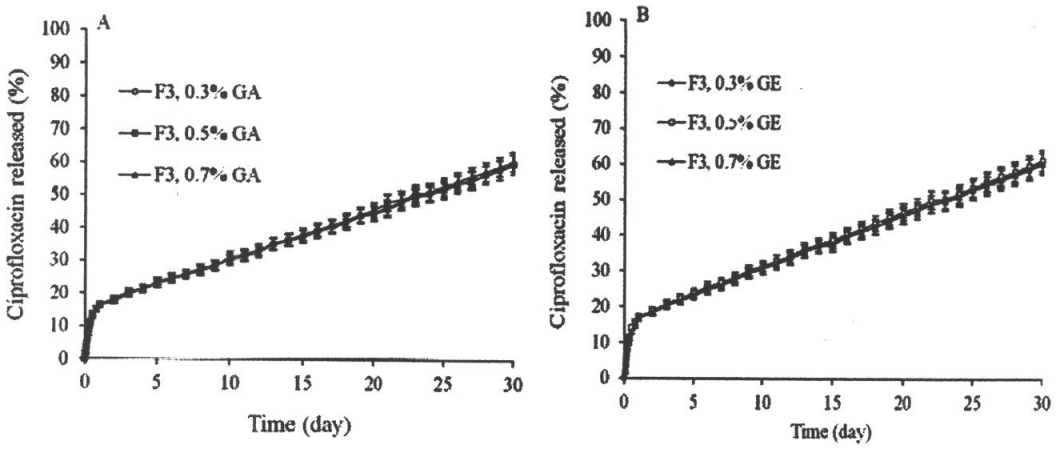

Fig. 3. The profile of cumulative ciprofloxacin released from implants crosslinked with glutaraldehyde (GA) or genipin (GE). Each point represents the mean ± SD of three determinations.

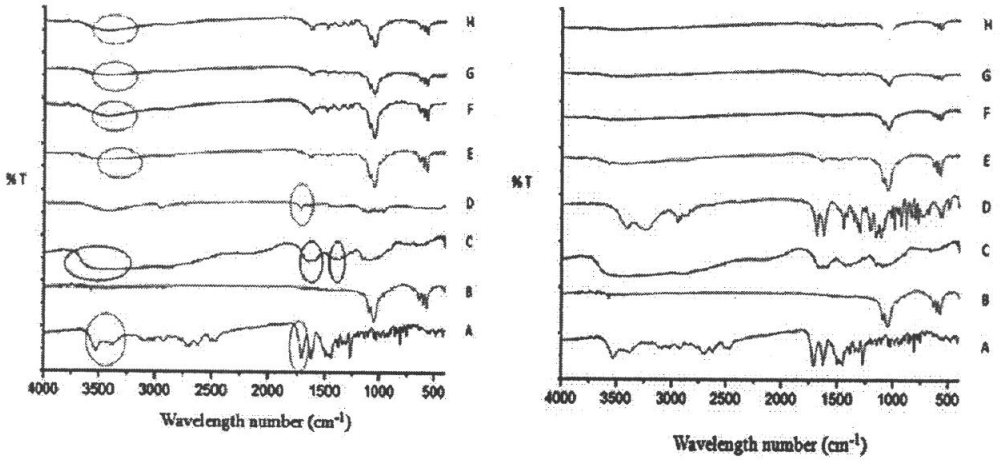

Fig. 4. Fourirer transform infrared spectra of (A) ciprofloxacin; (B) bovine hydroxyapatite; (C) chitosan; (D) glutaraldehyde; (E) formulatin 3, bovine hydroxyapatite-chitosan-ciprofloxacin implant (30:60:10); (F) formulation 3, 0.3% glutaraldehyde (left) and genipin (right); (G) formulation 3, 0.5% glutaraldehyde (left) and genipin (right); and (H) formulaion 3, 0.7% glutaraldehyde (left) and genipin (right).

FT-IR spectrum of BHA-chitosan-ciprofloxacin implant after crosslinking process using glutaraldehyde showed a peak shift characteristics of chitosan on wavenumbers 1658,67 cm^{-1} (C=O stretching in amide group) to the lower wavenumbers around 1630 cm^{-1}. This band (1630 cm^{-1}) is most probably composed of amide I band of chitosan (appears at 1658.67 cm^{-1}) and the C=N stretching band of Schiff's base that according to the literature appears at wave number 1620-1660 cm^{-1} (8). Moreover, the peak characteristic of aldehyde could not be seen in the FT-IR spectrum of BHA-chitosan-ciprofloxacin implant after crosslinking process using glutaraldehyde. This condition showed that the implant did not contain free aldehyde group. Based on the results of the FT-IR spectra, it was known that there was a shift of the N-H stretching vibrations and O-H stretching vibrations from chitosan molecules. In addition, the loss of peak at wave number 1363 cm^{-1} (the vibration bending of CH_3) and 1155 cm^{-1} (the vibration bending of C-O-C) observed in FT-IR spectrum of the implant compared to FT-IR spectrum of pure chitosan. FT-IR spectrum of BHA-chitosan-ciprofloxacin implant that has been crosslinked with genipin also can be seen in Fig. 4. The spectrum showed a characteristic peak of chitosan (C=O stretching of amides group) shift to the lower wavenumbers. In addition, increasing genipin concentration caused an increase of C=C bond intensity of genipin. The obtained data from FTIR study evidenced intermolecular interaction between components in the system.

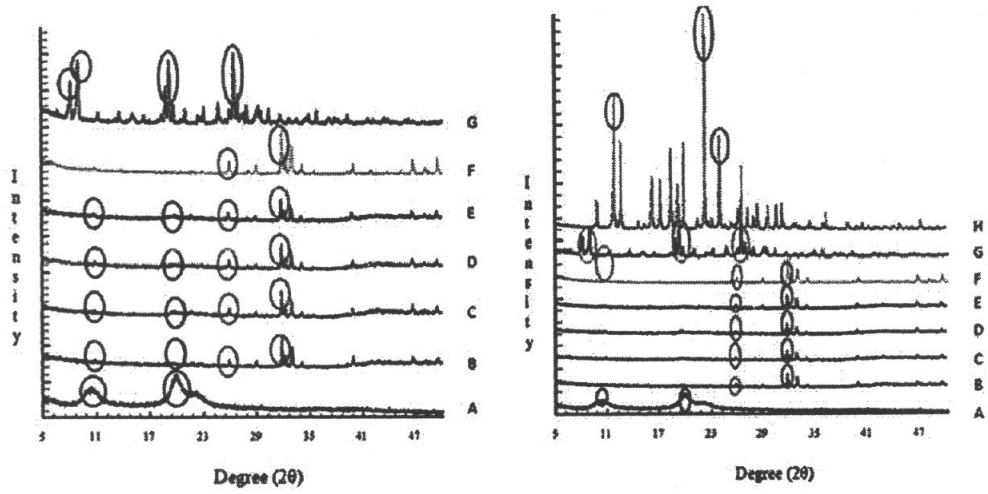

Fig. 5. X-ray diffraction spectra of (A) chitosan; (B) formulatin 3 bovine hydroxyapatite (BHA)-chitosan-ciprofloxacin implant (30:60:10); (C) formula 3, 0.3% glutaraldehyde; (D) formulation 3, 0.5% glutaraldehyde (left) and genipin (right); (E) formulation 3, 0.7% glutaraldehyde (left) and genipin (right); (F) BHA, (G) ciprofloxacin; and (H)

X-ray diffraction study

X-RD of the implants after crosslinking with glutaraldehyde and genipin are demonstrated in Fig. 5. Based on the results, it was known that the characteristic peak of ciprofloxacin in 2θ 8.2 °, 9.0 °, 19.3 °, 19.8 °, and 26.5 ° did not appear in a diffraction spectrum of BHA-chitosan-ciprofloxacin implant. This condition indicates that ciprofloxacin was molecularly dispersed in the implant. X-ray diffraction of the implant after crosslinking with glutaraldehyde or genipin showed that the peak intensity of BHA in 2θ ≈ 26 ° and 2θ ≈ 32 ° decreased compared to X-ray diffraction of pure BHA and the implants before the crosslinking process. The decreased of BHA crystallinity was in line with the increased of glutaraldehyde and genipin concentrations. This condition indicated the addition of glutaraldehyde and genipin damage regularity on BHA crystal lattice.

The X-ray pattern of chitosan shows major crystalline peaks at 2θ ≈ 10 ° and 2θ ≈ 20 °. But, these peaks became wider and weaker in X-ray diffraction of the implants. This finding could be due to decreased crystallinity of chitosan molecule caused by the deformation of hydrogen bond in the molecular structure of chitosan. Substitution of glutaraldehyde and genipin molecules destroyed the regular structure of chitosan molecules so that the structure of chitosan molecules became amorph (14)

DISCUSSION

The purpose of this research was to obtain chitosan-BHA composite containing ciprofloxacin as a bone implant. The obtained data showed that with the addition of genipin or glutaraldehyde as crosslinkers the implant has good physical characteristics and controlled drug release.

Fig. 1A shows the porosity of implants crosslinked with different concentrations of glutaraldehyde or genipin. Interestingly, as glutaraldehyde or genipin concentrations increased, the porosity of implant was also increased though not significant. In most studies, the porosity decreased with increasing crosslinking concentration. In agreement with our study, such phenomenon observed by Bie, *et al,* (15) when chitosan-collagen scaffold was crosslinked with genipin (0.1-2%). Gorczyca, *et al.* (16) also reported similar results when crosslinked porous chitosan–collagen–gelatin scaffolds were prepared using genipin with concentrations between 0.5-2%. These findings explained more favorable condition for ring-opening polymerization of genipin and its long-range crosslinking effect on polymeric blends.

The density of the implants after the crosslinking process with glutaraldehyde or genipin was lower than that before crosslinking process. This is probably due to the increased porosity of the implants after crosslinking. However, as shown in Fig. 1B,

there were no significant differences between densities of the implants prepared with three different concentrations of genipin or glutaraldehyde ($P > 0.05$). Based on these results, it could be concluded that the different concentrations of genipin or glutaraldehyde did not affect the implant density. This may be due to the outer layers of implants being crosslinked, thereby limiting crosslinking of inner layers (17).

As shown in Fig. 1C hardness of the implants was decreased greatly when the implants crosslinked with genipin and glutaraldehyde possibly due to increased porosity. Xu, *et al.* (18), also showed the mechanical strength of a calcium phosphate-chitosan scaffold depends mainly on porosity and lower porosity is helpful to enhance the biomechanical strength of the engineered constructs.

In agreement with our findings, Schiffman, *et al.* (19) showed that increasing glutaraldehyde concentration as the crosslinker more than 0.2 % decreased the mechanical strength of the implants. In another study by Mi, *et al.* (20), crosslinking of chitosan membrane with glutaraldehyde or genipin up to a certain concentration (0.5 mM) increased its ultimate strength. However, with further increasing the concentration of crosslinkers, the mechanical strength of membrane decreased. This finding was explained with disruption of hydrogen bond interaction between chitosan molecules and reduction of its crystallinity.

As it is shown in Figs. 1D and 1E, water absorption capacity and swelling ratio of the implants after crosslinking process with glutaraldehyde or genipin was higher than that before crosslinking process.

The crosslinks in implant formed by the glutaraldehyde and genipin increased the porosity and reduced the crystallinity as well as mechanical strength of the implants which increased the swelling ratio and water content of implants. However, we observed that increasing genipin or glutaraldehyde concentrations does not have a significant effect on water absorption capacity and swelling ratios of the implants.

The degradation test showed formulations containing 0.7% crosslinker has lowest degradation time.

In contrast, formulations containing 0.3% crosslinker indicated longest degradation time. This could be due to the lower mechanical strengh of formulations containing 0.7% crosslinker, thus the penetration of water to the implant structure became easier and the implants degraded faster. The degradation process is faster once genipin was used as crosslinking agent compared to glutaraldehyde.

There are many factors influencing the drug release rate from implants. This includes drug concentration in the formulation, drug solubility, and drug-carrier interaction. In addition, addition of crosslinker to the implant could control the drug release. Implants prepared with different concentrations of glutaraldehyde and genipin showed almost the same release profiles possibly due to the interaction of ciprofloxacin with implants' composite. Ciprofloxacin concentration released from the implants will meet the therapeutic range of ciprofloxacin according to Indonesian Ministry of Health (2-50 ug/mL) for 30 days. As shown in Fig. 3, the suitable drug release can be obtained with the lowest glutaraldehyde and genipin content in order to limit the toxicological effects of the cross linking agents.

CONCLUSION

To conclude with, bone implants containing ciprofloxacin using chitosan-BHA composite and crosslinkers glutaraldehyde or genipin 0.3% showed the best results. Therefore, the release of ciprofloxacin for 30 days meets the standard requirements (2-50 mg). Glutaraldehyde or genipin 0.3% had the potential effect to retard ciprofloxacin release from BHA-chitosan-ciprofloxacin implant for 30 days in the treatment of osteomyelitis.

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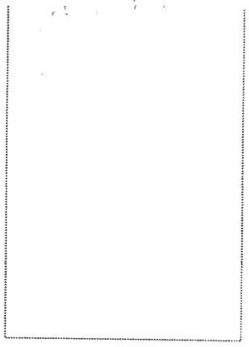

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Country	India - SIR Ranking of India
Subject Area and Category	Pharmacology, Toxicology and Pharmaceutics Pharmacology, Toxicology and Pharmaceutics (miscellaneous)
Publisher	Medknow Publications
Publication type	Journals
ISSN	17355362, 17359414
Coverage	2009-ongoing
Scope	Research in Pharmaceutical Sciences (RPS) is included in Thomson Reuters ESCI Web of Science (searchable at WoS master journal list), indexed with PubMed and PubMed Central and abstracted in the Elsevier Bibliographic Databases. Databases include Scopus, EMBASE, EMCare, EMBiology and Elsevier BIOBASE. It is also indexed in several specialized databases including Scientific Information Database (SID), Google Scholar, Iran Medex, Magiran, Index Copernicus (IC) and Islamic World Science Citation Center (ISC).

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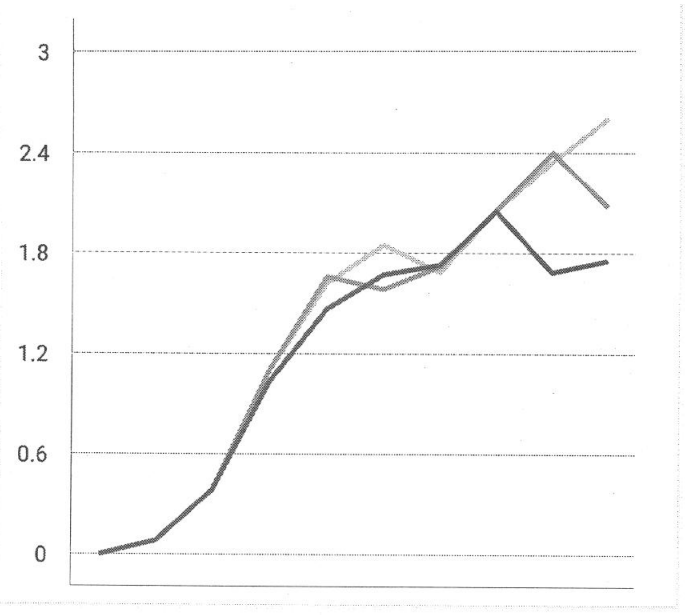

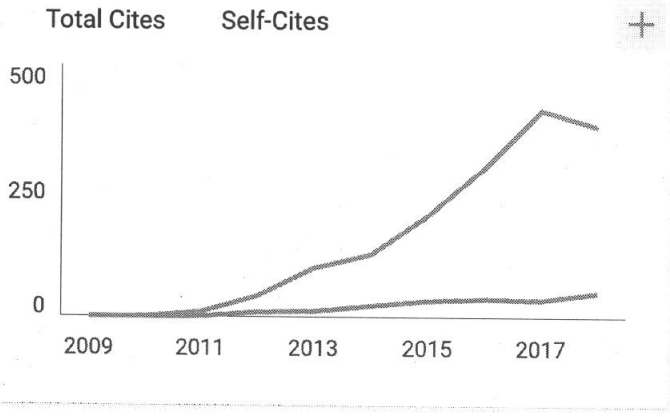

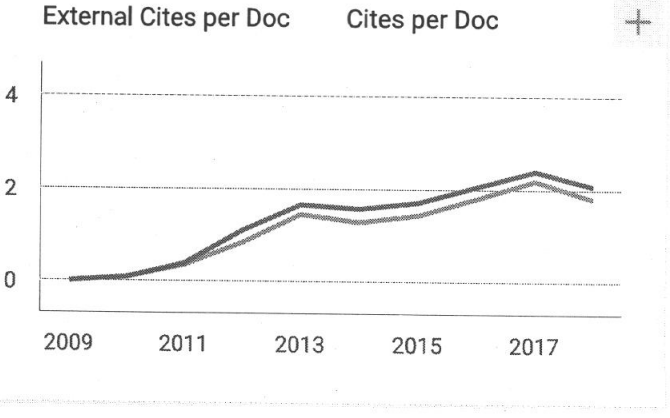

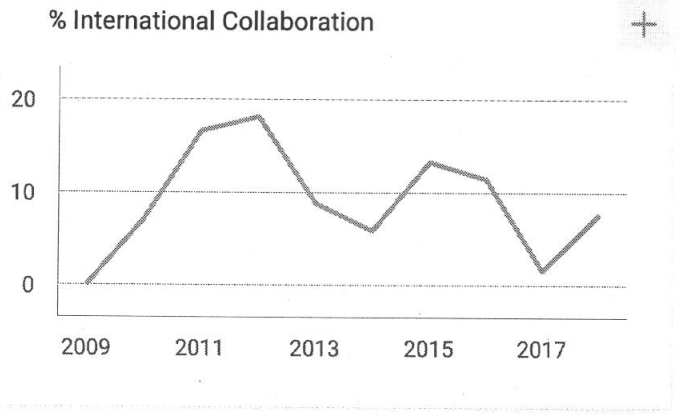

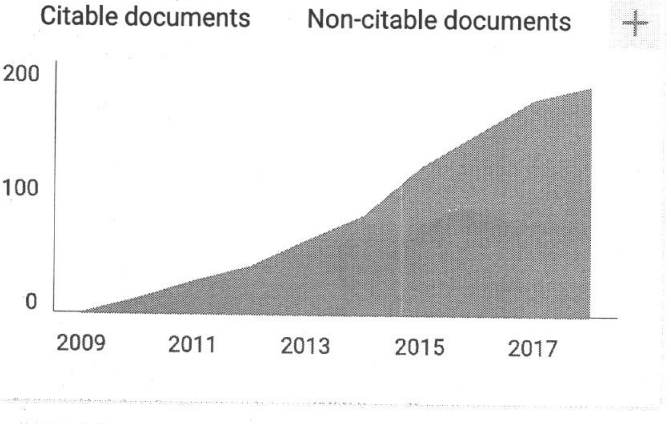

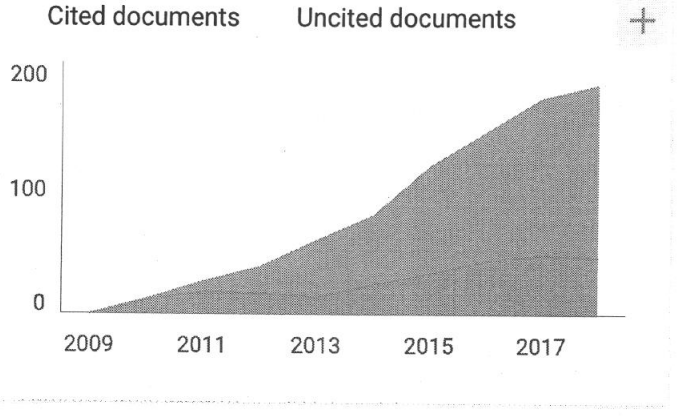

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