DRUG CARRIER POTENTIAL AND CHARACTERIZATION OF NANO-CELLULOSE 3D-NETWORKS PRODUCED BY *ACETOBACTER XYLINUM* OF FERMENTED AQUEOUS GREEN TEA EXTRACT

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ABSTRACT

Nano-cellulose 3D-networks (NA3D) could be produced by *Acetobacter xylinum (A. xylinum)* living in the fermented aqueous green tea extract. NA3Ds include nano fibers forming networks, which are capable of drug loading to form a prolonged release therapy to improve drug bioavailability. Ranitidine is a gastrointestinal H_2 receptor antagonist drug with low bioavailability (50%). In this study, NA3Ds are biosynthesized by *A. xylinum* in the standard medium (SM), coconut water (CW) and rice water (RW). The NA3Ds obtained from CW, and RW have the same characteristics as the NA3D obtained from the SM, and NA3Ds can be fabricated with the desired thickness and diameter in all three types of culture media. NA3Ds absorbed ranitidine in optimum condition did not differ statistically significantly ($p > 0.05$) in both ranitidine loading (111.6-116.7 mg) and ranitidine entrapment efficiency (61-63%). The NA3Ds were characterized by using field emission scanning electron microscopes (FE-SEM) and fourier transform infrared (FTIR) spectroscopy. Investigation of the NA3D structure using SEM showed that the cellulose fibers of NA3D-SM and NA3D-CW have a stable structure without structural change when loading drug. The results indicate the potential for using NA3D-SM and NA3D-CW to fabricate the drug delivery system.

Keywords: *Acetobacter xylinum (A. xylinum); drug delivery; drug loading; ranitidine; fermented aqueous green tea extract; nano-cellulose 3D-networks (NA3D)*

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TIỀM NĂNG MANG THUỐC VÀ ĐẶC TÍNH CỦA MẠNG LƯỚI 3D NANO-CELLULOSE ĐƯỢC SẢN XUẤT TỪ *ACETOBACTER XYLINUM* TRONG DỊCH CHÈ XANH LÊN MEN

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TÓM TẮT

Vật liệu cấu trúc mạng lưới 3D nano-cellulose (M3DC) có thể được tạo ra từ *Acetobacter xylinum* trong dịch chè xanh lên men. M3DC gồm các sợi với kích thước nano tạo mạng lưới có khả năng nạp thuốc nhằm tạo hệ trị liệu giải phóng kéo dài để cải thiện sinh khả dụng của thuốc. Ranitidine là thuốc đường tiêu hóa với sinh khả dụng thấp (50%). Trong nghiên cứu, M3DC được sản xuất từ môi trường chuẩn (MC), nước dừa (MD) và nước vo gạo (MG). M3DC thu được từ MD và MG có kích thước và các đặc tính tương đương M3DC thu được từ MC và có thể chế tạo được M3DC có độ dày và kích thước theo ý muốn ở cả 3 loại môi trường. Các M3DC được hấp thụ ranitidine trong điều kiện tối ưu không có sự khác nhau có ý nghĩa thống kê ($p > 0,05$) về lượng thuốc nạp vào (111,6-116,7 mg) và hiệu suất nạp thuốc (61-63%). Đặc tính của M3DC được xác định bởi kính hiển vi điện tử quét phát xạ trường (FE-SEM) và máy đo phổ hồng ngoại biến đổi Fourier (FTIR). Khảo sát cấu trúc M3DC bằng SEM cho thấy M3DC được nuôi cấy trong MC và MD, các sợi cellulose có độ cấu trúc ổn định, hầu như không có sự thay đổi trong cấu trúc khi được nạp thuốc. Kết quả nghiên cứu cho thấy vật liệu M3DC-MC và M3DC-MD có tiềm năng sử dụng làm chất mang để sản xuất hệ dẫn thuốc.

Từ khóa: *Acetobacter xylinum (A. xylinum); dẫn thuốc; nạp thuốc; ranitidine; dịch chè xanh lên men; mạng lưới 3D nano-cellulose (M3DC)*

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1. Introduction

The fermented aqueous green tea extract contains *Acetobacter xylinum (A. xylinum)* producing nano-cellulose 3D-networks (NA3D). The metabolites of *A. xylinum* during the fermentation include NA3D. The NA3D has the structure of super-thin nano-fibers with great tensile and mechanical strength. It is proved that the NA3D exposes the potential of being a delivery system by its properties. The use of NA3D on coconut jelly (made from coconut juice after the fermentation of *A. xylinum* in the coating for paracetamol by spraying technique was reported [1]. Their results indicated that the NA3D membranes were able to increase releasing time of the drug and improve the efficiency of drug use. NA3D membrane from the fermentation of *Gluconacetobacter xylinum* in the standard medium (Hestrin–Schramm) for transporting and releasing berberine *in vitro* was tested [2]. The study was controlled drug releasing of NA3D in artificial models including stomach and intestine. The gained information shows that berberine released with a low rate in acidic condition but normal rate in alkaline condition and high releasing rate in neutral pH condition.

Ranitidine is an anti-ulcer drug that has been extensively used as model drug with an extensive clinical history in the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease, and Zollinger-Ellison syndrome and elevated stomach hypersecretion in the endocrine multiple adenoma. It is an H_2 receptor antagonist which competitively inhibits gastric acid secretion with the interaction of histamine with its receptors. The bioavailability of ranitidine after oral administration is about 50% and is absorbed via the small intestine; this may be due to low intestinal permeability. The extent of drug release is also shorter, which requires repeated dose administration that leads to increased adverse effect. In order to overcome these problems an attempt was made to develop drug delivery systems for ranitidine. Mastiholimath et al. demonstrated that a microparticulate floating delivery system can be successfully designed to give controlled drug delivery, improved oral bioavailability and many other desirable characteristics for ranitidine [3]. Preparation of a drug delivery system that delivers ranitidine in the stomach in a sustained manner, as a floating drug delivery system was investigated [4]. It was shown that the proposed floating drug delivery system, based on the superporous hydrogel composite containing chitosan as a composite material, is promising for stomach-specific delivery of ranitidine. Hitesh and Chhaganbhai formulated a drug-delivery system based on bioadhesive superporous hydrogel composite for sustained delivery of ranitidine [5]. It is indicated that the proposed bioadhesive, mechanically stable as well as floating drug-delivery system based on superporous hydrogel composite containing carbopol 934P as a composite material is promising for stomach specific delivery of ranitidine. Joshi et al. illustrated the suitability of montmorillonite as a drug delivery carrier, by developing a new clay-drug composite of ranitidine intercalated in montmorillonite [6]. The synthesis and characterization of fatty acid salts of chitosan as novel matrices for prolonged intragastric drug delivery of ranitidine were studied by Bani-Jaber et al. [7]. This study demonstrated that fatty acid salts of chitosan and to evaluate the salts as matrices for sustained ranitidine release and prolonged gastric retention. Singha et al. synthesized gastro-retentive drug delivery system by simultaneously ionotropic gelation of alginate and aloe vera for the controlled release of anti-ulcer agent ranitidine [8]. The study was recently conducted to determine drug release kinetics of gastrotentive rantidine by using a natural polymer, sodium alginate matrix which is low cost, simplicity, and

biocompatibility and easily biodegradability [9]. Our research aims to evaluate the potential for using NA3D produced by *A. xylinum* from fermented aqueous green tea extract in selected culture media to fabricate the drug delivery system.

2. Methods

2.1. Materials and equipment

Acetobacter xylinum (*A. xylinum*) producing cellulose from fermented aqueous green tea extract [10], [11] was cultured in the clean laboratory of Microorganism – Animal, Institute of Scientific Research and Applications (ISA) – Hanoi Pedagogical University 2 (HPU2).

Ranitidine 99.5% (Sigma – USA), tablets, yeast extracts (USA), peptone (European Union), and other standard chemicals were used in analysis.

Field emission scanning electron microscopes (FE-SEM, Hitachi, Japan), Fourier transform infrared spectrophotometer (FTIR, Shimadzu, Japan), Spectrophotometers UV-Vis 2450 (Shimadzu, Japan), analytic scale (Sartorius, Switzerland); magnetic stirrer (IKA, Germany), low speed rotator (Orbital Shakergallenkump, England), shaker (Lab companion, SKF-2075, Korea), oven and incubator (Binder, Germany), antiseptic cabbin (Haraeus), and antiseptic autoclave (HV-110/HIRAIAMA, Japan) were used.

2.2. Preparation of Acetobacter bacteria from fermented aqueous green tea extract

The green tea leaves (20 g) was added to 1000 ml boiled water and allowed to infuse for 10-15 minutes. The infusion was filtered to remove the tea leaves. Sugar (100 g) was dissolved in hot aqueous green tea extract, and preparation was left to cool to room temperature. The aqueous green tea extract was then poured into sterile glass bottles. The bottles were then covered with sterile muslin cloth and incubated at 30^{o}C. The fermentation could be carried out to produce the NA3D [10], [11]. Trapping process of *A. xylinum* from fermented aqueous green tea extract was carried out according to established method of our previously published article [11]. All the bottles were observed for formation of thin cellulosic film (NA3D) at air liquid interface. Those bottles with NA3D growth were selected and purified the culture by repeated streaking on HS agar plates to obtain isolated colonies. Each distinct isolate was inoculated on screening media, that is, the enrichment media used was GY (glucose - yeast extract). Inoculated broth was incubated in GY at 30^{o}C for 2 days. Isolation was carried out on two different selective media for isolation of *A. xylinum*, GEM (glucose-ethanol medium) and GYC (glucose - yeast extract - calcium carbonate medium). The morphology and Gram nature of *A. xylinum* isolated on the selective media was determined. Its biochemical characterization involved catalase, oxidase, over oxidation of ethanol by use of Carr medium, oxidation of acetate and oxidation of lactate.

After receiving the *A. xylinum* from the fermented aqueous green tea extract [11], *A. xylinum* were cultured in selected nutrient media (SM, CW, RW) to produce the NA3Ds.

2.3. Fabrication and characterization of 3D-nano-cellulose network material (NA3D)

2.3.1. Acetobacter xylinum fermented in three selected culture media

Firstly, glucose (20 g), peptone (5 g), diammonium phosphate (2.7 g), yeast extracts (5 g), citric acid (1.15 g) and double-distilled water (1000 ml) were used in SM [12], [14]. Secondly, glucose (20 g), peptone (10 g), diammonium phosphate (0.5 g), amonia sulfate (0.5 g) and coconut water (1000 ml) were used in CW [13], [14]. Thirdly, glucose (20 g), peptone (10 g), diammonium phosphate (0.5 g), ammonia sulfate (0.5 g) and rice water (1000 ml) were used in RW [14].

2.3.2. Treatment of the NA3Ds before drug absorption

The NA3Ds obtained from culture media were treated with 0.3 M NaOH solution in an autoclave at 113^{o}C for 15 minutes to remove bacterial cells, debris and other culture medium impurities. The NA3Ds were thoroughly rinsed with distilled water until reaching neutral pH and stored at 4^{o}C for further use [13], [15], [16].

2.3.3. Evaluation of the purity of the NA3D

The present of D-glucose in the NA3D was determined by Fehling reagent. If there is a D-glucose present in the NA3D, the Fehling reagent will give a reddish precipitate [17], [18]. The presence of protein in NA3D was determined by the precipitation reaction with trichlor-acetic acid [17], [18].

2.3.4. Determination of the amount of the formed NA3D

Briefly, the purified NA3D was dried at 105°C until reaching a constant mass [13], [15], [16].

2.3.5. Determination of the structure of the NA3D

The samples were heated at 40^{o}C in 20 minutes, covered then a thin platinum layer and put into the sample chamber. The field emission scanning electron microscopes (FE-SEM, Hitachi S-4800 with magnification M = 20-800,000, resolution δ = 1.0 nm, piezoelectric accelerator U = 10 kV) was used for examination of the samples.

2.3.6. Determination of the interaction of the NA3D to drug

The samples were directly measured by reflectometry method in 20^{o}C, moisture 40-43%. The fourier transform infrared spectrophotometer (FTIR) was used for examination of the samples.

2.4. Evaluation of drug loading and entrapment efficiency of NA3Ds

The NA3Ds with a diameter of 1.5cm and a thickness of 1cm created from culture media (SM, CW, RW) are absorbed ranitidine in the optimized conditions (drug concentration: 200 mg/ml; temperature: 50^{o}C; shaking speed: 160 rpm; time of drug absorption: 120 minutes). The concentration of the ranitidine remaining in the loading solution was determined using a UV–Vis spectrophotometer (UV-Vis 2450, Shimadzu, Japan) at 314 nm [3], [6], [9]. A calibration curve of ranitidine solution in HCl 0.1N within the concentration range of 1 µg/ml to 6 µg/ml was used for determining ranitidine loadings in NA3Ds samples.

The amount of loaded ranitidine into NA3D was calculated according to formula 1.

$$m_{ab} = m_1 – m_2 \text{ (mg)} \quad (1)$$

Where: m_{ab} is the amount of ranitidine that is loaded into the NA3D; m_1 is the initial ranitidine dose in solution; m_2 is the excessive amount of ranitidine existing in the solution after a certain period of time NA3D absorbs the ranitidine.

The ranitidine entrapment efficiency (EE) of NA3Ds was calculated according to formula 2 [2].

$$EE\ (\%) = (m_{ab}/m_1)x100\% \quad (2)$$

2.5. Statistics

All results are processed by Excel 2010 and it is performed by the mean ± standard deviation and two-way ANOVA test. Results are considered to be significant with $p < 0.05$.

3. Results and discussions

3.1. Fabrication and characterization of the nano-cellulose 3D-networks (NA3D)

The NA3Ds with a diameter of 1.5cm and a thickness of 1cm were produced by *Acetobacter xylinum* in the culture media (SM, CW, RW) from 7 to 14 days [11], [20], [21]. According to previous studies, it is possible to create the NA3Ds with different shapes and thickness depending on the intended use [2], [14]. In present study, the NA3Ds with a thickness of 1 cm (depending on the time of culture) and a diameter of 1.5 cm (depending on the size of the culture well) were created for the application via oral route.

The thickness of the NA3D in different positions was measured by a ruler. The results showed that the thickness and the diameter of the M3NCs produced from the culture media were relatively homologous.

Fehling reagent was used to detect the presence of D-glucose in the NA3Ds. The results showed that there was no reddish brown precipitate. Therefore, the NA3Ds did not contain D-glucose. The protein in the NA3Ds was determined by the reaction of protein precipitate with trichlor-acetic acid. The result indicated thatthe presence of protein was not detected in the NA3Ds.

To determine the amount of formed NA3D, the purified NA3Ds were dried at 105°C until reaching a constant mass. The result showed that the dried mass of the NA3D created in SM was the highest.

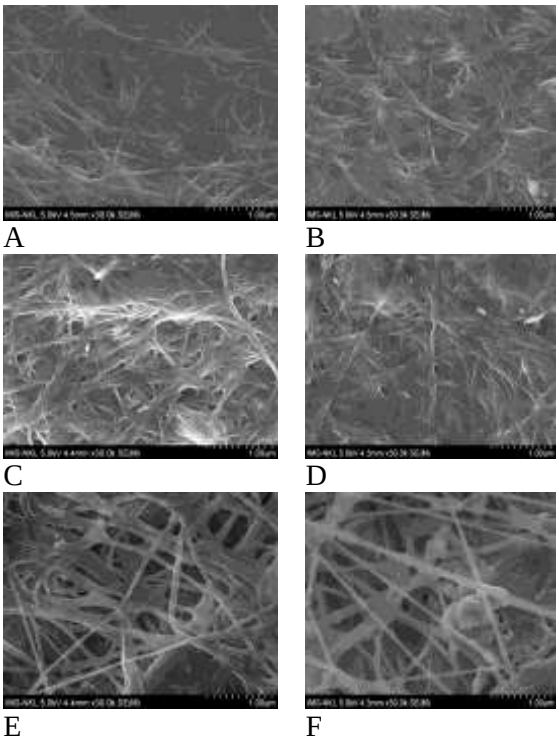

Figure 1. *The FE-SEM images of NA3D-SM, NA3D-CW and NA3D-RW (A, C, E) and ranitidine loaded NA3D-SM, ranitidine loaded NA3D-CW and ranitidine loaded NA3D-RW (B, D, F)*

A field emission scanning electron microscope (FE-SEM, Hitachi, Japan) was used to visualize the surface morphology of the samples. SEM images of the NA3Ds (SM, CW, RW) before and after loading ranitidine were shown in Figure 1. As the results, NA3Ds have the homogeneous fibers structure networks without significant changes in structure before and after ranitidine. These results are very similar to those of our previous study [11], [20].

3.2. Evaluation of drug loading and entrapment efficiency of NA3Ds

The experiment of the ranitidine absorption into NA3Ds was performed in optimum condition. At the end of the experiment, the sample was removed from the absorbent solution to measure OD, based on the drug's calibration curve to calculate the amount of loaded ranitidine and the ranitidine entrapment efficiency of the NA3Ds. The results in Table 1 showed that there were no differences in the amount of loaded ranitidine and ranitidine entrapment efficacy of NA3Ds which were produced from different culture media.

Table 1. *Evaluation of ranitidine loading and ranitidine entrapment efficiency of NA3Ds (n = 3)*

NA3D types	NA3D-SM	NA3D-CW	NA3D-RW
Loaded drug (mg)	111.6 ± 8.2	114.6 ± 10.5	116.7 ± 11.8
Efficiency (%)	62.0 ± 5.6	61.0 ± 6.4	63.0 ± 7.6

3.3. Determine the interaction of NA3D to ranitidine by FTIR

The FTIR spectra of NA3D-SM, NA3D-CW, and NA3D-RW are shown in Figure 2, 3 and 4.

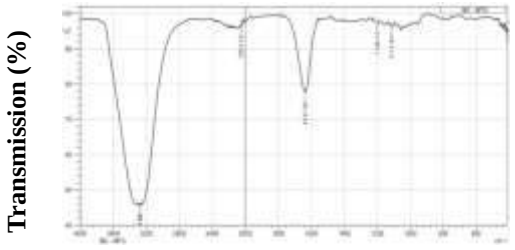

Figure 2. *FTIR spectra for NA3D-SM*

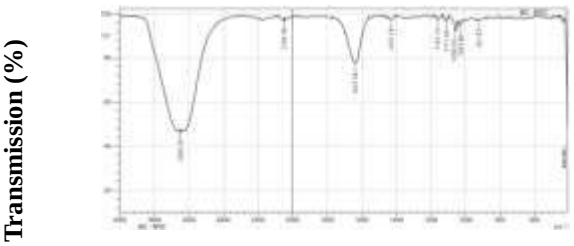

Figure 3. *FTIR spectra for NA3D-CW*

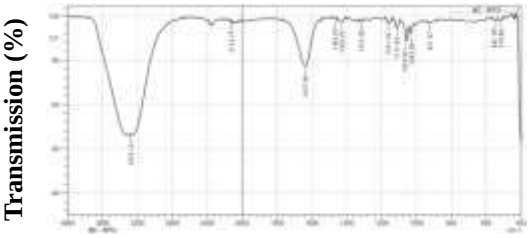

Figure 4. *FTIR spectra for NA3D-RW*

The FTIR spectra of NA3Ds (NA3D-SM, NA3D-CW, NA3D-RW) in Figures 2-4 displayed the typical features of cellulosic substrates with intense bands around 3300, 2880, 1100 and 700 cm^{-1}, associated with the vibrations of the –OH, C–H, C–O–C and –CH_2– groups, respectively [2], [11], [20]. These results are very similar to those of our previous study [2], [11], [20].

These results are consistent with other studies about the structure of NA3D including nano-sized cellulose fibers that make up the three-dimensional structure network [2], [11], [20], [21]. It is demonstrated that SEM images of NA3D-SM which generated from *Gluconacetobacter xylinum* after 24 hours treatment of some conditions (double-distilled water, artificial medium of stomach and intestine, NaOH medium) showed that porosity of the NA3D cultured in SM in acidic and alkaline media increasing when compared to neutral medium (double-distilled water). Therefore, it affirmed that have the contraction of cellulose fibers in these two conditions, and neutral medium does not affect to the cellulose fibers [2]. Moreover, the results also showed that NA3D is drug loaded and non-loaded with no apparent difference in results consistent with other studies [2], [11], [20]. For the NA3D-SM or NA3D-CW, the cellulose fibers have the stable structure without significant changes in structure when ranitidine loaded under optimum condition. For the NA3D-RW, the spatial structure of the cellulose fibers is noticeably altered after ranitidine loading, the size of the holes in the ranitidine loaded NA3D-RW changes, the cellulose fibers of NA3D-RW are loosely linked; the structure of NA3D-RW is unstable. In our previous study, NA3Ds produced by *A. xylinum* in SM, CW and RW were evaluated for some properties of pre- and post-curcumin loaded NA3Ds. FE-SEM results also showed that the NA3D produced from SM or CW consisted of stable cellulose fibers, with no significant change in structure before and after loading of ranitidine. FTIR spectra were determined without the formation of a covalent bond between NA3D and curcumin and no change in the chemical composition of curcumin during NA3D loading [20]. Compared to the NA3D produced by *Gluconacetobacter xylinum* from the standard culture [2], [11], [20], the NA3D structure in present study was not significantly different. It is concluded that the NA3Ds of the study have obtained by *A. xylinum* from fermented aqueous green tea extract in three types of selected culture media were effective in fabricating the ranitidine delivery system.

4. Conclusion

The present study has been a satisfactory attempt to prove the successful fabrication of NA3Ds by *Acetobacter xylinum* isolated from the fermented aqueous green tea extract in selected culture media and their characterization after absorbing with ranitidine. NA3D-CW and NA3D-RW have the same characteristics as the NA3D-SM, and NA3Ds can be fabricated with the desired thickness and diameter in selected culture

media. The present study concluded that NA3Ds absorbed ranitidine in optimum condition did not differ statistically significantly ($p > 0.05$) in both ranitidine loading (111.6-116.7 mg) and ranitidine entrapment efficiency (61-63%). Moreover, surface morphologies of the samples studied by SEM showed that the cellulose fibers of NA3D-SM and NA3D-CW have a stable structure without structural change when loading drug under optimum condition. The results demonstrated that the potential for using NA3D-SM and NA3D-CW to fabricate the drug delivery system.

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