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Biodegradable polymeric microcapsules for sustained release of riboflavin

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ABSTRACT

In the current study, a series of polylactic acid and polylactic-*co*-glycolic acid were prepared in an easy, simple, safe and economically feasible way with yield% greater than 90%. Studying the effect of a catalyst on polymerization process was performed. Riboflavin (RF) was chosen as a model drug and microencapsulated in different (drug: polymer) ratios to modify its performance via o/w emulsion solvent evaporation technique and characterized in terms of the morphology and entrapment efficiency (E.E.) and evaluated via in vitro RF release studies. It has been found that, the release rate consists a burst release at the first 12 h, followed by a gradual release over 3 days. The cumulative riboflavin release from these microcapsules formulations at the end of 3 days was 70% and 80% for PDLA and PDLAGA respectively. The kinetics of release profiles were zero order. The highest (E.E.) of RF obtained among all formulations was 85%.

1. Introduction

Polylactic acids (PLA) are not new polymers, the first aliphatic polyester from lactic acid was pioneered by Carothers in 1932, and this product was of a low molecular weight and possessed poor mechanical properties [1]. Further work by Dupont USA Company; resulted in a higher-molecular weight product that was patented in 1954 [2]. The first synthetic polymers designed specifically for use in the body as absorbable materials where the polyglycolides, also known as polyglycolic acids [3], which were used to make the Dexon sutures in 1970. In parallel, research on aliphatic polyesters from lactic acid was initiated and led to the first lactic/glycolic copolymer (PLAGA) exploited as vicryl suture [4]. Polylactic and polylactic-*co*-glycolic acids are considered as biocompatible and biodegradable polymers, thus they are widely used in the medical area [5]. Generally polylactic acid (PLA) and polylactic-*co*-glycolic acid at low molecular weight are used as drug delivery materials, while that of a high molecular weight can be processed into plastics, fibers, thin films and other materials [6–13]. It has good quality of biocompatibility and biodegradability; it can be completely degraded into CO_2 and H_2O [5]. There are two main methods to synthesis PLA, ring-opening polymerization of lactide and condensation polymerization of lactic acid [14–16]. The condensation of lactic acid is carried out with different catalysts e.g. Stannous octoate which is used worldwide either at the Lab or industrial scale. Zinc metal has been largely used in France in the laboratory and industrial [17]. Different drugs, vaccine [18] and hormones were microencapsulated with polylactic acid, e.g. chlordiazepoxide [19], cisplatin [20], protein [21,22], growth hormone [23] and insulin [24,25]. Perfluorooctylbromide was nanoencapsulated into polylactic acid followed by surface functionalization with graphene oxide and gadolinium-chelate; the prepared nanocapsules have a strong absorption in the near infrared (NIR) region, the nanocapsules could efficiently kill cancer cells under NIR laser irradiation [26].The ultimate goal of this study was to prepare Polylactic acid (PLA) and polylactic–co-glycolic acid (PLAGA) in an easy, simple, safe and economically feasible way with a high yield via a modified condensation process in presence of Zinc oxide as a safe, medicated and environmentally acceptable catalyst. The effect of catalyst concentration on polymerization process was performed. To evaluate the prepared polymers as drug carriers; riboflavin was chosen as a model drug, because of its characteristic crystalline structure, yellow in color; it is easily detected. It was microencapsulated with the prepared biodegradable polymers via o/w emulsion solvent

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evaporation technique [19]. All characterization and evaluation criteria for both the prepared polymers and microcapsules were performed.

2. Experimental

2.1. Materials

D(−) lactic acid, assay (87%) lactic in water from Beohringer (England), Glycolic acid, assay (70%) from MERCK (Germany), zinc oxide from Dr. Paul Lohmann GMBH KG, Riboflavin USP from BASF (Germany), Polyvinyl alcohol (PVA) (Medium Viscosity from 40 to50 mpa's per 4% w/w solution) with molecular weight 130,000 from CHANG CHUN PETROCHEMICAL CO., LTD. (TAIWAN), Xylene from MERCK (Germany), Chloroform, Diethyl ether, absolute ethyl alcohol, and Methylene chloride from El-Nasr pharmaceutical Co. for Chemicals (Egypt).

2.2. Equipment

Dean&Starck apparatus equipped with a round bottomed flask, condenser, and measuring cylinder. Filtration unit with Millipore type 0.45 μm HV Model DURAPORE MEMBRANE FILTERS and vacuum pump. Rotatory evaporator Model Heidolph WBECO (Germany), vacuum oven (L O. Vacuum-1 Model HERAEUS) (Germany). Homogenizer Model ULTRA-TURRAX T25, mechanical stirrer Model Heidolph (Germany), sonication apparatus Model JP Selecta (Spain), microscope with USB camera, centrifugation apparatus Model Meditronic Selecta (Spain), rotatory bottle apparatus Model Varian (USA), Automatic polarimeter Model ATAGO AP-300 (England), UV/Vis. Spectrophotometer Model PERKIN ELMER Precisely Lambda 35 (USA), FTIR Spectrometer Model PERKIN ELMER (USA), ^{1}H NMR spectroscopy model Varian ^{1}H-Gemini 200 spectrophotometer in chloroform-d_5 using tetramethyl silane as an internal reference. X-ray diffractograms of various forsterite samples were measured by a copper Kα radiation of wavelength 1.54 Å from a Bruker D8 advance instrument, Oven Model HERAEUS (Germany), and Scanning electron microscope (JEOL−JSM-T 330A) and GPC Agilent 1100 series of molecular weight measurements, Germany, Detector: Refractive Index PLgel particle size (5 μm), pore type (100, 10^4, 10^5 A°) on series, length 7.5 × 300 mm (1000, 5000000).

2.3. Preparation of polylactic acid

Lactic acid polymer was prepared by direct condensation reaction of lactic acid in xylene as solvent and **zinc** oxide as a catalyst using the Dean&Stark apparatus to remove water from the reaction medium until the theoretical amount of water was separated. The condensation adduct (PDLA) was subjected to purification process using chloroform, diethyl ether and finally with absolute ethyl alcohol. The PDLA was dried in vacuum oven at 50 °C.

2.4. Preparation of polylactic-co-glycolic acid (PLAGA)

Copolymerization of lactic acid and glycolic acid in an equimolar ratio (50:50) was performed by the condensation reaction of lactic acid and glycolic acid using xylene as a solvent and zinc oxide as a catalyst in Dean&Stark apparatus to remove water from the reaction medium until the theoretical amount of water was separated. The produced copolymer (PDLAGA) was subject to purification and drying according to the previously mentioned method. Mechanism of synthesis of poly D(−)lactic acid [PDLA] and poly [D(−)lactic-*co*-glycolic] acid [PDLAGA] are represented in Fig. 1.

2.5. Preparation of riboflavin microcapsules

Polymer (PLA) or (PLAGA) (250 mg) was dissolved in methylene chloride (MeCl) (15 ml) by sonication; polyvinyl alcohol (PVA) (20 mg) was dissolved in 30 ml of distilled water and added to the polymer solution. Riboflavin (250 mg) was added to the polymer/PVA mixture. This solution was stirred at 700 rpm and the temperature was maintained at 25 °C and poured into 40 ml distilled water at 70 °C with stirring. Stirring was continued for 5 min. The temperature rapidly raised between (40–45 °C) resulting rapid solvent evaporation and consequent formation of microcapsules. This mixture was allowed to settle in a water bath maintained at 40 °C for 15 min, cooled to room temperature and the supernatant water was discarded. The microcapsules were further washed with distilled water several times and dried.

2.6. In vitro riboflavin release from its microcapsules [19]

Samples of prepared riboflavin microspheres were introduced in dissolution bottles of rotatory bottle apparatus (50 ml distilled water at 37 °C and maintained at 44 rpm for 72.00 h). 50 μl was taken after 0.25 h and diluted in 10 ml distilled water and analyzed for riboflavin dissolution and repeating this step at 0.50, 1.00, 2.00, 4.00, 6.00, 8.00, 12.00, 24.00, 48.00, 72.00 h. Riboflavin released from microcapsules into distilled water was determined from the measurement of absorbance at 270 nm [27] and a standard curve in distilled water.

3. Result and discussion

3.1. Characterization of polymers

The prepared homopolymer (PDLA) and copolymer (PDLAGA) were characterized by different spectroscopic analyses, e.g. FTIR, ^{1}HNNMR, X-ray diffraction, SEM. In addition the physical characteristics were determined, e.g. optical properties, and molecular weight.

3.2. FTIR for polylactic acid (PLA) and polylactic-co-glycolic acid (PLAGA)

FTIR spectra were recorded on a FTIR spectrophotometer (PERKEN ELMER from 4000 to 400 cm^{-1}, USA) using PDLA and PDLAGA solutions in chloroform. Table 1 and Fig. 2a,b show

Table 1
Characteristic peaks for poly D(−)lactic acid and poly [D(−)lactic-*co*-glycolic] acid.

Bands No.	Cm^{-1}	Intensity	Assignments
1a 1b	35123487	Broad Broad	OH of COOHOH of COOH
4a 4b	17561754	Very strongVery strong	C=O of COO C=O of COO
2a 2b	29962994	Medium Medium	CH of CH_3 CH of CH_3
3a 3b	29462949	Medium Medium	CH CH OF CH_2
5a 6b	16471650	Medium Medium	COO COO
6a 9b	12681272	Medium Medium	C—O C—O