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Preparation, characterization and evaluation of drug-delivery systems: Pectin and mefenamic acid films

R.B. Moreira [a], J.A. Teixeira [b], A.M. Furuyama-Lima [c], N.C.de Souza [a], A.B. Siqueira [a,*]

[a] Universidade Federal de Mato Grosso, Rodovia MT-100, Km 3,5, Barra do Garças, MT CEP 78600-000, Brazil
[b] Universidade Federal de Mato Grosso, Cuiabá, MT CEP 78060-900, Brazil
[c] Universidade Estadual Paulista, IBILCE, São José do Rio Preto, SP CEP 15054-000, Brazil

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ABSTRACT

Mefenamic acid (H-Mef) is a nonsteroidal anti-inflammatory drug (NSAID). Various adhesive dosage forms of NSAIDs have been developed, which include adhesive tablets, gels, ointments, patches and more recently, polymeric films. The objective of this study was the development of H-Mef adhesive films to be used as a drug-delivery system with different ratios of pectin and calcium chloride dihydrate by the casting technique. The materials were characterized by TG–DSC coupled FTIR, AFM (atomic force microscopy) and spectroscopic techniques. The results provided information about the dehydration, film roughness, surface morphology, thermal decomposition, as well as identification of gaseous products evolved during thermal decomposition. The characterizations indicated the A5 and A6 films functioned well, with 99% H-Mef released within 15 min at pH 5, suggesting these degradable films could be used as a topical delivery system.

1. Introduction

Systems composed of organic or inorganic materials mixed with pharmaceutical products have been used to study drug delivery or to improve pharmacological properties, and the characterization of these materials are important in understanding how they can be applied [1]. Systems containing drugs and others compounds can result in two types of mixtures [2]:

(1) Physical mixtures: the compounds can be kept their own characteristics, this type are good systems to use in drug delivery system.
(2) Chemical mixture: the compounds can interact one with other, normally chemical mixtures have new properties, but they can also be used in drug delivery system.

Various polymeric drug delivery systems have been investigated in an effort to optimize physicochemical properties, hydrolysis rates and drug release profiles to accommodate diverse biomedical treatments [2].

Natural polymers, such as sodium alginate, pectin, chitosan and carrageenan, used as barriers affecting drug release, are of interest to researchers. Pectins, natural carbohydrates composed of a mixture of heteropolysaccharides, are primarily found in higher plant middle lamellae and primary cell walls. The dominant feature of pectin is a linear chain of (1–4) linked α-D-galacturonic acid residues that are often methyl-esterified at O-6 and sometimes acetyl-esterified at O-2 or O-3 [3]. Pectins are composed of structural elements such as homogalacturonan (HG), xylogalacturonan (XGA), rhamnogalacturonan type I (RGI), rhamnogalacturonan type II (RGII), arabinan and arabinogalactan [3,4].

Pectin is often used due to its availability and ever-increasing demand for high-performance natural matrices for use in biomedical and pharmaceutical applications, such as organ regeneration and tissue engineering, wound dressings, suture material, artificial limbs, as well as controlled drug delivery systems and films [5–8].

In the recent years, many drug delivery system of the pharmaceutical groups are focusing their research on rapid release, mainly in the treatment dolor [9]. Some properties of responsive drug delivery should be further investigated. The preparation of films stands out for its experimental simplicity and presents the possibility of evaluating the molecular interactions between differents materials used in the films [10]. The production

* Corresponding author. Tel.: +55 66 9237 6800.
E-mail address: buzutti@cpd.ufmt.br (A.B. Siqueira).

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of films can be manipulated to prepare films that can be used as desired drug delivery system.

Pectin/mefenamic acid films were produced using two solvents with/without calcium chloride dihydrate, casting and drying, to determine their effects on film formation. The films were evaluated by infrared spectroscopy, simultaneous thermogravimetry and differential scanning calorimetry coupled with infrared spectroscopy (TG–DSC coupled FTIR), and other methods of analysis.

Mefenamic acid (2-[(2,3-dimethylphenyl)amino]benzoic acid) (H-Mef) is classified as a nonsteroidal anti-inflammatory drug (NSAID) which also displays antioxidant and antiproliferative activity *in vitro* against cells of three human cancer cell lines (human breast cancer cell line, bladder cancer cell line and non-small cell lung carcinoma) [4,11]. The therapeutic activity of NSAIDs is due to their ability to inhibit the biosynthesis of prostaglandins by competitive interaction with the cyclooxygenase-arachidonic acid complex in a reversible/irreversible manner (meclofenamic and indomethacin) or by radical quenching activity that interferes with the initiation of cyclooxygenase synthesis [4]. H-Mef has been found to exert neuroprotective effects and improve cognitive impairment *in vitro* and *in vivo* in Alzheimer's disease models and also demonstrates neuroprotective activities against neurodegeneration [12].

Materials and methods

1.1. Reagents

Pectin, mefenamic acid (H-Mef), and calcium chloride dihydrate purchased from Sigma–Aldrich were the main reagents used for film synthesis. All other reagents used in this study were of analytical grade.

1.2. Film preparation

Pectin and H-Mef films were cast using 3 different conditions as follows (Table 1 for the amounts of each reagent used). (1) Aqueous pectin solutions were mixed with H-Mef solutions with stirring for 2 h (Table 1 for composition). H-Mef solutions were prepared by dissolving H-Mef powder in ethyl acetate/ethanol 80:20 (v/v) solution and mixtured with aqueous pectin solutions. The calcium chloride dihydrate was added in the mixture and it was stirred at room temperature for 20 min, transferred to a petri dish and placed in a kiln at 373 K for 48 h (A1–A4 samples). (2) H-Mef powder was added to aqueous pectin solutions, stirred for 1 h, after the calcium chloride dihydrate was added and stirred for 48 h. The mixtures were transferred to petri dishes and placed in a kiln at 323 K for 36 h (A5 and A6 samples, H-Mef was not added to A7 sample). (3) Film were created as described above (1) but dried at 333 K for 48 h (A8–A10 samples).

1.3. Instrumentation

The attenuate total reflectance infrared spectra of films as well as those of its isolated materials were recorded on a PerkinElmer Spectrum-100 spectrophotometer within the 4000–600 cm^{-1} range, using an ATR accessory with a Diamond/ZnSe window.

Simultaneous TG–DSC curves were obtained using a Mettler TG–DSC thermogravimetric analyser coupled to a Nicolet FTIR spectrophotometer with a gas cell and a DTGS KBr detector. The furnace and the heated gas cell (523 K) were coupled through a heated (T = 473 K) 120 cm stainless steel transfer line with a 3-mm diameter, both purged with dry air (50 mL min^{-1}). The FTIR spectra were recorded at 32 scans per spectrum at a resolution of 4 cm^{-1}. Purge gas flow rate was 50 mL min^{-1} and a heating rate of 20 K min^{-1} was used with 10 mg samples weighing. Alumina crucibles were used for the TG–DSC analysis.

Film morphology was studied with a NanoSurf Instruments atomic force microscope EasyScan II in the tapping mode (pixels) under ambient conditions. The tapping mode was selected (instead of the contact mode) because it is less damaging to the surfaces under investigation, [13] as less energy is transferred and the tip does not exert a significant lateral force on the surface. A sample area of 5 $\mu m \times 5\ \mu m$ was scanned, images acquired and film roughness determined using NanoSurf Instruments software.

The drug-delivery system assessed H-Mef absorbance values in solutions at pH 1.5, 5 and 8. The films were soaked in the solution of the desired pH and absorbance determined. The absorbance were recorded at 219 nm with UV–vis spectrophotometer (PerkinElmer-Lambda 25). The pH values used in the model were representative of dissolution in body fluids such as stomach acid (pH c.a. 1.5), sweat (pH c.a. 5) and intestinal secretions (pH c.a. 8).

Results and discussion

1.4. Films formation

The A1–A4 and A8–A10 samples did not form homogeneous films when the solvents were evaporated, suggesting film formation was affected by the addition of ethyl acetate/ethanol as solvents. A5–A7 formed soft films and suggested calcium chloride dihydrate dissolved in distilled water were fundamental to film formation.

1.5. FTIR analysis

In Fig. 1 are shown Infrared Spectra of the H-Mef and pectin. The principal vibrational modes of H-Mef are C=O, O–H and N–H stretching [6]. A wavenumber of 3311 cm^{-1} was assigned to the stretching mode of the N–H group and 3348–3325 cm^{-1} to the stretching of intermolecular hydrogen bonding due to dimer

Table 1
Film preparation – mass and volume of reagents and solvents in the mixtures.

Sample	Solvent[a]	H-Mef (g) c.a.	Pectin (g) c.a.	$CaCl_2 \cdot 2H_2O$ (g) c.a.	Volume of solution (mL)
A1	1	0.25	0.25	2.77	25
A2	1	0.13	0.25	2.77	25
A3	1	0.08	0.25	2.77	25
A4	1	0.03	0.25	2.77	25
A5	2	1.00	1.00	11.00	100
A6	2	0.50	1.00	11.00	100
A7	2	0	1.00	11.00	100
A8	1	0.08	0.25	0	25
A9	1	0.13	0.25	0	25
A10	1	0.18	0.25	0	25

[a] 1: 40% ethyl acetate/10% ethanol/50% distilled water. 2: distilled water.