Sensors and Actuators A 241 (2016) 238–244

Contents lists available at ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

Nanoparticle-enabled wireless monitoring and characterization of physical degradation kinetics in pharmaceutical gelatin films

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ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form 11 February 2016
Accepted 15 February 2016
Available online 18 February 2016

Keywords:
Wireless monitoring
Rapid screening
Pharmaceutical films
Gelatin
Ferrogelatin
Degradation

ABSTRACT

Degradation kinetics of pharmaceutical excipient films effect their overall performance and drug release profile. Characterizing them is traditionally labor-intensive and time-consuming, requiring spectroscopy or periodic mass measurements. Here we present an alternative rapid technique for electrically (and wirelessly) measuring the polymeric matrix swelling and material degradation in aqueous media for characterizing functional films. The film is loaded with ferromagnetic nanoparticles and used as the core of a planar coil whose resonant frequency is monitored remotely. When placed in an aqueous solution, swelling and dissolution of the film induce contrasting changes in the capacitance and inductance of the coil, respectively, allowing identification of the swelling and dissolution phases. The dissolution profile of iron oxide-loaded gelatin is compared with spectrophotometry data, further demonstrating the technique can distinguish among films with various levels of crosslinking (showing a resonant frequency difference of 116 kHz between completely non-crosslinked and fully crosslinked gelatin). The key characteristics of the film degradation kinetics can be captured within 20–30 min of data collection.

1. Introduction

Tunable and environmentally-responsive pharmaceutical films offer a convenient vehicle for delivering drugs at specific locations in the body in a controlled fashion due to their biocompatibility, biodegradability, and modifiable properties [1–6]. As a result, researchers have developed a plethora of drug delivery systems, from ingestible capsules/tablets to topical and buccal delivery strips, which may rely on layered arrangements or coatings of such films to program the delivery of various drugs. For these systems, the dissolution and erosion/degradation kinetics of the excipient play a crucial role in the drug release profile from polymeric-matrix systems. Typically, these systems are characterized by spectroscopic absorbance of a released drug [7–12]. More importantly, the drug release can actually be thought of as a secondary process, whereby the drug solute migrates towards the polymer's outer surface and then to the release media. It is generally believed that the solute diffusion, polymeric matrix swelling, and material degradation kinetics are the main driving forces for solute diffusion from polymeric films/matrices [13]. Therefore, it would be advantageous to have a means to characterize the polymeric matrix swelling and degradation kinetics, rather than measuring the secondary process (solute diffusion and/or dissolution).

In one approach to characterize the swelling, the excipient film is removed from its solution and characterized at various time points during its dissolution by drying it and measuring its mass [8] and/or its thickness (by ellipsometry) [14,15]. Others have used a penetrometer or a video-microscope equipped with an image analyzer to visually distinguish between gelled and glassy regions in the film. While these techniques are suitable in many cases (e.g., small-scale quality control studies of film dissolution or drug release), there are several limitations rendering these methods suboptimal for high-throughput film screening; these include reliance on manual methods (and the resulting low sampling frequency), the need for complex fluidic setups (especially if attempting parallel experiments), and the requirement for continuous stirring (which may further alter the dissolution kinetics of the film).

A more convenient approach would be a non-contact (i.e., non-invasive), automated, electrical method for assessing film integrity of multiple samples during dissolution. Electrical techniques are advantageous due to their ease of interfacing with a variety of data acquisition systems commonly found in many laboratories. Unfortunately, most pharmaceutical excipients do not possess strong

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http://dx.doi.org/10.1016/j.sna.2016.02.028
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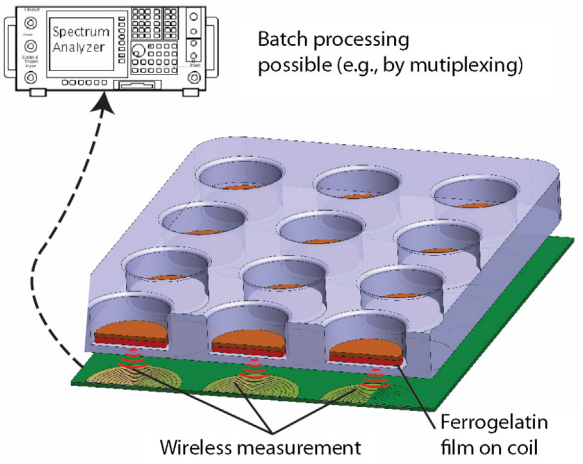

Fig. 1. Schematic showing the use of the described measurement technique adapted for multi-sample, wireless, high-throughput screening of pharmaceutical films. Drug excipient films are loaded with ferromagnetic particles, cast into dry discs, and mounted on the electromagnetic test platforms.

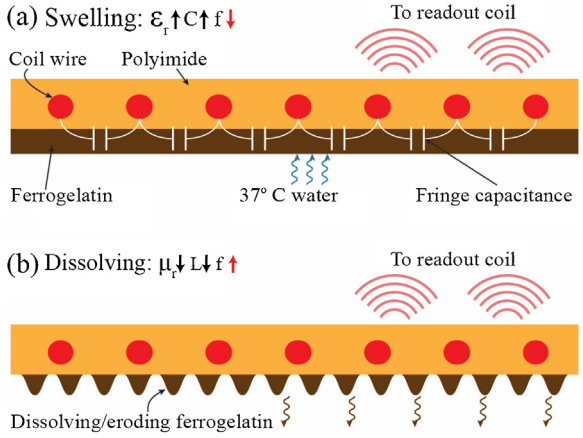

Fig. 2. Illustration of the sensing mechanism used to characterize the ferrogelatin degradation with time. The diagram shows the cross-section of a polyimide-embedded coil with an attached ferrogelatin film; (a) initially ferrogelatin film swells upon immersion in water, changing the effective dielectric constant of the film (from about 2–4 for dry proteins to about 80 for water), causing an increase in the fringe capacitance of the coil (depicted as white capacitors) and a drop in its resonant frequency; (b) subsequent dissolution of the film erodes away the ferromagnetic material, decreasing the magnetic permeability of the coil and thus increasing its resonant frequency.

electromagnetic properties that can be monitored. To circumvent this shortcoming, we have developed a sensing scheme for wirelessly monitoring the matrix swelling and degradation kinetics of established pharmaceutical film materials by incorporating biocompatible [16,17] ferromagnetic nanoparticles; as a result, the films exhibit a measurable degradation-dependent change in the resonant frequency of the coil/film device. In this paper, we present a proof-of-concept demonstration of this technique. Here, we use gelatin (of various degrees of crosslinking: un-, partially-, fully-crosslinked gelatins [18]) loaded with iron oxide nanoparticles to create "ferrogelatin". When the film is placed in close proximity to a resonant (LC) circuit, the swelling and dissolution of the ferrogelatin can be remotely monitored by measuring the resonant frequency of the circuit [19]. This method offers additional advantages over other techniques like those based on detecting and differentiating between the initial swelling and the subsequent dissolution phase, including a higher temporal resolution, and spatial scalability. Rather than inspecting the film manually (which is typically done at intervals of 5–15 min), it is possible to conduct electrical measurements with a sampling rate on the order of seconds or faster, thus allowing data collection in time intervals shorter than one minute. Furthermore, by virtue of being completely electrical, this technique is suitable for implementing as a batch-screening arrangement (e.g., with a multiplexing circuit) to conduct a simultaneous screening of multiple gelatin samples, as depicted in Fig. 1.

2. Operation principle

The working principle of the sensing scheme is illustrated in Fig. 2. Monitoring is achieved by placing a flat coil adjacent to the ferrogelatin film as it dissolves in the dissolution medium (e.g., 37 °C water or saline). Thus, the ferrogelatin behaves as the core of the coil, increasing its inductance. Once placed in an aqueous medium, the ferrogelatin film initially absorbs water, thus also altering the local permittivity (2–4 for dry proteins, but about 80 for water) [20] around the inductor. Similar to other soluble films when exposed to aqueous environments, physical degradation of the gelatin film proceeds by two driving mechanisms: swelling and subsequent dissolution. As a result, when the physical properties of the film change (i.e., by swelling or erosion), the local magnetic permeability and permittivity change. Such changes alter in turn the inductance or capacitance of the LC tank. These changes are detected wirelessly by monitoring the self-resonant frequency of the inductor via a second (read-out) coil using the phase-dip method [19].

A unique feature of this monitoring technique is the integration of inductive as well as capacitive sensing, which in combination can be used to differentiate among the various stages of film degradation, i.e., initial swelling when placed in the medium, transition to dissolution, and complete dissolution. This type of differentiation is possible since the swelling and degradation of ferrogelatin cause the resonant frequency of the system to change in opposing directions. To understand these effects, we consider the ferrogelatin and coil system as an LC circuit (L being the inductance of the coil and C in this case representing the parasitic capacitances associated with it, i.e., the capacitors between various turns with electric flux going through the ferrogelatin film or surrounding aqueous media), whose self-resonant frequency is given by $f_0 = \frac{1}{\sqrt{LC}}$. The inductance depends primarily on the geometry of the coil and the amount of ferromagnetic material (i.e., permeability) in the film, whereas fringe/parasitic capacitance is a function of the geometric design of the coil and the permittivity of the ferrogelatin film (which as mentioned above depends mainly on its water content). When ferrogelatin is immersed in an aqueous medium the capacitance and inductance are affected at different stages: permittivity, and hence capacitance, is primarily affected during the initial absorption of water following immersion, whereas inductance primarily during the degradation phase. As shown in Fig. 2a, swelling of ferrogelatin increases fringe capacitance in the sensing coil due to the elevated relative permittivity (i.e., of water), resulting in a reduced resonant frequency. In contrast, as gelatin degrades, the loss of ferro-particles reduces the magnetic permeability (and hence inductance), resulting in an increased frequency, Fig. 2b. Thus, by observing the change in the resonant frequency, it is possible to identify the various phases of the film degradation process.

The resonant frequency can be detected through inductive coupling; the external coil energizes the ferrogelatin LC circuit, which provides a load impedance that is reflected back to the external coil [19]. Briefly, the impedance phase dip, $\Delta\phi_{DIP} \cong \arctan\left(\frac{2\pi f_0 M^2}{L_e R_S}\right)$, is a function of the resonance frequency f_0, the mutual inductance between the external coil and LC circuit, M, the inductance of the external coil L_e, and series resistance of the LC circuit, R_S. At the