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Study of release kinetics and diffusion coefficients in swellable cellulosic thin films by means of a simple spectrophotometric technique

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ABSTRACT

Measurement of diffusion in gel is an essential task for pharmaceutic technology and biochemical engineering. In this work we investigate diffusion coefficients and release kinetics of colored substances loaded in polymeric thin strips, by extending a simple spectrophotometric technique from catalysis science to swellable polymer matrices. Absorbance can be a measure of the average solute concentration in the swollen gel so that the time decay of film absorbance can be a quantitative measure of the release kinetics and henceforth of the diffusion coefficient in the swollen gel. Thin film dissolution is carried out in a newly proposed microfluidic continuous flow-through device. Hydroxypropyl methylcellulose (HPMC) is used as filming polymer. Film thickness, uniformity of content and swelling time-scales are accounted for in the estimation of the effective diffusion coefficient.

Keywords: Oral strips; Swelling; Diffusion coefficient; Drug release; UV–vis spectrophotometry

1. Introduction

Polymeric thin films have recently appeared as a very promising pharmaceutical dosage form (Murata et al., 2010; Nishigaki et al., 2012). In the last few years, they have attracted much attention, because of their substantial advantages on traditional alternatives: enhanced bioavailability, high patient compliance, patent life extension of well-known active pharmaceutical ingredients (Hearnden et al., 2012). Oral strips are films with thicknesses less that 100 μm, similar in size and shape to a postage stamp. They are usually composed of a hydrophilic polymer, drug, plasticizers and excipients (Dixit and Puthli, 2009). In contact with saliva, films rapidly hydrate and gel, adhere onto the site of application and disintegrate, without the need of water (Morales and McConville, 2011; Semalty et al., 2008). Drug transport through polymeric matrices is a key aspect to estimate the kinetics of drug release (Narasimhan, 2001; Gao and Fagerness, 1995). Gel from tablets and (rarely) films of bioerodible polymers have been studied in pharmaceutical science with this aim (Siepmann et al., 1999). Diffusion of solute substances in gels has been object of extensive research. No single method can be considered valid in all situations, but different methods must be adopted for different solute/polymer systems (Andersson et al., 1997). A number of experimental techniques have been proposed at this purpose (Dickson et al., 2012; Westrin et al., 1994; am Ende and Peppas, 1997; Ye et al., 2012; Brandl et al., 2010; Garcia-Aparicio et al., 2012). Latest research tendencies are oriented towards diffusion studies which could give real-time information about drug release, as a potential alternative to traditional dissolution testing methods (Boetker et al., 2013; Gauno et al., 2013).

In this work, we study diffusion coefficients and release of colored active ingredients initially loaded in glassy thin films, by extending a simple spectrophotometric technique known in catalysis science (Takahashi et al., 2000, 2001) to swellable gels. This technique has been originally applied to the measurement of the diffusion coefficient of nickel nitrate in wet silica gel, which is a non-swelling gel. We adopt this experimental method to determine the effective diffusion coefficient

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Table 1 – Composition and thickness of dry films. MAD: acronym for maximum absolute deviation.

Film	Concentration % by weight ± MAD	Thickness μm ± MAD
HPMC	Pure	20 ± 3
Methyl orange	1.5 ± 0.09	17 ± 3
Vitamin B12	1.61 ± 0.16	12 ± 2

of methyl orange and Vitamin B12 in hydroxypropyl methylcellulose (HPMC) films. HPMC is a swellable cellulosic polymer widely used in drug delivery. Absorbance can be a measure of the average solute concentration in the swelling/swollen gel so that the time decay of film absorbance can be a quantitative measure of the release kinetics and henceforth of the diffusion coefficient in the swollen gel. We operate dissolution in a newly proposed continuous flow-through device (Italian patent, 2013) with extremely low hold-up volumes.

2. Materials

Hydroxypropyl methylcellulose (HPMC) Methocel K15M Premium was a kind gift from Colorcon. Methyl orange solution 0.1% in water and Vitamin B12 pharmaceutical secondary standard were purchased by Fluka. Distilled water was used as solvent.

3. Methods

3.1. Stock solutions

Stock solution of HPMC 2% by weight in distilled water was prepared.

Polymer powder was thoroughly dispersed under vigorous magnetic stirring at 90 °C. The resulting mixture was cooled down by external heat exchange and deaerated in mild vacuum for at least 24 h.

As colored solutes, methyl orange and Vitamin B12 were used. Methyl orange solution was used as purchased. Stock solution of Vitamin B12 0.05% by weight in distilled water was prepared and kept protected from light. HPMC and Vitamin B12 stock solutions were stored at 5 °C.

3.2. Film casting

Films were prepared by casting solution technique. Pure HPMC films were obtained by casting HPMC stock solution. Casting solutions for films containing methyl orange and Vitamin B12 were prepared by vigorously mixing the corresponding stock solutions with the HPMC stock solution for at least 6 h. Solutions were deaerated in oven at 40 °C under mild vacuum for at least 24 h. All films were cast on inox plates at room conditions, 20–25 °C and dried in oven at 37 °C. Fig. 1 shows three dry films: pure HPMC, one containing methyl orange (yellow film) and one containing Vitamin B12 (pink film).

Casting thickness of colored films was imposed at 50 mils (1 mils = 0.001 in.) by means of a BYK-Gardner square film applicator, to improve homogeneity of the sample. Dry films were peeled-off and stored at room temperature, protected from light. Compositions of the colored films (as dry) are reported in Table 1.

Fig. 1 – Thin dry films: pure HPMC, methyl orange in HPMC (yellow) and Vitamin B12 in HPMC (pink). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.3. Thickness and uniformity content

Thickness of dry films was measured by means of a Mitutoyo Digimatic Micrometer, instrument error ±2 μm. Measurements were taken at 5 different points for each film.

Uniformity of content was analyzed for colored films, by dissolving a known quantity of sample in 8 g of distilled water, then analyzing the obtained solutions by visible spectrophotometry (Perkin Elmer spectrophotometer Lambda 2240). Methyl orange was evaluated at 465 nm, Vitamin B12 at 550 nm. Tests were repeated in triplicate.

Measured thicknesses L_0 are reported in Table 1 as average value ± maximum absolute deviation. Results of content uniformity tests are also reported in Table 1 in terms of absolute deviation from the expected average value. Deviations are less than 15% of the average value.

3.4. Swelling equilibrium study

The swelling behavior was studied on pure HPMC films, being the phenomenon completely controlled by the polymer behavior (Bettini et al., 2001). Films were cut, weighted and inserted in a bowl of dimensions 3.5 cm × 3.5 cm × 0.7 cm, the bottom punched to avoid the stagnation of non-absorbed water. Water was poured to submerge the film. At regular time intervals, non-absorbed water was drained and wet film + bowl were weighted. Experiments were performed with water at room temperature (Test 1) and water in ice bath at 0 °C (Test 2). Each test was repeated in triplicate.

We define W_t as the weight of the wetted HPMC film at time t and W_0 as the weight of the dry film. Swelling data are reported as $SW(t) = W_0/W_t \cdot 100$.

3.5. Diffusion study

Diffusion studies were carried out on films with colored solute using the microfluidic device proposed in Italian patent (2013).

The dissolution cell of the device is made in Plexiglass and it has dimensions 2 mm × 2.8 cm × 1.8 cm. These dimensions were chosen to assure a regular flow through the device also

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