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Release kinetics from oral thin films: Theory and experiments

Alessandra Adrover[a,b,*], *Michela Nobili*[a]

[a] *La Sapienza Università di Roma, Italy*
[b] *Dipartimento di Ingegneria Chimica, Materiali e Ambiente, Via Eudossiana 18, 00184 Rome, Italy*

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ABSTRACT

In this work, a new millifluidic flow-through device is proposed for drug release studies from oral strips. The flow-through device mimics mouth physiological conditions thanks to the laminar tangential solvent flow, flow rates order of 1 mL/min and low hold-up volume (1 cm^3).

Drug release experiments have been performed on HPMC K15M thin films loaded with methyl orange with different initial drug loadings. A detailed analysis of data reproducibility and influence of flow-rates, film thickness and drug dosage on release curves is presented.

A two-dimensional moving boundary model, describing drug transport in the swelling film and in the solvent flow channel is presented and solved numerically by FEM (finite elements method).

The theoretical model strongly supports the experimental observation that the time scales for complete drug release are significantly longer than expected when fluid dynamical conditions (close to mouth in-vivo conditions) are properly implemented in the experimental apparatus, and properly accounted for in the numerical modelling.

1. Introduction

Polymeric thin films have recently appeared as a very promising pharmaceutical dosage form (Murata et al., 2010; Nishigaki et al., 2012). Oral strips are films with thicknesses less that 100 μm (OTFs oral thin films), 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 and/or dissolve (Morales and McConville, 2011; Semalty et al., 2008; Kathpalia and Gupte, 2013).

In the pharmaceutical industry, both in drug development and quality control, dissolution testing is an important tool to measure the dissolution rate of an active drug from a dosage formulation under standardized conditions of liquid/solid interface, temperature, and solvent composition.

From a regulatory standpoint, the legally-binding documents to carry out the dissolution tests are reported in the 8th edition of European Pharmacopoeia (EP), the 37 United States Pharmacopoeia (USP), and the 16th edition of Japanese Pharmacopoeia (JP).

Buccal films have not been included yet in any standardization and drug release studies reported in literature are generally performed using apparatuses approved for other solid oral dosage forms (Dixit and Puthli, 2009; Brown et al., 2011; Shimoda et al., 2009; Liew et al., 2012; Juliano et al., 2008), i.e. Basket apparatus (USP 1), Paddle apparatus (USP 2), Reciprocating Cylinder apparatus (USP 3, not accepted in the Japanese Pharmacopoeia) and Flow through cell (USP 4).

Problems with film positioning, poor reproducibility of the experimental data as well as large hold-up volumes (designed to simulate the gastrointestinal tract) make the use of standard USP apparatuses unable to properly evaluate the release profile of OTFs (Brown et al., 2011; Sievens-Figueroa

* *Corresponding author at*: La Sapienza Università di Roma, Italy. Tel.: +39 0644585609; fax: +39 0644585451.
E-mail address: alessandra.adrover@uniroma1.it (A. Adrover).
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et al., 2012a,b) and a more discriminative and suitable drug release method which can better reflect the fluidynamical conditions of mouth in vivo conditions is required.

In this work we make use of a new millifluidic continuous flow-through device for drug release from oral dissolving strips. The flow-through device mimics mouth physiological conditions because of the laminar tangential solvent flow, flow rates order of 1 mL/min (Watanabe and Dawes, 1990) and low hold-up volumes (1 cm^3).

In a recent work (Adrover et al., 2014), drug release tests of commercially available melatonin strips obtained with the flow-through device were compared with those obtained using the official USP XXXVII basket (USP 1) and paddle (USP 2) apparatuses. We observed that variability between the repeated experiments in the flow-through device is extremely low and significantly lower than in USP devices. Furthermore, the millifluidic method rarely exhibits tests failures, which have been rather frequent when USP basket or paddle apparatuses are used for pharmaceutical thin films. Moreover we observed that, even for the highest flow rate conditions (Q = 20 mL/min, at least five times the normal salivary flow rate) the millifluidic device shows slower release profiles characterized by approximately 10–15 min of delay with respect to the other two investigated methods. Therefore, official methods seem to significantly overestimate the release kinetics and consequently to underestimate the time for complete drug release.

In this article drug release tests are performed on HPMC K15M thin films (thicknesses 20–30 μm) realized in our laboratories and loaded with methyl orange with different initial drug loadings. In this way we can control the film composition and thickness and avoid the presence of thickeners, stabilizers and emulsifiers that are usually present in commercial OTFs in unknown quantities. This can lead to a better understanding of the release kinetics with the support of a theoretical model coupling the film swelling dynamics with solute transport equations.

The theoretical model has a big added value as it strongly supports the experimental observation that, also for the so-called fast-dissolving films, the time scales for complete drug release are significantly longer than expected when fluid dynamical conditions (close to mouth in vivo conditions) are properly implemented in the experimental apparatus, and properly accounted for in the numerical modelling.

The theoretical 2-dimensional model describes the interaction between drug transport in the swelling film and drug transport in the solvent flow channel (Ranade and Mashelkar, 1995), thus (1) leading to a quantitative estimate of the thickness of the mass-transfer boundary layer (BL) at the gel–solvent interface, (2) evaluating how the BL depends on the solvent flow rate and (3) clearly showing how, for low flow rates (comparable with salivary flow rates), we are very far from the usually adopted perfect sink conditions.

The article is organized as follows. In Section 3 we illustrate the experimental methods adopted for preparing thin films and for performing swelling and drug release studies.

In Section 4 we analyze swelling data and estimate the effective diffusion coefficient of solvent (water) in the swelling polymer by means of a one-dimensional moving boundary transport model of solvent in the swelling polymer/water system.

In Section 5 we present drug release profiles obtained with the flow-through device. A detailed analysis of data reproducibility and influence of flow-rates, film thickness and drug dosage on release curves obtained with the millifluidic device is presented. Release data show good reproducibility and reliability. A preliminary analysis of release data gives us information on the effective diffusion coefficient of the drug (methyl orange) in the swelling film (see Appendix I).

In Section 6 a two-dimensional moving boundary model, describing drug transport in the swelling film and in the solvent flow channel is presented and solved numerically by FEM (finite elements method). Numerical results are in excellent agreement with experimental data. The practical benefit of the model is to identify film thickness and flow rate to achieve a desired release profile.

Numerical issues related to the solution of both the 1-d swelling model and the 2-d drug release model are discussed in Appendix II.

2. Materials

Hydroxypropyl methylcellulose (HPMC) Methocel K15M Premium was a kind gift from Colorcon. Methyl orange solution 0.1% in water was 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.

Methyl orange was used as solute. Methyl orange solution was used as purchased.

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 were prepared by vigorously mixing the corresponding stock solutions with the HPMC stock solution for at least 6 h.

We started with the same amount of HPMC stock solution (100 g) and added the methyl orange–water solution (methyl orange at 0.1% by weight) in order to obtain a desired weight ratio [g methyl orange /(g methyl orange + g HPMC)].

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 25 °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 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 films (as dry) are reported in Table 1. Two different initial loadings of methyl orange are analyzed.

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.