Available online at www.sciencedirect.com
ScienceDirect
Journal of Magnetic Resonance 185 (2007) 103–109
JMR Journal of Magnetic Resonance
www.elsevier.com/locate/jmr

A study of tablet dissolution by magnetic resonance electric current density imaging

Urša Mikac [a,*], Alojz Demsar [b], Franci Demsar [a], Igor Serša [a]

[a] *Jožef Stefan Institute, Jamova 39, 1000 Ljubljana, Slovenia*
[b] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia*

Received 24 July 2006; revised 16 November 2006
Available online 21 December 2006

Abstract

The electric current density imaging technique (CDI) was used to monitor the dissolution of ion releasing tablets (made of various carboxylic acids and of sodium chloride) by following conductivity changes in an agar–agar gel surrounding the tablet. Conductivity changes in the sample were used to calculate spatial and temporal changes of ionic concentrations in the sample. The experimental data for ion migration were compared to a mathematical model based on a solution of the diffusion equation with moving boundary conditions for the tablet geometry. Diffusion constants for different acids were determined by fitting the model to the experimental data. The experiments with dissolving tablets were used to demonstrate the potential of the CDI technique for measurement of ion concentration in the vicinity of ion releasing samples.

Keywords: Magnetic resonance imaging (MRI); Current density imaging (CDI); Dissolution process; Ion diffusion

1. Introduction

Electric current density imaging (CDI) is a magnetic resonance imaging (MRI) technique that images the induced electric current density and electric conductivity distribution within any sample containing water with mobile ions [1,2]. The intensity of the CD image is proportional to the electric current flowing through the sample. The sensitivity of the CDI technique depends on the sample impedance, the applied voltage, the total duration of current pulses, and the signal to noise ratio of the conventional MR image [3,4]. Sensitivity and resolution studies of the CDI method on a model sample showed that with a properly chosen electric current density and electric current pulse duration, the signal to noise ratio of the electric current density image is comparable to the signal to noise ratio of conventional images.

CDI can measure the electric current density in three different frequency ranges: at zero frequency using the direct current density imaging technique, DC-CDI [1,2], in the kiloHertz frequency range using the alternating current density imaging technique, AC-CDI [5], and at the Larmor frequency using the radiofrequency current density imaging technique, RF-CDI [6,7]. The methods have been used to image current distribution *in vitro* [8–11], to monitor chemical processes [12,13] and also to image current pathways and tissue conductivity *in vivo* [14–18].

Among its pharmaceutical properties, the disintegration and dissolution properties of a tablet, as well as the free diffusion of substances, are of considerable importance. In recent years increasing attention has been paid to development of tablets which can rapidly dissolve or disintegrate in the mouth. The impact of fast disintegrants [19,20], the procedure used for tablet preparation [21,22] and ageing [23–25] on the dissolution of a tablet are of a great interest. The aspirin tablet matrix was proposed as a model formulation for comparison of disintegrant efficiency and testing the performance consistency for quality control purposes [20].

* Corresponding author. Fax: +386 1 477 3191.
E-mail address: urska.mikac@ijs.si (U. Mikac).

1090-7807/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.jmr.2006.12.002

In this paper, the feasibility of the CDI method for monitoring dissolution processes in tablets was studied. Electric conductivity images, acquired by the DC-CDI method, were used for tracing the dissolution of tablets and ion migration processes. The diffusion coefficients of various acids (tartaric, citric, oxalic, and maleic) and sodium chloride (NaCl) were determined from the CD image signal intensity acquired at different times after the beginning of the dissolution process.

2. Theory

The surface of a tablet that is in contact with an aqueous medium disintegrates into granules that in turn disaggregate into fine particles. Let us assume that the threshold concentration at which ions are formed and can be imaged by CDI is C_N. In our experiments, dissolution at the top and bottom of the tablet was obstructed because the samples were capped at the ends with electrodes. Additionally, the sample tablets had cylindrical symmetry so that ion migration and diffusion was only radially dependent (Fig. 1).

The mathematical model is divided into two parts. The first part corresponds to the time from the beginning of the experiment until the tablet is completely dissolved ($0 < t < t_0$) and considers tablet dissolution as well as ion diffusion, while the second part corresponds to time after the tablet is completely dissolved ($t > t_0$) and considers only ion diffusion.

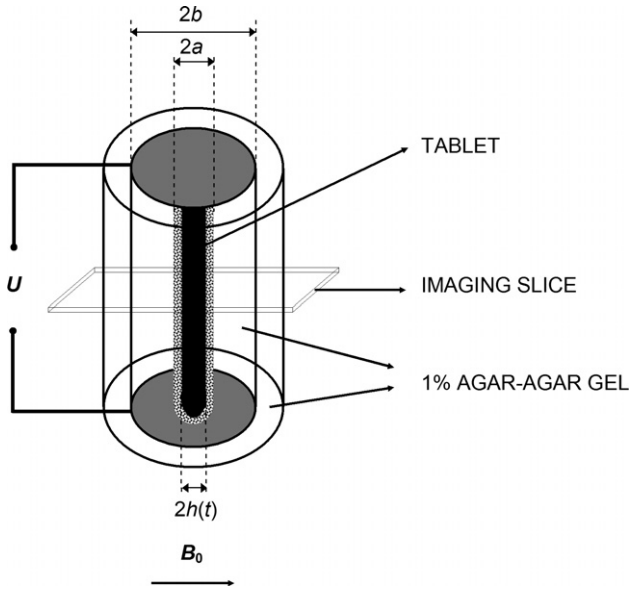

Fig. 1. The Plexiglas cell for tablet dissolution experiments. The cell has two concentric cylinders, each of length 12 mm. The inner cylinder of a diameter $2b = 10$ mm was capped at the ends with copper electrodes. The electrodes were connected to a voltage amplifier of a maximum output voltage of 220 V. The direction of the electric current was perpendicular to the static magnetic field B_0. The outer cylinder of 16 mm diameter was used as a reference with no electric current flowing through it. Both cylinders were filled with 1% agar–agar gel. A tablet with initial dimensions of diameter $2a = 4$ and 12 mm height was placed at the beginning of each experiment in the centre of the inner cylinder. During the experiment the tablet dissolved and at time t had a diameter $2h(t)$.

At low ion concentrations, the dependence of the diffusion coefficient on the ion concentration is weak and in the range of experimental error [26,27]. At very high ion concentrations the diffusion coefficient can become critically dependent on ion concentration. In our experiments the region of high ion concentration occurs only in the narrow layer close to the solid tablet. To simplify the model, the diffusion coefficient was assumed to be independent of ion concentration in the whole region. In this approximation the diffusion equation for cylindrical geometry is given by

$$\frac{\partial c_1(r,t)}{\partial t} = \frac{D}{r}\left[r\frac{\partial^2 c_1(r,t)}{\partial r^2} + \frac{\partial c_1(r,t)}{\partial r}\right] \quad \text{for } h(t) < r < b, \tag{1}$$

$$c_1(h(t),t) = C_N, \tag{2a}$$

$$\left.\frac{\partial c_1(r,t)}{\partial r}\right|_{r=b} = 0, \tag{2b}$$

$$c_1(r,0) = \begin{cases} C_0, & r \leqslant a, \\ 0, & a > r > b. \end{cases} \tag{3}$$

Here, c_1 denotes ion concentration, D the ion diffusion constant, C_0 the ion concentration in the solid tablet, a initial tablet radius, b inner cylinder radius, t_0 time in which the tablet is completely dissolved, and $h(t)$ the position of the tablet/gel boundary at time t. Mass conservation at the moving boundary $h(t)$ leads to the following equation [28] for the moving boundary position:

$$C_N\frac{\partial h(t)}{\partial t} = D\left.\frac{\partial c_1(r,t)}{\partial r}\right|_{r=h(t)}, \tag{4}$$

where C_N is the concentration of released ions that can freely diffuse per unit volume.

The diffusion equation (1) with the boundary conditions (Eqs. (2a) and (2b)) and the initial condition (Eq. (3)) was solved numerically with the finite difference method [28–30]. The cylinder radius r is divided into i space intervals Δr, and time is divided into j time intervals Δt. The concentration at a certain grid point $c_1(i\Delta r,(j+1)\Delta t)$ for a new time step can be calculated from Eq. (1) when the concentrations at the same grid point at the previous time step $c_1(i\Delta r, j\Delta t)$ and the concentrations of the nearest neighbours $c_1((i-1)\Delta r, j\Delta t)$ and $c_1((i+1)\Delta r, j\Delta t)$ are known. At time $t = 0$, the concentration profile is given by the initial condition (Eq. (3)). At boundaries $r = h(t)$ and $r = b$, the concentrations are given by Eqs. (2a) and (2b). After the concentration is calculated for each time interval, a new position of the moving boundary $h(t)$ is calculated using Eq. (4) and the grid is redistributed so that the boundary $h(t)$ is a nodal point. With a new grid the whole procedure for computing the concentration profile at a new time step is repeated until $h(t) \geqslant 0$ and the whole tablet dissolves.