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Floating gastroretentive drug delivery systems: Comparison of experimental and simulated dissolution profiles and floatation behavior

Veronika A. Eberle [a], Joachim Schoelkopf [b], Patrick A.C. Gane [b,c], Rainer Alles [a], Jörg Huwyler [a,*], Maxim Puchkov [a]

[a] Department of Pharmaceutical Sciences, Division of Pharmaceutical Technology, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland
[b] Omya International AG, 4665 Oftringen, Switzerland
[c] School of Chemical Technology, Aalto University, FI-00076 Aalto, Helsinki, Finland

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ABSTRACT

Introduction: Gastroretentive drug delivery systems (GRDDS) play an important role in the delivery of drug substances to the upper part of the gastrointestinal tract; they offer a possibility to overcome the limited gastric residence time of conventional dosage forms.
Aims: The aim of the study was to understand drug-release and floatation mechanisms of a floating GRDDS based on functionalized calcium carbonate (FCC). The inherently low apparent density of the excipient (approx. 0.6 g/cm^3) enabled a mechanism of floatation. The higher specific surface of FCC (approx. 70 m^2) allowed sufficient hardness of resulting compacts. The floating mechanism of GRDDS was simulated *in silico* under simulated acidic and neutral conditions, and the results were compared to those obtained *in vitro*.
Methods: United States Pharmacopeia (USP) dissolution methods are of limited usefulness for evaluating floating behavior and drug release of floating dosage forms. Therefore, we developed a custom-built stomach model to simultaneously analyze floating characteristics and drug release. *In silico* dissolution and floatation profiles of the FCC-based tablet were simulated using a three-dimensional cellular automata-based model.
Results: In simulated gastric fluid, the FCC-based tablets showed instant floatation. The compacts stayed afloat during the measurement in 0.1 N HCl and eroded completely while releasing the model drug substance. When water was used as dissolution medium, the tablets had no floating lag time and sank down during the measurement, resulting in a change of release kinetics.
Conclusions: Floating dosage forms based on FCC appear promising. It was possible to manufacture floating tablets featuring a density of less than unity and sufficient hardness for further processing. *In silico* dissolution simulation offered a possibility to understand floating behavior and drug-release mechanism.

1. Introduction

Compared to conventional dosage forms, gastroretentive drug delivery systems (GRDDS) are designed to remain in the stomach for a prolonged, predictable time. Consequently, gastric residence time of drug substances is extended and bioavailability improved (Arora et al., 2005). GRDDS are suitable for a number of drugs, including substances whose sites of action are in the stomach (Bardonnet et al., 2006) (e.g. antibiotics such as metronidazole used for the eradication of *Helicobacter pylori* (Adebisi and Conway, 2013)) and drugs that exhibit a narrow absorption window in the stomach or the upper part of the small intestine (Streubel et al., 2006a) (e.g. simvastatin (Jagdale et al., 2013) and norfloxacin (Guguloth et al., 2011)). Moreover, GRDDS are suited for drugs degraded in the intestinal or colonic environment (e.g. captopril (Nur and Zhang, 2000)), as well as substances that are poorly soluble in alkaline media (e.g. diazepam (Sheth and Tossounian, 1984)).

Various approaches have been proposed to achieve gastric retention and avoid unpredictable gastric emptying of dosage forms. These approaches include co-administration of drugs or pharmaceutical excipients that influence the gastric motility pattern and thereby delay gastric emptying (Gröning and Heun, 1989, 1984), magnetic systems (Fujimori et al., 1995), muco-adhesive systems

* Corresponding author. Tel.: +41 (0)61 267 15 13; fax: +41 (0)61 267 15 16.
E-mail address: joerg.huwyler@unibas.ch (J. Huwyler).

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(Dhaliwal et al., 2008), systems that increase in size due to swelling (Deshpande et al., 1997) or unfolding (Michaels, 1974), density-controlled systems that either float on gastric contents (Baumgartner et al., 2000; Stops et al., 2008) or sediment (Devereux et al., 1990), and combination systems (Jiménez-Castellanos et al., 1994). However, despite the multitude of options, the broad application of GRDDS remains an unsatisfied need.

Pawar et al. considered floating drug delivery systems (FDDS) a logical approach developing GRDDS (Pawar et al., 2011). FDDS are low-density systems with a density less than that of gastric fluids (approx. 1.004 g/cm^3) (Pawar et al., 2011). Therefore, dosage forms float on gastric contents and are retained in the stomach while releasing drug (Singh and Kim, 2000).

According to literature data, enhanced gastric residence times of floating pharmaceutical dosage forms are achievable under fasted conditions (Babu and Khar, 1990; Desai and Bolton, 1993; Xu et al., 1991). Since the introduction of the concept of floating tablets by Davis (1968), many research groups have invented varying strategies to prepare FDDS. Floatation is achieved by incorporating low-density materials (Streubel et al., 2002), by swelling (Sheth and Tossounian, 1978), or by generation and entrapment of gas (Atyabi et al., 1996). Because excipients with a density <1 provide immediate floatation of the delivery device, their use is highly favored for formulation development (Streubel et al., 2006b). However, design of floating dosage forms is technically demanding. First, traditional *in vitro* dissolution methods are not able to predict *in vivo* behavior with a sufficiently high accuracy (Pawar et al., 2012). Neither the European Pharmacopeia nor the American Food and Drug Administration (FDA) describe any specific methods to assess dissolution behavior and floating characteristics of FDDS. Second, methods for preparation of FDDS are often cumbersome and expensive. Third, cost-effective large-scale production of FDDS remains a challenge.

Optimal floating tablets must feature two, often self-excluding characteristics: high porosity to promote floatation on stomach contents, but also sufficient hardness to withstand destruction by gastric peristalsis. A novel pharmaceutical excipient that exhibits a highly porous meshwork with a lamellar surface structure to interlock particles tightly was identified in the paper industry (Stirnimann et al., 2013). Due to its unique properties, functionalized calcium carbonate (FCC) holds promise in the preparation of FDDS. It offers the possibility to compact tablets that can be further processed at a relative density <1.

The objective of this work was to design an FDDS using the novel excipient FCC and the model drug caffeine. To overcome the drawbacks of existing dissolution methods, we introduced a custom-built stomach model to simultaneously evaluate drug release and floating characteristics of dosage forms. Using a 3D cellular automata-based computational model, an attempt was made to evaluate *in silico* the floating characteristics and drug release. The theoretical background of the cellular automata-based software is described in the next section.

2. Mathematical model: cellular automata-based dissolution model for floating tablets

Use of cellular automata (CA) for modeling drug release profiles from solid dosage forms has previously been described for polymer-containing formulations (Zygourakis and Markenscoff, 1996). In this study, the standard three-dimensional CA dissolution model (Kimura, 2013; Puchkov et al., 2013) with extended rule set was used to account for medium absorption kinetics by porous materials. In addition, output statistics were collected to obtain information about every automaton state at every sampling interval. This allowed calculation of tablet density during *in silico* experimentation and thus assessment of tablet floatation. Tablet densities >1 g/cm^3 indicated that the dissolving tablet sank. General automata rules used in this study can be split into 3 main categories: rules for active pharmaceutical ingredients (API), rules for polymers, and rules for porous FCC material.

2.1. CA rules for active pharmaceutical ingredients

Fig. 1a displays the dissolution of non-hydrophobic API cells. Solvation of the solid is controlled by a C_1 constant of an automaton. This primary constant defines the number of iterations needed to change the "solid" state of the API cell into a "liquid" state. Each "liquid" cell in the 3D Moore neighborhood (Kari, 2005) of an API cell subtracts one unity at a time from the C_1 value of the API cell. Automaton changes its state at reaching the C_1 value of zero and irreversibly converts itself into a "liquid" cell. Physical meaning of the C_1 value is the reciprocal of the product of solid–liquid interface surface and *diffusion* coefficient divided by the thickness of the boundary layer. In other words, the C_1 value is reciprocal to the constant term of the Noyes–Whitney equation (Noyes and Whitney, 1897). This basic rule applies to all automaton states except the "liquid" state.

2.2. CA rules for polymer component

Spatial changes of the hydrated materials, i.e. swelling, require separate governing rules and control parameters. In this study, the C_2 constant was used for polymer materials to control the degree of swelling.

The swelling cell state mimics the properties of a component which shows an increase in volume after contact with the dissolution medium (see Fig. 1b). The "liquid" cells in the 3D Moore neighborhood of the swelling compound are converted into "hydrated" polymer cells and obtain a C_1 value which is calculated by dividing C_1 by the C_2 value. Therefore, the higher the C_2 value, the lower is the swelling capacity of a component. From the physical point of view, the relationship between C_1 and C_2 constants of the swelling polymer component can be expressed as the logarithm of C_1 of base C_2 (Eq. (1)):

$$q = 1 + \log_{C_2} C_1 \tag{1}$$

where q is the volumetric swelling ratio $\left(q = \frac{\text{Volume of swollen gel}}{\text{Volume of dry gel}}\right)$.

Solving Eq. (1) for C_2 yields the following relationship:

$$C_2 = C_1^{\frac{1}{q-1}} \tag{2}$$

When applying Eq. (2), the values for C_2 can be obtained experimentally for different polymers or gels in different media.

2.3. CA rules for porous materials such as FCC

Unlike swelling, liquid sorption into porous particles does not result in spatial changes but requires dedicated governing rules and a control parameter. In this case, C_2 is the constant responsible for the rate of liquid sorption into porous particle meshwork.

Fig. 1c and d shows the behavior of porous state cells after contact with dissolution medium. Division of the C_2 value by the number of surrounding "liquid" cells gives the number of iterations needed to change a porous "dry" state cell into a "wet" state, respecting the 3D Moore neighborhood. Considering the physical meaning of the value for C_2, it is possible to experimentally obtain this constant for different materials and media by liquid sorption measurements.

To obtain experimental values for the C_1 constant of the polymer components and C_2 constant of porous FCC, the liquid sorption kinetics have to be determined. The sorption rate is the slope