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In silico simulation of niacin release from lipid tablets: Theoretical predictions and independent experiments

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ABSTRACT

A mechanistically realistic mathematical model is presented allowing for the quantification of niacin release from lipid tablets, based on glyceryl dibehenate. The systems were prepared either by direct compression or via hot-melt extrusion/grinding/compression. The model assumptions are based on a thorough physico-chemical characterization of the tablets before and after exposure to the release medium. Importantly, the model allows for the first time for the quantitative prediction of the effects of the composition, dimensions and type of preparation method of the tablets on the resulting niacin release kinetics. These quantitative theoretical model predictions were confirmed by several sets of independent experimental results. Furthermore, *in silico* simulations revealed the fundamental importance of limited niacin solubility within the lipid tablets: during major parts of the release periods, very steep concentration gradients exist and net vitamin flux is restricted to specific regions within the tablets.

1. Introduction

Mathematical modeling of mass transport in controlled drug delivery systems can be highly beneficial: on the one hand, the underlying drug release mechanisms can be elucidated; on the other hand, time-consuming and cost-intensive series of trial-and-error experiments can be replaced by rapid *in silico* simulations [1–4]. More than 50 years ago, T. Higuchi published his seminal paper on modeling drug release from thin ointment films [5,6], which he later extended to other geometries [7,8]. Since then, many more mathematical theories have been proposed for a large variety of drug delivery systems, including for instance biodegradable devices [9], locally releasing implants [10], and highly swellable tablets [11]. However, compared to other scientific domains, *in silico* simulations and computer-assisted device design are yet rarely applied in practice in pharmaceutics.

A mechanistically realistic mathematical theory should always be based on a thorough physico-chemical characterization of the dosage form before and after exposure to the release medium. Based on this knowledge, appropriate model assumptions should be defined. Ideally, only the dominant mass transport phenomena should be included, whereas processes which have only a minor impact, should be neglected in order to keep the model straightforward and simple to use. Examples for mass transport phenomena, which might play a role in oral controlled drug delivery systems include water penetration into the system [12], drug particle dissolution [13], drug diffusion through water-filled channels and/or polymeric networks [2,14–17], polymer swelling, degradation and/or dissolution [18–21], time- and position-dependent changes in the mobility of water and drug within the dosage form [22], and system disintegration. In certain cases, only one of these phenomena might be dominant and the mathematical description of the delivery system might be straightforward [23]. However, in other cases a multitude of processes might be decisive at the same time and an accurate mathematical treatment is complex [24]. Due to the large variety of controlled release dosage forms it can also not be expected that one single model could be valid for all types of systems. Instead, on a case-by-case basis, the validity of a model must be evaluated for each type of systems.

Some reports are available on lipid controlled drug delivery systems, in which a drug is embedded within a lipid matrix former [25,26]. For instance, the group of W.I. Higuchi presented very interesting models describing drug release from wax matrices, including theories taking into account drug diffusion and matrix tortuosity [27,28]. Also, lipid *implants* have been studied in some more detail and different mathematical theories have been proposed quantifying drug transport in these systems [26,29]. However, these models (i) were either developed for relatively complex systems, in which for instance protein precipitation due to the presence of co-dissolved polyethylene glycol is of importance [30–32], or (ii) take only one single mass transport phenomenon into account, e.g. diffusion [33–37]. Yet, there is a lack of appropriate, mechanistically realistic mathematical theories quantifying mass transport in lipid tablets and allowing for the prediction of the impact of key formulation and processing parameters, such as the initial drug loading, tablet

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height and tablet radius as well as the manufacturing procedure of the systems on the resulting drug release kinetics.

The aims of this study were to (i) identify such a mathematical theory for glyceryl dibehenate-based tablets prepared either by direct compression or via hot-melt extrusion/grinding/compression, (ii) use this theory to better understand the relative importance of the involved mass transport processes, (iii) use this theory to quantitatively predict the impact of the tablet design (namely, of the composition, dimensions and type of preparation method) on the resulting release kinetics, and (iv) evaluate the validity of these model predictions using several sets of independent experimental results. The vitamin niacin was used as "model drug".

2. Materials and methods

2.1. Materials

Niacin (Sigma-Aldrich, Steinheim, Germany); glyceryl dibehenate (Compritol® 888; Gattefosse, Saint Priest, France); lactose (monohydrate, Flowlac 100; Meggle, Wasserburg, Germany); magnesium stearate (Fagron, Waregem, Belgium).

2.2. Tablet preparation

2.2.1. Direct compression

Niacin, lactose and glyceryl dibehenate powders were sieved (0.71 mm) and blended: 10 min manually using a pestle and mortar, followed by 15 min with a turbula mixer at 64 rpm (Bachoven, Basle, Switzerland). Magnesium stearate was added and the powders were further blended in the turbula mixer for 2 min. The percentages of lactose and magnesium stearate were kept constant in all formulations: 12.4 and 0.5% (w:w), respectively. The niacin:lipid ratios were varied as indicated. The blends were compressed on a single punch tableting machine (EK 0, Korsch, Berlin, Germany), equipped with flat-faced punches. The tablet diameter and height were varied as indicated. The tablet weight (500 mg) and hardness (60 N, Dr. Schleuniger Pharmatron, Solothurm, Switzerland) were kept constant.

2.2.2. Hot-melt extrusion/grinding/compression

Niacin and glyceryl dibehenate powders were sieved (0.71 mm) and blended: 10 min manually using a pestle and mortar, followed by 15 min with a turbula mixer at 64 rpm (Bachoven). The blend ratio was varied as indicated. The mixtures were hot-melt extruded using a Leistritz "Nano 16" apparatus (Leistritz, Nuremberg, Germany), equipped with a co-rotating twin screw (diameter = 16 mm, 5 heating zones, kneading elements in zones 2 and 3, diameter of the die orifice = 1 mm). The screw speed and feeding rate were kept constant at 50 rpm and 5 mL/min, respectively. The feeding zone (zone 1) was kept at room temperature. The temperature of zones 2 to 5 was 60, 60, 60, and 65 °C, respectively (the melting point of the lipid being equal to 70 °C). The extrudates were air-cooled and manually ground using a pestle and mortar for 10 min. The obtained powder was sieved (0.71 mm) and blended with sieved lactose (0.71 mm). The mixture was blended manually using a pestle and mortar for 10 min, followed by 15 min in a turbula mixer (64 rpm, Bachoven). Magnesium stearate was added, and mixing was continued for 2 min. The percentages of lactose and magnesium stearate were kept constant in all formulations: 12.4 and 0.5% (w:w), respectively. The obtained powder blend was compressed using a single punch tableting machine (EK 0), as described above.

2.3. Tablet characterization

In vitro niacin release from the lipid tablets was measured using the USP 35 paddle apparatus (900 mL, 0.1 N HCl; 37 °C; 100 rpm; $n = 6$) (Sotax, Basle, Switzerland). At predetermined time points, 3 mL samples were withdrawn (not replaced), filtered (0.45 μm) and analyzed UV-spectrophotometrically ($\lambda = 261.0$ nm; Shimadzu UV-1650PC, Shimadzu France, Champs-sur-Marne, France). The tablet dimensions (diameter and height) and potential dynamic changes thereof upon exposure to the release medium were measured using a thickness gauge (samples were treated as for the *in vitro* vitamin release measurements). The tablet morphology was observed with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with a Zeiss camera (AxioCam ICc 1, Zeiss, Jena, Germany) before and after exposure to the release medium (under the same conditions as described above), as well as by scanning electron microscopy before exposure to the release medium (S-2700; Hitachi High-Technologies Europe, Krefeld, Germany; after covering the samples under an argon atmosphere with a fine gold layer: 20 nm; SCD 030; BAL-TEC, Witten, Germany). The initial porosity of the tablets was calculated from helium pycnometer measurements ($n = 3$) (AccuPyc 1330, Micromeritics, Norcross, USA) and the tablets' apparent volumes. The thermal properties of the tablets were determined by differential scanning calorimetry (DSC; DSC821e; Mettler Toledo, Giessen, Germany; approximately 5 mg samples were heated in aluminum pans; investigated temperature range: 20 to 200 °C, heating rate: 10 °C/min).

2.4. Equilibrium solubility measurements

The equilibrium solubility of niacin powder (as received) was determined in agitated flasks in 0.1 M HCl. Excess amounts of niacin were exposed to 100 mL medium at 37 °C under horizontal shaking (80 rpm, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). Every 24 h, samples were withdrawn, filtered and analyzed by UV-spectroscopy for their vitamin content (as described above) until equilibrium was reached. Each experiment was conducted in triplicate.

3. Results and discussion

3.1. Model development

A mechanistically realistic mathematical model should be based on a thorough physico-chemical characterization of the respective dosage form before and after exposure to the release medium. Crucial features to be studied include potential changes in the system's geometry and size (e.g. due to device disintegration and/or dissolution), limited drug/vitamin solubility effects (within the dosage form and/or the surrounding bulk fluid) as well as time- and/or position-dependent changes in the conditions for mass transport (e.g. due to excipient swelling). Fig. 1 shows macroscopic pictures of glyceryl dibehenate-based tablets loaded with 30% niacin before and after 24 h exposure to 0.1 N HCl at

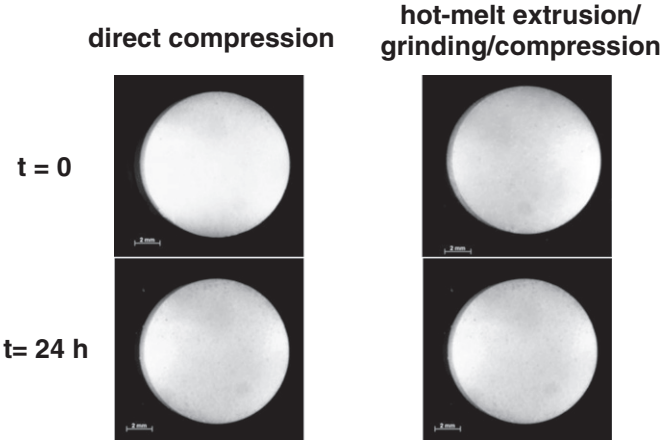

Fig. 1. Macroscopic pictures of niacin-loaded, glyceryl dibehenate-based tablets prepared by direct compression or hot-melt extrusion/grinding/compression before and after 24 h exposure to the release medium (30% initial vitamin loading).