

**Charakterisierung gastraler Parameter und deren
Einfluss auf das Freisetzungerverhalten aus
gastroretentiven Arzneiformen**

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Abkürzungsverzeichnis

<i>EMA</i>	European Medicines Agency
<i>FDA</i>	Food and Drug Administration
<i>MMC</i>	Migrierender motorischer Komplex
<i>MRT</i>	Magnetresonanztomographie
<i>WHO</i>	World Health Organisation

1 Einleitung und Zielstellung

1.1 Einleitung

»Hergegen wollen andere behaupten/ daß der Stein Bezoar eine der [...] fürtrefflichsten Antidotorum [...] seye/ welche auff der Welt mögen gefunden werden [...]«

(Laurent Catelan, 1627)

Orientalische Bezoare, steinartige Objekte mit teils glatter Oberfläche, wurden im mittelalterlichen Europa nahezu mit Gold aufgewogen [1, 2]. Ihnen wurde nachgesagt, dass Sie als Universalgegengift jedwede Krankheit heilen können. So erlangten sie enorme Bedeutung in der medizinischen Praxis der damaligen Zeit [1]. Bereits zu Zeiten Galens wusste man um Bezoare, wobei ihre Entstehung jedoch zunächst unklar blieb [1]. Erst im Laufe der Zeit wurde den Gelehrten zunehmend bewusst, dass es sich bei diesen Objekten um unverdauliche, jedoch unwirksame Ansammlungen aus Tiermägen handelt, die vermutlich über einen langen Zeitraum entstanden waren.

Auch beim Menschen wurden bereits Bezoare beschrieben, die häufig aus pflanzlichen Bestandteilen (Phytobezoare), seltener auch aus Haaren (Trichobezoare) bestehen [3]. Die Bildung letzterer steht in engem Zusammenhang mit dem Herausreißen (Trichotillomanie) und dem Verschlucken der eigenen Haare (Trichophagie). Im Magen angelangt, können die Haare scheinbar nur schwer in den Dünndarm weiter transportiert werden und ballen sich, bei fortwährender Ingestion, über einen langen Zeitraum zu einem Knäuel zusammen, welches den gesamten Magen und sogar weite Teile des Dünndarms auskleiden kann [4, 5]. Bezoare treten klinisch allerdings erst relativ spät in Erscheinung und führen dabei zu unspezifischen Symptomen, wie Erbrechen oder chronischen Abdominalschmerzen [3, 6].

In Anbetracht der physiologischen Funktionen des Magens, die unter anderem die Zerkleinerung und den aboralen Transport selbst großer unverdaulicher Objekte umfassen, ist die Bildung von Bezoaren beim Menschen noch weitestgehend unverstanden [7, 8]. Warum speziell Haare nicht aus dem Magen entleert werden können, ist bis heute Gegenstand von Diskussionen. Es wird vermutet, dass sie sich in den Falten des Magens verfangen und von der gastralnen Peristaltik nicht erfasst werden können [7, 8].

Aus pharmazeutischer Sicht wäre ein detailliertes Wissen um die genaue Entstehung von Bezoaren unter Umständen relevant für die Entwicklung innovativer Darreichungsformen. So könnten künstlich erzeugte Bezoare als Arzneistoffträger tatsächlich enorme

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Vorteile mit sich bringen – ganz im Gegensatz zum orientalischen „Allheilmittel“. Im Bereich der oralen Arzneimitteltherapie werden Arzneiformen mit modifizierter Wirkstofffreisetzung, die über längere Zeiträume im Magen verbleiben sollen, als gastroretentive Systeme bezeichnet [9–11]. Die Wirkstofffreisetzung kann hierbei langsam, schnell oder pulsartig erfolgen [9, 11, 12]. Ähnlich wie ihre altertümlichen Pendants, werden gastroretentive Systeme in der jüngeren Fachliteratur regelrecht mystifiziert. Die erfolgreiche Entwicklung einer zuverlässig funktionierenden gastroretentiven Arzneiform gleicht der Entdeckung des „Heiligen Grals“ der oralen Arzneimitteltherapie [13]. Dies hat vor allem mit den enormen Vorteilen zu tun, die solche Systeme aus therapeutischer Sicht mit sich bringen würden.

Besonders Arzneistoffe, welche im intestinalen Milieu instabil beziehungsweise sehr schwer löslich sind oder vornehmlich im oberen Dünndarm resorbiert werden, könnten von einer gastroretentiven Formulierung profitieren [9, 11, 14, 15]. Unter Nutzung der Gastroretention wäre es möglich, dass entsprechende Arzneistoffe über einen langen Zeitraum kontinuierlich aus dem Magen in obere Dünndarmabschnitte gelangen, um dort möglichst vollständig zur Resorption gebracht zu werden. Hierdurch ließe sich die Bioverfügbarkeit vieler Arzneistoffe, deren Absorption im unteren Dünndarm aus bestimmten Gründen eingeschränkt ist, deutlich erhöhen [9, 11, 14, 15]. Bereits im Jahr 1976 zeigte Levy eindrucksvoll, dass die Verlängerung der Magenaufenthaltszeit von Riboflavin zu einer Erhöhung der Bioverfügbarkeit führt [16]. Darüber hinaus könnten bei Arzneistoffen, die über eine sehr kurze Plasmahalbwertszeit verfügen, durch Gastroretention effektive Wirkstoffkonzentrationen im Plasma über längere Zeiträume aufrechterhalten werden. Hierdurch wären Plasmaspiegel spitzen, wie sie nach mehrmals täglicher Einnahme schnell freisetzender Arzneiformen auftreten können, vermeidbar. Die gleichzeitig sinkende Einnahmefrequenz würde zudem zu einer deutlich gesteigerten Adhärenz der Patienten führen [11]. Neben einer verbesserten systemischen Therapie wäre zudem eine intensive lokale Behandlung bestimmter Abschnitte des oberen Gastrointestinaltrakts möglich [9, 11, 14, 15]. Ein solcher Ansatz könnte beispielsweise bei der Therapie von Infektionen mit *Helicobacter pylori* erfolgversprechend sein, da dieses Bakterium bevorzugt den Magen besiedelt [17]. Infektionen mit *Helicobacter pylori* haben global betrachtet eine außerordentliche Relevanz. So wurde dieses Bakterium 2017 von der WHO als einer der 12 gefährlichsten Keime der Welt eingestuft [18]. Eine Infektion mit *Helicobacter pylori* kann zur Bildung von gastroduodenalen Ulzera führen und erhöht ferner das Risiko an Magenkrebss zu erkranken drastisch [17]. Eine lokale Antibiotika-Therapie unter Nutzung gastroretentiver Arzneiformen stellt einen vielversprechenden Therapieansatz dar.

Diese potentiellen Vorteile gastroretentiver Systeme wurden bereits vor 40 Jahren erkannt. Eine der ersten als gastroretentiv bezeichneten Arzneiformen war ein dichte-kontrolliertes System, das durch Aufschwimmen auf dem Mageninhalt für einen ver-

gleichsweise langen Zeitraum im Magen verweilen sollte. Dieses System wurde im Jahr 1978 von *Sheth* und *Tossounian* zum Patent angemeldet [19] und wenige Jahre später schließlich unter dem Namen *hydrodynamically balanced system* (HBS) kommerziell vermarktet [20, 21]. Seitdem wird intensiv an der Entwicklung gastroretentiver Arzneiformen geforscht. Innerhalb dieser Zeit wurden verschiedenste Ansätze entwickelt, um das Ziel einer Gastroretention von Arzneiformen zu erreichen [9, 22]. In der Hauptsache konzentrieren sich die Entwicklungen dabei auf folgende Prinzipien: Mukoadhäsion, Flotation, Sedimentation und Expansion beziehungsweise Entfaltung (Abbildung 1) [9, 10, 17, 23, 24].

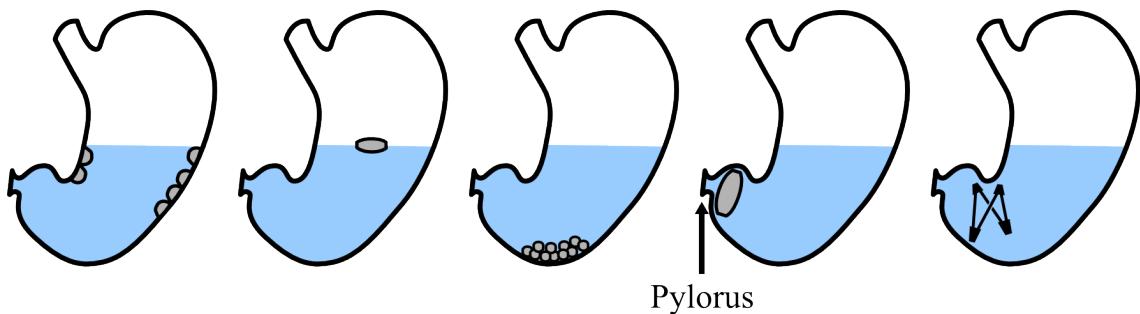


Abbildung 1: Schematische Darstellung der Prinzipien der Gastroretention. Von links nach rechts: Mukoadhäsion, Flotation, Sedimentation, Expansion, Entfaltung.

Bei der Mukoadhäsion werden Polymere wie Chitosan, Polyacrylsäure oder Natriumalginat verwendet, um eine möglichst feste Anheftung an die Magenwand zu gewährleisten [17, 22, 25]. Diese Arzneiformen sollen dabei förmlich an der Schleimhaut kleben, um von dort aus ihren Wirkstoff in den Magen freizusetzen. Beim Ansatz der Flotation wird das Ziel verfolgt Systeme zu produzieren, die sich durch Aufschwimmen auf dem Mageninhalt möglichst lange der Entleerung über den weiter unten gelegenen Pylorus entziehen [10, 17, 24]. Das zur Flotation gegensätzliche Prinzip der Sedimentation hat eine Deposition der Arzneiform im Sinus des Magens und damit unterhalb des Pylorus zum Ziel, wofür mittels geeigneter Hilfsstoffe eine Dichte von deutlich über $1,004 \text{ g/cm}^3$ angestrebt wird [10, 17]. Einen weiteren sehr häufig verfolgten Ansatz stellen expandierende, beziehungsweise sich entfaltende Systeme dar, die innerhalb kurzer Zeit enorm an Größe gewinnen sollen, um der Entleerung durch den relativ engen Pylorus zu widerstehen [23, 26]. Des Weiteren sind Kombinationen aus den beschriebenen Prinzipien denkbar [10]. So haben *Arza* und Kollegen beispielsweise eine Arzneiform entwickelt, die gleichzeitig expandieren und flotieren soll [27].

Der hohen Zahl der in den letzten Jahren veröffentlichten Übersichtsartikel und Originalarbeiten zu dem Thema steht eine relativ geringe Anzahl an tatsächlich vermarkteten gastroretentiven Arzneiformen gegenüber [24]. Dabei handelt es sich vor allem um expandierende (z.B. Glumetza[®] 500, Gralise[®]) sowie um flotierende Arzneiformen (z.B. Madopar[®] Depot, Valrelease[®]) [22, 24]. Trotz umfassender *In vitro*-Charakterisierungen

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solcher Systeme gelang es bislang nicht, das Ziel einer stabilen und reproduzierbaren Gastroretention *in vivo* zu erreichen [10, 22, 23]. Besonders unter Nüchternbedingungen scheint dies schwer bis unmöglich [13, 23]. Das Scheitern vieler Systeme *in vivo* ist nicht zuletzt auch der Tatsache geschuldet, dass die physiologischen Bedingungen für Arzneiformen im Magen, trotz ihrer herausragenden Bedeutung für oral applizierte Arzneimittel, erst in den letzten Jahren näher untersucht und verstanden wurden. Die gastralnen Bedingungen haben mitunter entscheidenden Einfluss auf das Zerfalls- und Transitverhalten von Arzneiformen und letztlich ebenso auf die Resorption von Wirkstoffen aus dem Darm [28–30]. Die genaue Charakterisierung der Bedingungen im Magen ist demnach von übergeordneter Bedeutung für die Entwicklung und Testung von gastroretentiven Systemen, sowohl *in vitro* als auch *in vivo*.

Der technische Fortschritt der letzten Jahrzehnte führte dazu, dass sich ein zunehmend detailliertes Bild der physiologischen Bedingungen im Magen ergibt [31, 32]. Mit Hilfe von funktionsdiagnostischen und bildgebenden Verfahren lassen sich heute Parameter, wie Volumen, Motilitätsmuster, pH-Wert, Temperatur und Druck vergleichsweise einfach und präzise bestimmen. Zu den wichtigsten Verfahren zählen hierbei die Magnetresonanztomographie (MRT), die Szintigraphie, die Endoskopie sowie telemetrische Kapseln. Insbesondere Letztere sind dank der fortschreitenden Entwicklung im Bereich der Sensortechnik heute in der Lage, ausgewählte gastrale Parameter zeitlich hoch aufgelöst zu ermitteln [33–35]. Solche Kapseln messen auf ihrem Weg durch den Gastrointestinaltrakt beispielsweise den pH-Wert oder die Temperatur (Heidelberg Kapsel, IntelliCap®, SmartPill®). Die gesammelten Daten werden mittels einer Antenne kontinuierlich an einen Datenempfänger übertragen. Aus den generierten pH-Profilen lassen sich dann anhand bestimmter Verläufe die Transitzeiten durch die einzelnen Abschnitte des Gastrointestinaltrakts abschätzen [33, 34]. Als einzige unter den telemetrischen Kapseln ist die SmartPill® darüber hinaus in der Lage, Informationen über die im Gastrointestinaltrakt auftretenden Drücke zu liefern [36]. Mit Hilfe des eingebauten Drucksensors lassen sich beispielsweise Motilitätsmuster des Magens untersuchen, um mögliche Ursachen für eine gestörte Magenentleerung zu ermitteln. Neben der Abklärung einer solchen Gastroparese kann die SmartPill® ebenso zur Diagnostik chronischer Obstipationen eingesetzt werden [37, 38]. Im Rahmen der oralen Biopharmazie kann dieses System aber auch dazu genutzt werden Bereiche hoher Belastungen im Gastrointestinaltrakt zu identifizieren [36, 39]. Diese hohen Belastungen können eine Ursache für ein schlagartiges Freisetzen der gesamten Arzneistoffdosis (*dose dumping*) sein und sind daher besonders relevant für das Verständnis des Anflutungsverhaltens vieler Arzneiformen [40].

Die durch solche freibeweglichen, telemetrischen Kapseln gemessenen Parameter sind zu einem gewissen Grad auch vergleichbar mit den Einflüssen, die auf große, monolithische Arzneiformen einwirken, wie beispielsweise expandierende gastroretentive Systeme [33]. Mit ihrer Hilfe lassen sich also auch die gastralnen Parameter charakterisie-

ren, welche in den entsprechenden *In vivo*-Untersuchungen solcher Arzneiformen auftreten. Diese Daten können demnach dazu genutzt werden, um die korrekte Interpretation von Daten aus Humanstudien zu gewährleisten und die Entwicklung gastroretentiver Arzneiformen gezielt voranzutreiben. In klinischen Arzneimittelstudien findet die Arzneimittelapplikation unter standardisierten Bedingungen, häufig an nüchternen gesunden Probanden, statt. Für solche Studien gibt es von den entsprechenden Zulassungsbehörden, wie der EMA oder der FDA, genaue Vorgaben in Form von Leitlinien. Diese fordern, dass die teilnehmenden Probanden für mindestens 8–10 h vor der Gabe des zu testenden Arzneimittels auf die Aufnahme von Nahrungsmitteln verzichten. Die Arzneimittelgabe erfolgt typischerweise am Morgen zusammen mit 150–240 mL Wasser [41, 42]. Im Hinblick auf die Konzepte der Gastroretention ist es naheliegend, dass das hiernach resultierende intragastrale Volumen insbesondere für flotierende Arzneiformen ein entscheidender Faktor ist. Mit Hilfe bildgebender Verfahren, wie der MRT, konnte die Volumenkinetik im Magen nach Nüchternennahme in den letzten Jahren präzise beschrieben werden. So zeigte sich, dass das in klinischen Studien häufig eingenommene Volumen von 240 mL Wasser unter Nüchternbedingungen innerhalb von etwa 30 min vollständig aus dem Magen entleert wird [43, 44]. Nach dieser Zeit bleibt lediglich ein Residualvolumen von etwa 10–50 mL zurück, das in etwa dem Volumen vor Einnahme der Flüssigkeit entspricht [43–47]. Im Fall von flotierenden gastroretentiven Systemen wird diese Beobachtung oft als einer der Hauptgründe für deren wiederholtes Scheitern unter Nüchternbedingungen angeführt [23]. Das geringe Residualvolumen scheint diesbezüglich nicht auszureichen, um die notwendige Distanz zum Pylorus über einen längeren Zeitraum aufrecht zu erhalten.

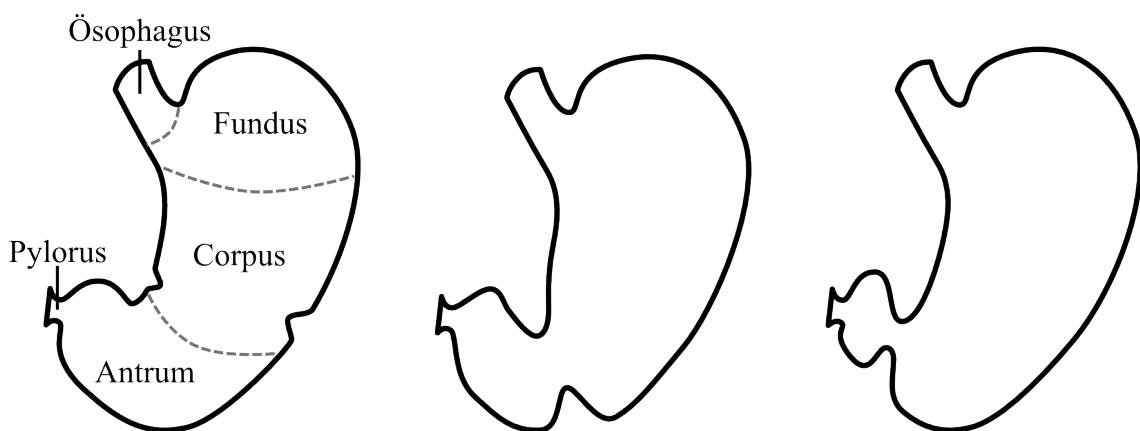


Abbildung 2: Anatomie des Magens und schematische Darstellung der antralen Kontraktionswellen.

Neben den Flüssigkeitsvolumina ist die Magenmotilität von entscheidender Bedeutung für gastroretentive Arzneiformen. Diese ist unter Nüchternbedingungen gekennzeichnet durch die vier Phasen des migrierenden motorischen Komplexes (MMC) [48, 49]. Kontraktionswellen unterschiedlicher Intensität beginnen hierbei im Corpus des Magens und durchziehen anschließend das Antrum hin zum Pylorus (Abbildung 2). Die

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Phase I, welche etwa 40–60 min andauert, ist geprägt von wenig bis keiner Kontraktilität [48, 49]. In Phase II (etwa 30–45 min) treten unregelmäßige, stärker werdende Kontraktionswellen auf, deren Intensität schließlich in der 10–15 minütigen Phase III ihren Höhepunkt findet [48, 49]. Diese sogenannten *housekeeper waves* der Phase III sind in der Lage, größere unverdauliche Objekte zu entleeren, welche zum Beispiel nach beendeter Verdauung im Magen verbleiben oder im Nüchternzustand eingenommen wurden [36]. Mit den *housekeeper waves* gehen höchste Belastungen einher, die, wie bereits beschrieben, zum *dose dumping* führen können [40, 50, 51]. Die Phase IV gilt als kurze Übergangsphase zu Phase I [48].

Die Einnahme von kalorischen Flüssigkeiten oder Nahrung führt dazu, dass der Zyklus der Nüchternmotilität durchbrochen wird und die postprandiale Motilität dominiert [52, 53]. Diese ist wiederum gekennzeichnet von gleichmäßigen Kontraktionen, die mit einer Frequenz von etwa 3 min^{-1} über eine Strecke von circa 15 cm in Richtung Pylorus mit zunehmender Okklusion das Antrum durchwandern [54, 55]. Die auftretenden Belastungen durch diese Kontraktionen entsprechen in ihrer Stärke etwa der Phase II der Nüchternmotilität [30]. Kurz vor Erreichen des Pylorus schließt dieser, wobei bereits ein Teil der flüssigen Phase sowie darin dispergierte kleinere Partikel entleert werden [56]. Durch den resultierenden Druckanstieg vor der antralen Welle kommt es zum intensiven Durchmischen und Zerkleinern des Chymus (antrale Mühle). Dabei wird der Nahrungsbrei durch die noch vorhandene Öffnung der antralen Welle gepresst und zurück in proximale Bereiche des Magens befördert (Retropulsion) [56].

Um den Einfluss aufgenommener Nahrung auf das Anflutungsverhalten von Arzneistoffen zu untersuchen, wird im Rahmen von Nahrungsmittelstudien die Arzneimitteleinnahme unter postprandialen Bedingungen durchgeführt [41, 57]. Dazu wird vor der Arzneimittelapplikation eine Mahlzeit verzehrt [41, 42]. Die eigentliche Arzneimitteleinnahme erfolgt dann, entsprechend der beschriebenen Bedingungen für die Nüchterneinnahme, zusammen mit 240 mL Wasser, 30 min nach Beginn der Mahlzeit [41]. Um eine möglichst extreme physiologische Antwort bezüglich der aufgenommenen Nahrung zu erzeugen, wird die Einnahme einer hochkalorischen, fettreichen Standardmahlzeit empfohlen [41]. Die amerikanische Gesundheitsbehörde (FDA) gibt in ihrer Leitlinie sogar ein konkretes Beispiel an, wie sich dieses Standardfrühstück zusammensetzen kann. Die Mahlzeit umfasst zwei Scheiben Toast mit Butter, zwei in Butter gebratene Spiegeleier, zwei Streifen Frühstücksspeck sowie 113 g Röstkartoffeln [41]. Zusätzlich sollen etwa 240 mL Vollmilch getrunken werden, was in der Summe zu einem Kaloriengehalt von 800–1000 kcal führt (50% davon aus Fett stammend) [41]. Trotz der enormen Relevanz der FDA-Standardmahlzeit gibt es bislang wenige Daten, die die gastralnen Bedingungen nach deren Einnahme beschreiben. Neben einer *In vitro*-Untersuchung zu ausgewählten physikochemischen Parametern des zerkleinerten Standardfrühstücks, wurde dessen Magenentleerung *in vivo* kürzlich von Koziolek und Kollegen mittels MRT quan-

tifiziert. [57, 58]. Sie konnten zeigen, dass es mehr als 6 h dauert, bis die im Nüchternzustand gemessenen Volumina nach Einnahme des Standardfrühstücks wieder erreicht werden [57]. Der Fettgehalt war selbst nach 6,25 h noch deutlich erhöht, was in der Folge zu einer anhaltenden Unterbrechung der Nüchternmotilität führen kann.

Die dargestellten komplexen Bedingungen im menschlichen Magen werden im Zuge von *In vitro*-Untersuchungen gastroretentiver Arzneiformen bislang unzureichend berücksichtigt. Typischerweise richten sich die angewendeten Methoden zur Untersuchung der gastroretentiven Eigenschaften, aufgrund der unterschiedlichen Ansätze, nach dem jeweiligen Gastroretentionsprinzip. So werden die mukoadhäsiven Eigenschaften beispielsweise durch die Kraft definiert, welche nötig ist, um eine mit Polymer beladene Oberfläche von *Ex vivo*-Gewebe zu trennen [17, 59]. Des Weiteren wurde ein Test beschrieben, bei dem die Zeit gemessen wird, innerhalb der das kontrollierte Abspülen eines Polymers von einer Geweboberfläche möglich ist [59]. Die Schwimmeeigenschaften flotierender Systeme werden häufig über die *floating lag time* sowie die *floating time* charakterisiert. Diese Messgrößen geben an, wie viel Zeit vergeht, bis die entsprechenden Arzneiformen in einem Becherglas auf einer in der Regel niedrigviskosen, wässrigen Flüssigkeit aufschwimmen und wie lange die Flotation anschließend anhält [60]. Daneben wird auch die Auftriebskraft solcher Systeme zur Charakterisierung herangezogen [60, 61]. Bei der *In vitro*-Charakterisierung expandierender Systeme wird hingegen häufig der Quellungsindex bestimmt, der angibt, welche Masse an Wasser das entsprechende System innerhalb einer bestimmten Zeit aufgenommen hat [60]. Daneben werden nicht quellende, sich entfaltende Systeme mit dem *exposed size parameter* beschrieben, der sich hauptsächlich aus den Dimensionen nach der Entfaltung errechnet [60]. Es ist nicht schwer sich vorzustellen, dass diese Methoden nur eine begrenzte Vorhersagekraft in Bezug auf das spätere gastroretentive Potential des jeweiligen Systems *in vivo* haben können.

Neben solchen Funktionsuntersuchungen werden, insbesondere im Fall von retardiert freisetzenden Systemen, Freisetzungsumtersuchungen durchgeführt. Ebenso wie die bisher beschriebenen *In vitro*-Verfahren zur Charakterisierung der gastroretentiven Eigenschaften, ist die Vorhersagekraft der genutzten Methoden zur Überprüfung des Freisetzungsumtersuchens allerdings in Frage zu stellen. Die überaus komplexen gastralnen Bedingungen können von kompendialen Methoden nur bedingt nachgestellt werden. Nichtsdestotrotz wird die Wirkstofffreisetzung gastroretentiver Arzneiformen häufig unter Verwendung herkömmlicher Freisetzungsumtersuchungen (Körbchen- und Blattrührer-Apparatur) untersucht [60]. Das Freisetzungsumtersuchensverhalten hängt dabei nicht nur von der verwendeten Apparatur, sondern ebenfalls von der Art der gastroretentiven Formulierung ab. Insbesondere im Fall flotierender Arzneiformen gibt es besondere Herausforderungen bei der Festlegung der Freisetzungsumtersuchungen. Um ein zu starkes Aufschwimmen in der Blattrührer-Apparatur zu unterbinden, werden typischerweise Sinker ver-

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wendet. Bei einer gleichzeitig expandierenden Arzneiform kann jedoch die dreidimensionale Expansion durch Verwendung von Sinkern beeinträchtigt sein. Dasselbe gilt für die Drehkörbchen-Apparatur, wodurch sich das Freisetzungsverhalten weniger reproduzierbar darstellen lässt [62, 63]. *Pillay et al.* sowie *Burns et al.* schlugen daher den Einsatz eines Siebes vor, über dem sich der Blattrührer drehen kann [62, 64]. Ein Aufschwimmen wird unterbunden und die Arzneiform kann sich ungehindert ausdehnen. *Dürig et al.* verwendeten zwei Siebe zwischen denen die Arzneiform während der Versuche platziert wurde und konnten so die Variabilität der Freisetzungsdaten im Vergleich zur kompendialen Blattrührer-Apparatur verringern [65]. *Nakagawa* und Kollegen erkannten schließlich die Notwendigkeit, in Freisetzungsexperimenten die Motilität zu berücksichtigen und verwendeten daher für die Untersuchung ihres gastroretentiven Systems eine Methode, die 1992 von *Aoki* und Kollegen vorgestellt wurde [66, 67].

Aoki et al. postulierten bereits vor mehr als 25 Jahren, dass die *In vitro*-Simulation der im Magen auftretenden Kräfte einen entscheidenden Einfluss auf die Wirkstofffreisetzung haben kann. Dementsprechend wurde eine abgewandelte Methode der kompendialen Blattrührer-Apparatur vorgeschlagen, bei der Kunststoffkugeln definierter Größe im Freisetzungsgefäß zu einer erhöhten Belastung führen sollen [67, 68]. Trotz guter Vergleichbarkeit der Freisetzungsdaten mit *In vivo*-Daten aus einer Hundestudie ist zu erwarten, dass die zusätzlich erzeugten Kollisionen durch die Kugeln zu gleichmäßigen Belastungen während des gesamten Versuchszeitraums führen [67, 68]. Daten zu gastralen Drücken offenbarten jedoch, dass die Belastungen *in vivo* vor allem schlagartig zu bestimmten Zeitpunkten auftreten [36, 69]. Mit dem *Dissolution Stress test Device* konnten *Garbacz* und Kollegen ein Freisetzungstestgerät entwickeln, das einen deutlich stärkeren Bezug zur Physiologie des humanen Gastrointestinaltrakts hat. Mit Hilfe dieser Apparatur waren sie in der Lage, unerwartete Plasmaspiegelprofile einer Diclofenac-Retardformulierung über das Auftreten gastrointestinaler Drücke zu erklären [40]. Im *Dissolution Stress test Device* übt ein Ballon unterschiedlich hohe Drücke auf eine in einem Körbchen befindliche Arzneiform aus. So können unterschiedlich starke Belastungen zu definierten Zeitpunkten auf die Arzneiform einwirken und zum Beispiel die Magenentleerung oder der Übertritt in das Caecum während der Freisetzungstests simuliert werden [40, 50]. Der Einfluss solcher Belastungen auf die Wirkstofffreisetzung aus diversen Retardformulierungen, insbesondere aus Hydrogelmatrixtabletten, wurde in weiteren Studien eindrucksvoll nachgewiesen [40, 50]. Es ist wahrscheinlich, dass der gleiche Effekt auch bei vielen gastroretentiven Systemen mit modifizierter Wirkstofffreisetzung auftritt. Dies wurde jedoch bislang nicht untersucht. Daher war die Nutzung des *Dissolution Stress test Device* zur Untersuchung des Freisetzungsverhaltens gastroretentiver Arzneiformen ein Ziel der vorliegenden Arbeit.

Neben den beschriebenen Modellen wurden in den letzten Jahren noch weitaus komplexe Modelle entwickelt. Das *Dynamic Gastric Model* zum Beispiel wurde ursprünglich

für Fragestellungen aus der Lebensmittelforschung entwickelt [70–72]. Neben der Simulation der Magensaftsekretion und der Enzymaktivitäten, die während der Verdauung im Gastrointestinaltrakt auftreten, wird bei diesem Modell ebenso Wert gelegt auf eine möglichst realistische Simulation der physiologischen Motilität. So konnte unter Vergleich mit der MRT gezeigt werden, dass unterschiedlich stabile Agargel-Kugeln vom Modell in einer Weise zerkleinert werden, wie sie auch im menschlichen Magen zu beobachten ist [70]. Das Modell mit der wahrscheinlich höchsten Komplexität ist das von TNO (Zeist, Niederlande) entwickelte TIM-1 System [73–75]. Dieses Modell besteht aus vier Kompartimenten, die den Magen, das Duodenum, das Jejunum sowie das Ileum repräsentieren. Die Kompartimente sind über Ventile miteinander verbunden und durch Anlegen eines hydrostatischen Drucks auf die inneren, flexiblen Bereiche der einzelnen Kompartimente können Belastungen realisiert werden [76, 77]. Weiterhin können Enzyme und Gallensalze eingeleitet sowie der pH-Wert reguliert werden [77]. In einer Weiterentwicklung des Modells (TIMagc) wurde die *In vitro*-Simulation gastralner Drücke physiologischer gestaltet und anschließend mit SmartPill®-Daten verglichen [78]. Die Daten haben jedoch nur wenig Aussagekraft und eine korrekte Simulation der *In vivo*-Bedingungen ist anzuzweifeln.

Dennoch konnten mit den beschriebenen Modellen bereits unterschiedlichste physiologische Einflüsse auf das Freisetzung- sowie Anflutungsverhalten oral applizierter Arzneiformen erklärt werden [40, 50, 71, 78]. Solche neueren Apparaturen sind dabei in vielerlei Hinsicht den stark vereinfachten Arzneibuchmethoden überlegen [79, 80]. Mit steigendem Grad an Komplexität steigt jedoch der Arbeitsaufwand und die Variabilität der generierten Daten [79, 80]. Zumindest die hochkomplexen Modelle eignen sich daher weniger für die routinemäßige Überprüfung der Wirkstofffreisetzung, und dienen wahrscheinlich auch in Zukunft eher Untersuchungen zum mechanistischen Verständnis als der reproduzierbaren Kontrolle der Produktqualität [80]. Zusätzlich können solche Modelle auch genutzt werden, um die Entwicklung neuer Arzneiformen, wie beispielsweise gastroretentive Systeme, effektiver und kosteneffizienter zu gestalten und unser Verständnis vom Einfluss der gastralnen Parameter bei deren oraler Applikation zu verbessern [80, 81].

1.2 Zielstellung der Arbeit

In der vorliegenden Arbeit sollte untersucht werden, inwieweit das Zusammenspiel aus verschiedenen gastralen Parametern und den Eigenschaften einer gastroretentiven Formulierung deren Wirkstofffreisetzung unter physiologisch relevanten Bedingungen beeinflusst. Hierzu war es zunächst von Nöten die Bedingungen im nüchternen und postprandialen Magen mit Hilfe des SmartPill®-Systems genau zu charakterisieren und miteinander zu vergleichen. Diese *In vivo*-Untersuchungen sollten sich an den Vorgaben von FDA und EMA für Bioverfügbarkeits- und Bioäquivalenzprüfungen orientieren und insbesondere die im Magen auftretenden Drücke detailliert beschreiben. Die gewonnenen Daten sollten im weiteren Verlauf der Arbeit als Grundlage für die im nächsten Schritt zu entwickelnden physiologisch relevanten *In vitro*-Freisetzungsmethoden dienen. Zu diesem Zweck sollten die im Arbeitskreis entwickelten *In vitro*-Freisetzungstestapparaturen, das *Dissolution Stress test Device* und der *Dynamic Open Flow-Through Test Apparatus* entsprechend optimiert werden. Die Überprüfung der erfolgreichen Implementierung der physiologischen Daten in die biorelevanten Modelle sollte unter Nutzung des SmartPill®-Systems und im Vergleich zu verschiedenen kompendialen Freisetzungsmethoden erfolgen. Mit den optimierten Methoden sollten anschließend die Auswirkungen der Simulation physiologisch auftretender Drücke auf das Wirkstofffreisetzungsverhalten aus verschiedenen, als gastroretentiv deklarierten Arzneiformen (Glumetza® 1000 sowie Madopar® Depot) untersucht werden. Hierzu sollte insbesondere überprüft werden, inwiefern die Simulation realistischer gastraler Drücke die Freisetzung aus diesen Modellarzneiformen beeinflusst. Die im Zuge dieser Arbeit gewonnenen Erkenntnisse sollten ferner dazu genutzt werden, neue Konzepte für die Gastroretention von oralen Darreichungsformen zu entwickeln. Die dargestellten Aufgaben lassen sich wie folgt zusammenfassen:

1. Planung und Durchführung einer SmartPill®-Studie unter Nüchternbedingungen und unter postprandialen Bedingungen (nach Einnahme der FDA-Standardmahlzeit).
2. Auswertung und Vergleich der generierten Daten
3. Implementierung der Daten in die im Arbeitskreis zur Verfügung stehenden Modelle unter Nutzung der SmartPill®
4. Überprüfung des Einflusses der Simulation gastraler Drücke auf das Freisetzungsverhalten aus verschiedenen auf dem Markt erhältlichen gastroretentiven Arzneiformen
5. Übertragung der Erkenntnisse aus den *In vitro*-Untersuchungen auf die Entwicklung innovativer gastroretentiver Formulierungen

2 Diskussion der Ergebnisse

Trotz 40 Jahren Forschung zu gastroretentiven Arzneiformen sind erstaunlich wenige solcher Systeme auf dem Markt erhältlich [24]. Dies verwundert umso mehr, wenn man an die enormen Vorteile denkt, die sie für die orale Arzneimitteltherapie mit sich brächten. Die Gründe hierfür sind vielfältig. Humanstudien bleiben zwar der Goldstandard, wenn es darum geht die gastroretentiven Eigenschaften eines Systems zu charakterisieren, jedoch könnten diesbezüglich gute *In vitro*-Tests bereits viel im Voraus leisten. Die häufig angewendeten *In vitro*-Untersuchungen sind jedoch bislang wenig vorhersagekräftig und so bleibt eine korrekte Evaluierung neuerer Systeme extrem aufwändig und kostenintensiv. Zur Entwicklung neuer *In vitro*-Testmethoden für gastroretentive Arzneiformen ist es nötig die gastralnen Bedingungen umfassend zu verstehen, sodass dieses Wissen dann in die Entwicklung einfließen kann. Daher war es zunächst unser Ziel, ausgewählte Parameter des oberen Gastrointestinaltrakts, insbesondere mit einem Einfluss auf gastroretentive Systeme, unter standardisierten Studienbedingungen zu quantifizieren.

In Kooperation mit der Probandenstation des Instituts für Pharmakologie wurden daher SmartPill®-Daten erhoben, die die gastrointestinalen Transitbedingungen in Bezug auf Temperaturen, pH-Werte und Drücke nach Einnahme der hochkalorischen Standardmahlzeit umfangreich charakterisierten. Die SmartPill® wurde hierbei 30 min nach vorheriger Zufuhr der FDA-Standardmahlzeit von gesunden Probanden zusammen mit 240 mL Wasser eingenommen. Es wurde dabei großer Wert darauf gelegt, dass das Studienprotokoll den Empfehlungen der FDA in allen Punkten folgt und so ein Datensatz generiert werden konnte, der die Bedingungen in klinischen Studien möglichst realistisch beschreibt [41]. In einem zusätzlich durchgeführten Studienarm, in dem die Applikation eines Arzneimittels auf nüchternen Magen simuliert wurde, erhielten 9 der 19 bereits erfolgreich untersuchten Studienteilnehmer die SmartPill® folglich ohne vorherige Einnahme der FDA-Standardmahlzeit, unter aber sonst identischen Bedingungen. Für jeden der 9 Probanden existieren also entsprechend einer Cross-over-Studie Daten zu den oben genannten Parametern nach nüchternem und postprandialer Applikation der SmartPill®.

Die SmartPill®-Daten nach Nüchterneinnahme wiesen eine hohe Variabilität insbesondere im Hinblick auf den Zeitpunkt der Magenentleerung auf. Die Transitzeit der SmartPill® schwankte dabei zwischen wenigen Sekunden und etwa 2,7 h. Literaturwerte zur Magenentleerung nicht zerfallender, größerer Arzneiformen liegen im selben Rahmen

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[82–84]. So ermittelten beispielsweise Cole und Kollegen mit Hilfe der Szintigraphie Transitzeiten von 0,1–2,9 h für magensaftresistente Kapseln der Größe 0 [83]. Das Transitverhalten der SmartPill® unter Nüchternbedingungen entspricht also durchaus dem monolithischer, nicht zerfallender Arzneiformen. Damit lassen sich die von der SmartPill® ermittelten Daten auch auf viele gastroretentive Systeme übertragen. Tatsächlich wird in der Literatur beschrieben, dass solche Systeme vor allem unter Nüchternbedingungen häufig versagen. So weisen viele mukoadhäsive, flotierende und auch expandierende Systeme in Humanstudien nach Nüchterneinnahme keine nennenswerten gastroretentiven Eigenschaften auf [85–90]. Aufgrund der Tatsache, dass die starken *housekeeper waves* selbst große Objekte in den Dünndarm befördern können, ist das Auftreten dieser intensiven Kontraktionen vermutlich einer der Hauptgründe für die fehlende Gastroretention der beschriebenen Systeme [23, 91]. Der korrekten Simulation solcher *housekeeper waves* in *In vitro*-Untersuchungen kommt demnach eine herausragende Rolle zu [23, 81].

Da das Entleerungsverhalten großer, unverdaulicher Objekte hauptsächlich vom Zeitpunkt des Auftretens der *housekeeper waves* abhängt, ist die Motilität des Magens vermutlich für die hohe Variabilität der Magenverweildauer der SmartPill® verantwortlich [36]. Die Nüchternmotilität bleibt durch die Einnahme von Wasser unbeeinflusst und es besteht folglich eine starke Abhängigkeit von der vorherrschenden Zyklusphase des MMC zum Zeitpunkt der Einnahme der SmartPill®. Die Dauer für einen kompletten Durchlauf des MMC wird oft mit etwa 2 h angegeben, unterliegt jedoch hoher interindividueller Variabilität [92–94]. So wurden Zykluslängen von etwa 1,5 h bis über 3 h beobachtet, was durch unsere SmartPill®-Daten bestätigt werden konnte [93, 94].

Die postprandiale Motilität war nicht in der Lage die SmartPill® zu entleeren. Demnach führte der vorherige Verzehr der FDA-Standardmahlzeit zu drastischen Veränderungen hinsichtlich des Zeitpunkts der Magenentleerung der SmartPill®. Dies ist vor allem auf die Dimensionen der SmartPill® (13 mm × 26 mm) zurückzuführen. Die steigende Wahrscheinlichkeit der Magenretention unter postprandialen Bedingungen mit zunehmender Größe der Formulierung wurde bereits von verschiedenen Arbeitsgruppen beobachtet [95, 96]. So zeigten Khosla und Davis, dass 13 mm große Tabletten postprandial länger im Magen verweilen als 11 mm große Tabletten, welche wiederum länger verweilen als 7 mm große Tabletten [96]. Dieses Wissen lässt sich für die Entwicklung von gastroretentiven Systemen nutzen. Klausner und Kollegen leiten die anzustrebende Größe eines expandierenden gastroretentiven Systems von der Größe diverser Fremdkörper ab, die in medizinischen Eingriffen aus dem Magen entfernt werden mussten [26]. Aus ihrer Sicht gilt es, eine Länge von etwa 5 cm oder einen Durchmesser von etwa 3 cm zu erreichen [26]. Obwohl es naheliegend scheint, dass solche großen Objekte den Pylorus nicht passieren können, gibt es verschiedene Literaturstellen, die beschreiben, dass die Magenentleerung von Objekten vergleichbarer Größe möglich ist [91, 97, 98]. Neben

der Größe scheinen somit noch andere Parameter bei der Magenentleerung eine Rolle zu spielen. Zu diesen zählen beispielsweise die Oberflächenbeschaffenheit oder die Elastizität [81, 91].

Im Hinblick auf die postprandiale Applikation der SmartPill® muss berücksichtigt werden, dass die Zufuhr von Nahrung den MMC unterbricht. Die zyklische Nüchternmotilität wird dabei so lange unterbrochen, bis etwa 90% der aufgenommenen Nahrung aus dem Magen entleert sind [36]. Weitere Nahrungszufuhr führt daher zu einer zusätzlichen Verzögerung der Magenentleerung großer Objekte [36, 52, 53]. In einer Studie von Ewe und Kollegen wurde die Magenverweilzeit von 11 mm × 6 mm großen, nicht zerfallenden Tabletten durch stetige Nahrungszufuhr auf bis zu 10 h verzögert [53]. Unsere SmartPill®-Daten bestätigten den enormen Einfluss der weiteren Nahrungsaufnahme auf das Transitverhalten von Arzneiformen. Zum Teil wurden Magenentleerungszeiten von über 20 h beobachtet, was besonders bei der *In vivo*-Untersuchung gastroretentiver Systeme berücksichtigt werden muss. Häufig ist das Studiendesign in klinischen Studien mit gastroretentiven Darreichungsformen jedoch so gestaltet, dass ein genauer Rückchluss auf die gastroretentiven Eigenschaften erschwert oder gar unmöglich gemacht wird. So sorgt beispielsweise die mehrmalige Einnahme von hochkalorischen Mahlzeiten dafür, dass die Nüchternmotilität nicht auftreten kann. Dementsprechend werden größere, nicht zerfallende gastroretentive Arzneiformen nicht aus dem Magen entleert und die Formulierung wird fälschlicherweise als gastroretentiv deklariert [11].

Während ihres Magentransits lieferte die SmartPill®, neben Daten zum Entleerungsverhalten, wertvolle Informationen über diverse intragastrale Parameter. Hierbei scheint die intragastrale Temperatur bei erster Betrachtung ein eher unwichtiger Parameter zu sein. Wie Chiwele und Kollegen jedoch zeigen konnten, sind vor allem Arzneiformen auf Gelatinebasis empfindlich gegenüber Temperatureinflüssen. So nehmen etwa die Zerfallszeiten von Hartgelatinekapseln unterhalb von 30 °C drastisch zu, was sich letztlich auch auf die Wirkstofffreisetzung auswirken kann [99, 100]. Der Grund hierfür ist das verspätete Auflösen der Gelatine bereits unter leicht erniedrigten Temperaturen [99]. Die SmartPill®-Daten zeigten einen deutlich messbaren Temperaturgradienten im nüchternen Magen nach Einnahme von 240 mL Wasser bei Raumtemperatur. Die Temperatur stieg über einen Zeitraum von 20 min von etwa 22 °C auf 36 °C fortwährend an. Innerhalb dieser Zeit wurden bereits 5 der 9 telemetrischen Kapseln entleert. Für gastroretentive Arzneiformen auf Gelatinebasis können sich hierdurch drastische Konsequenzen ergeben. Viele Autoren schlugen beispielsweise expandierende Systeme in einer Hartgelatinekapsel vor [101–103]. Solche Systeme könnten bei deutlich verzögter Zerfallszeit der Kapsel insbesondere unter Nüchternbedingungen vorzeitig aus dem Magen entleert werden. Die mögliche Folge wäre eine Expansion im Dünndarm mit anschließendem Darmverschluss. Um den Temperatureinfluss möglichst gering zu halten, schlugen Chiwele und Kollegen vor, Arzneiformen auf Gelatinebasis stets mit war-

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men Flüssigkeiten einzunehmen [99]. Dasselbe gilt für Systeme, welche auf der Bildung eines Gases basieren. Beispielsweise wurde von *Michaels* und Kollegen ein expandierendes System vorgeschlagen, bei welchem die Wirkstofffreisetzung sowie die Expansion über das Verdampfen einer Flüssigkeit gesteuert wird, deren Siedetemperatur nahe der Körpertemperatur liegt [101, 102]. Die Daten der von uns durchgeführten Studie zeigen, dass die intragastrale Temperatur bei der Entwicklung von gastroretentiven Systemen durchaus Relevanz haben kann und ihr Einfluss deshalb bereits in präklinischen *In vitro*-Untersuchungen überprüft werden sollte. Entsprechende Untersuchungen mit einem neueren *In vitro*-Modell, dem *Dynamic Open Flow-Through Test Apparatus*, wurden bisher nur für schnell freisetzende Hartgelatinekapseln beschrieben [100]. Der Einsatz des Modells bei der Untersuchung gelatinebasierter gastroretentiver Systeme ist aber durchaus denkbar.

Neben den intragastralen Temperaturverläufen konnten wir mit Hilfe der SmartPill®-Daten die entsprechenden Verläufe des pH-Wertes unter nüchternen und postprandialen Bedingungen umfassend charakterisieren. Die intragastralen pH-Profiles nach Nüchterneneinnahme deckten sich dabei weitgehend mit den Daten einer anderen, ebenfalls nüchtern eingenommenen telemetrischen Kapsel [33]. Die gleichzeitige Einnahme von 240 mL Wasser resultierte in initial gemessenen pH-Werten von etwa pH 4,6, welche spätestens nach etwa 14 min wieder unter pH 2 lagen. Unter postprandialen Bedingungen unterlag der intragastrale pH-Wert besonders hohen Schwankungen. Der pH-Verlauf innerhalb der ersten 4 h ist durch einen annähernd linearen Abfall gekennzeichnet. Nach dieser Zeit wurden wieder pH-Werte von etwa pH 1 erreicht. Zu vergleichbaren Ergebnissen kamen auch *Dressman* und Kollegen, nach Gabe einer ähnlich hochkalorischen Mahlzeit [104]. Bei genauerer Betrachtung der Einzelwerte wurde jedoch ersichtlich, dass die gastralnen pH-Werte große Fluktuationen aufweisen. Dies lässt sich unter anderem mit der Ausbildung von Sekretionsschichten begründen. Innerhalb der ersten Zeit nach Einnahme der FDA-Standardmahlzeit wurden vermutlich bereits große Mengen an saurem Magensaft sezerniert [105–107]. In Abhängigkeit der aufgenommenen Nahrung kann die initial beobachtete Magensaftsekretionsrate bis zu 10 mL/min betragen [105]. Eine solch hohe Sekretionsrate sowie die fortwährende Mukusproduktion sind wahrscheinlich die Hauptgründe für das Scheitern von mukoadhäsiven Systemen [9, 13, 108]. Vermutlich werden diese von der Schleimhaut förmlich abgespült. In einer MRT-Studie von *Sauter* und Kollegen bestand der Mageninhalt 100 min nach der Einnahme einer Testmahlzeit zu etwa 50% aus Sekreten [106]. Bedingt durch den hohen Fettgehalt der Nahrung ist es möglich, dass sich ein Großteil des sezernierten Magensafts auf dem Nahrungsbrei ablagert. Eine solche Sekretionsschicht wurde bereits von mehreren Autoren mittels MRT beobachtet [106, 107]. Der Mageninhalt zeichnet sich folglich durch Bereiche hoher und niedriger pH-Werte aus [109, 110]. Dabei ist zu vermuten, dass im Zentrum Nahrungsbreis aufgrund geringer Durchmischung mit den sauren Sekreten ein

höherer pH-Wert vorherrscht als in wandnahen Bereichen, in denen die Durchmischung höchstwahrscheinlich schneller vonstatten geht.

Aufgrund der angestrebten langen Magenverweildauer gastroretentiver Systeme sind diese von gastralen Fluktuationen des pH-Wertes in besonderem Maße betroffen. So kann das pH-Profil im Magen maßgeblich die intragastrale Löslichkeit von ionisierbaren Arzneistoffen bestimmen [111]. In Abhängigkeit der Formulierung kann dadurch die Wirkstofffreisetzung aus der Arzneiform stark vom pH-Wert abhängen [112]. Daneben können die physikochemischen Eigenschaften (zum Beispiel das Quellungsverhalten) von bestimmten Polymeren ebenfalls vom vorliegenden pH-Wert abhängen und so die Wirkstofffreisetzung beeinflussen [113]. Nicht zuletzt werden dadurch auch die gastroretentiven Eigenschaften der Arzneiform selbst beeinflusst [114, 115].

Aufgrund der Relevanz des pH-Werts sind die oben beschriebenen Daten von Bedeutung für die Entwicklung neuer *In vitro*-Testmethoden. Die Daten zeigten, dass die Bedingungen während der üblichen Freisetzungstestung von gastroretentiven Arzneiformen wenig Bezug zu den *In vivo*-Bedingungen aufweisen. Der Einsatz von Medien mit pH-Werten von pH 1–2 macht deutlich, dass die Azidität des Mageninhalts insbesondere zu Beginn des Magenaufenthalts häufig überschätzt wird [33, 60]. Daneben bleiben die starken Fluktuationen des pH-Wertes unberücksichtigt. Bei entsprechender Implementierung der Daten in biorelevante Testmethoden könnte bereits in *In vitro*-Untersuchungen festgestellt werden, ob ein gastroretentives System über den gesamten Bereich des physiologisch möglichen gastralen pH-Wertes reproduzierbar funktioniert.

Weitaus wichtiger als der pH-Wert ist jedoch die möglichst korrekte *In vitro*-Simulation der gastralnen Motilität und die dadurch hervorgerufenen Belastungen. Aufgrund der verlängerten Magenaufenthaltszeit ist zu vermuten, dass gastroretentive Systeme besonders hohe Belastungen erfahren, welche eine Beschleunigung der Wirkstofffreisetzung zur Folge haben können [40, 50, 67]. Die SmartPill®-Daten zeigten aber, dass die Magenentleerung nach Nüchternennahme der telemetrischen Kapseln nicht zwangsläufig mit starken Drücken einhergeht. Bei vier Probanden erfolgte die Magenentleerung ohne das Auftreten nennenswerter Drücke. Bei drei dieser Probanden wurde allerdings eine Transitzeit von unter 2 min beobachtet. Ein Grund dafür könnte eine von der Phase III des MMC unabhängige Magenentleerung sein, wie sie bereits in der Literatur beschrieben wurde [36]. Die niedrigen Drücke würden demnach eher propulsiven Kontraktionen der Phase I oder II des MMC zuzuschreiben sein, welche in ihrer Intensität deutlich geringer ausfallen, als die der Phase III [48]. Nichtsdestotrotz war der Magen jedoch der Abschnitt des Gastrointestinaltrakts, in dem die höchsten messbaren Belastungen auftraten, mit Drücken von bis zu 460 mbar.

Auf der Basis dieser physiologischen Betrachtungen wurden die im Arbeitskreis entwickelten biorelevanten Freisetzungssapparaturen optimiert. Speziell zur Simulation der Nüchternbedingungen entwickelten Grabacz und Kollegen den

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Dynamic Open Flow-Through Test Apparatus [100]. Die Möglichkeit einer Druckbelastung der Arzneiform ist durch dasselbe Ballonsystem gegeben, das bereits im *Dissolution Stress test Device* Anwendung fand (Abbildung 3). Da in bisherigen Studien mit dem *Dynamic Open Flow-Through Test Apparatus* die am Manometer des Modells einge-

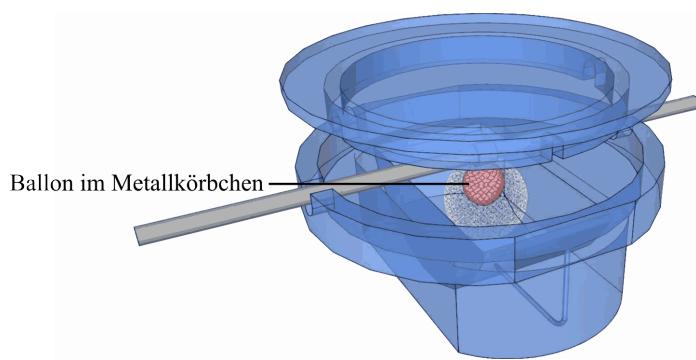


Abbildung 3: Schematische Darstellung des Magenkompartment des *Dynamic Open Flow-Through Test Apparatus*.

stellten Druckwerte lediglich auf Literaturwerten basierten und die auf die Arzneiformen übertragenen Drücke im Modell bislang unbekannt waren, wurden diese zunächst mittels der SmartPill® im Modell quantifiziert. Der Einsatz der SmartPill® ermöglichte auf diese Weise erstmals den Vergleich mit *In vivo*-Daten. Vollständige, im Nüchternarm der SmartPill®-Studie beobachtete, gastrale Druckprofile wurden hierfür erfolgreich mit dem Modell simuliert. Das Ballonsystem erwies sich in der Lage, realistische Drücke zeitlich definiert zu übertragen, wobei die am Manometer einzustellenden Werte in bisherigen Studien unterschätzt wurden [100]. Dasselbe lässt sich dementsprechend für das *Dissolution Stress test Device* sagen [40, 50].

Im Gegensatz dazu waren die Standardapparaturen der Arzneibücher nicht in der Lage, entsprechend hohe Drücke auf die SmartPill® auszuüben. Selbst bei höchsten Umdrehungszahlen und trotz extremer Rotationsbewegungen der SmartPill® konnten keine nennenswerten Drücke in der Blattrührer-Apparatur gemessen werden. In einer Studie von Vardakou und Kollegen wird diese Beobachtung ebenfalls bestätigt [70]. Die Autoren zeigten, dass die Blattrührer-Apparatur selbst bei hohen Umdrehungszahlen nicht in der Lage ist, Agargel-Kugeln unterschiedlicher Bruchkraft zu zerkleinern und Kräfte zu erzeugen, wie sie für gewöhnlich *in vivo* auftreten [70]. Ähnliche Beobachtungen wurden zuvor bereits von anderen Arbeitsgruppen gemacht [68, 116].

Die höchsten Drücke wurden im eintauchenden Zylinder beobachtet. Im Vergleich zur Blattrührer-Apparatur wird angenommen, dass der eintauchende Zylinder den *In vivo*-Bedingungen durch erhöhte Belastungen während der Versuche näher kommt als andere Standardapparaturen [117, 118]. Die maximal gemessenen Drücke lagen jedoch nur bei etwa 14 mbar. Weitere Berechnungen ergaben, dass die im eintauchenden Zylinder und Zerfallstester gemessenen Werte hauptsächlich durch die beim Eintauchen entstehende Wassersäule über der SmartPill® hervorgerufen werden. Dafür sprachen die der Diprate entsprechenden Fluktuationen der gemessenen Drücke sowie die Reduktion der Werte durch Verringerung des Testvolumens. Die Freisetzungsprofile, vor allem von Hydrogel-matrixsystemen, können jedoch bei Erhöhung der Diprate (eintauchender Zylinder) be-

ziehungsweise der Umdrehungszahl (Blattrührer-Apparatur) beschleunigt werden [119]. Da es unter Nutzung der Standardapparaturen keinen Zusammenhang zwischen gemessenen Drücken und Steigerung der Diphase beziehungsweise der Umdrehungszahl gab, lag es nahe, dass vor allem hohe Scherkräfte und nicht etwa Druckbelastungen, für die häufig zu beobachtende Beschleunigung der Freisetzung solcher Arzneiformen *in vitro* verantwortlich waren [120, 121]. Dabei muss angemerkt werden, dass die in den Standardapparaturen auftretenden Scherkräfte für gewöhnlich höher sind, als man es *in vivo* erwarten würde [71, 122].

Die Eignung der Standardapparaturen bei der Untersuchung von gastroretentiven Arzneiformen *in vitro* scheint demnach fragwürdig. In Anbetracht der Tatsache, dass sich solche Systeme über sehr lange Zeit im Magen aufhalten sollen und dieser als Ort höchster Belastungen identifiziert werden konnte, kommt der Simulation gastraler Drücke während der Wirkstofffreisetzungsversuche enorme Bedeutung zu. Die Daten konnten zeigen, dass es mit den im Arbeitskreis entwickelten biorelevanten Freisetzungsapparaturen möglich ist, diese Drücke realistisch abzubilden. Da die Einnahme von gastroretentiven Systemen allgemein postprandial erfolgt und das FDA-Standardfrühstück in entsprechenden *In vivo*-Studien eine übergeordnete Rolle spielt, sind die ermittelten SmartPill®-Daten unter postprandialen Bedingungen extrem wichtig für die Entwicklung realistischer *In vitro*-Testverfahren zur Untersuchung der Wirkstofffreisetzung gastroretentiver Arzneiformen.

Postprandial waren im Gegensatz zum Nüchternarm stets Drücke von mehr als 240 mbar während des Magenaufenthalts messbar. Da diese hohen Drücke zeitlich teils deutlich vom pH-Anstieg getrennt waren, war anzunehmen, dass diese nicht beim Übertritt in den Dünndarm auftraten, sondern bereits in distalen Abschnitten des Magens. Der Pylorus scheint also nicht zwangsläufig der Ort der höchsten Belastung zu sein. Diese Beobachtungen werden auch durch Manometrie-Daten von DeSipio und Kollegen bestätigt [123]. Während der Magenpassage traten postprandial maximal messbare Drücke von annähernd 500 mbar auf. Im Extremfall kann es hierdurch zum *dose dumping* kommen. Die Folgen für den Patienten wären besonders bei hochpotenten Wirkstoffen dramatisch.

Interessanterweise zeigte die SmartPill®-Studie, dass die weitere Einnahme von Nahrung das Auftreten von starken und hochfrequenten Drücken unter Umständen begünstigen kann. Bei fünf Probanden führte beispielsweise die Aufnahme des standardisierten Mittagessens nach 4,5 h zu Drücken von über 200 mbar. Bei drei weiteren Probanden wurden Drücke von etwas mehr als 100 mbar in Folge der Aufnahme eines leichten Abendbrots registriert. Die eingenommene Nahrung kann hierbei größere Objekte, wie die SmartPill®, in tiefere Abschnitte des Magens drücken, was vermutlich erhöhte Belastungen nach sich zieht [124, 125]. In den meisten Fällen traten allerdings während des Magentransits der SmartPill® im postprandialen Studienarm trotz weiterer Nahrungs-

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aufnahme nur geringe messbare Druckbelastungen auf.

Der Einfluss der beschriebenen Belastungen auf das Freisetzungerverhalten aus vermeintlich gastroretentiven Arzneiformen konnte mittels des *Dissolution Stress test Device* zweifelsfrei nachgewiesen werden. Hierbei wurden drei realistische Druckprofile während der Freisetzungstests simuliert, vergleichbar mit den Ergebnissen aus dem *Dynamic Open Flow-Through Test Apparatus* für die Druckprofile nach Nüchterneinnahme. Da die Einnahme solcher Arzneiformen häufig postprandial erfolgen soll, wurden die Druckprofile des postprandialen Studienarms genutzt, um die unterschiedlichen Transitszenarien zu entwickeln. Mit diesen drei Druckprofilen wurde dann zum einen Glumetza® 1000 getestet, eine ovale Tablette, die durch ihre Größe ausreichend gastroretentiv sein soll. Zum anderen wurde Madopar® Depot getestet. Dabei handelt es sich um eine Hartgelatinekapsel, deren Inhalt einen mukösen Körper mit einer Dichte kleiner als 1 g/cm^3 bildet und so auf dem Mageninhalt aufschwimmen soll [21].

Die kontrollierte Wirkstofffreisetzung soll im Fall von Glumetza® 1000 durch einen diffusionskontrollierenden Überzug erfolgen. Die Ergebnisse zeigten jedoch, dass bei fort schreitender Testdauer die vom Modell übertragenen Drücke zu einer Ruptur des Überzugs führten und somit letztendlich zur vollständigen Wirkstofffreisetzung. Die simulierte Magenentleerung mit höchsten Belastungen nach etwa 23,5 h hatte dementsprechend keine Auswirkungen mehr. Der Einfluss von frühen Drücken war deutlich geringer als der späterer Drucksequenzen. Dies lässt darauf schließen, dass die Tabletten im unvollständig gequollenen Zustand weniger anfällig für Belastungen sind. Die Daten lassen jedoch ebenfalls vermuten, dass *in vivo* bereits durch die postprandiale Motilität eine vollständige Wirkstofffreisetzung hervorgerufen werden könnte. Die beschriebene Drucksensitivität muss auch nicht zwangsläufig zu scharfen Spitzen in Plasmakonzentrationsprofilen führen. Es ist denkbar, dass sich ein beträchtlicher Anteil an Arzneistoff unter den Nahrungsbrei mischt und die durch die Mahlzeit bedingte, langsame Magenentleerung pharmakokinetisch eine intakte Arzneiform mit kontrollierter Wirkstofffreisetzung suggeriert. Ein häufiges Problem bei der Interpretation von *In vivo*-Daten zu solchen Arzneiformen ist der fehlende oder unbewiesene Zusammenhang zwischen der Pharmakokinetik und den gastroretentiven Eigenschaften des Systems [23]. Daher sollte bei der Überprüfung der gastroretentiven Eigenschaften einer Arzneiform möglichst auch ein bildgebendes Verfahren genutzt werden [23]. Darüber hinaus fehlen in einigen Studien Referenzformulierungen oder es werden schnell freisetzende Formulierungen zum Vergleich eingesetzt [23, 86, 126–128]. In den meisten Fällen wären jedoch vergleichbare Plasmaspiegelverläufe zu erwarten, wenn man das entsprechende gastroretentive System gegen eine nicht gastroretentive Arzneiform ähnlicher Größe jedoch mit identischer Wirkstofffreisetzung testen würde [23].

Aufgrund ähnlicher Dimensionen der Tabletten ($12 \text{ mm} \times 20 \text{ mm}$) im Vergleich zur SmartPill® gehen wir davon aus, dass die gastrointestinalen Bedingungen, welche die

Arzneiform erfährt, mit den SmartPill®-Daten vergleichbar sind. Dementsprechend ist zu erwarten, dass zuvor eingenommene Nahrung entscheidend zu einer verlängerten Magenaufenthaltsdauer beiträgt. Die Einnahme unter Nüchternbedingungen würde demnach unzureichende gastroretentive Eigenschaften offenbaren. Einen Hinweis auf ein solches Verhalten liefern unter anderem Daten aus *In vivo*-Studien, in denen Glumetza® 500 sowohl im Anschluss an eine hochkalorische Standardmahlzeit als auch unter Nüchternbedingungen eingenommen wurde. Szintigraphische Daten suggerieren zunächst in der Tat eine erfolgreiche Gastroretention mit Magenaufenthaltszeiten von mindestens 5,5 h [129]. Bei Einnahme unter Nüchternbedingungen bricht die orale Bioverfügbarkeit jedoch im Vergleich zur postprandialen Applikation um mehr als 40% ein [90, 129]. Bereits eine Reduktion des Fettgehalts der zuvor eingenommenen Mahlzeit auf 30% resultierte in einer deutlichen Verkürzung der Magenaufenthaltsdauer [89, 90, 129].

Im Falle von Madopar® Depot führten frühe Drücke bereits zur vollständigen Wirkstofffreisetzung. Eine kontrollierte Freisetzung im Magen während der Verdauung scheint auf Basis der Ergebnisse eher unrealistisch. Tatsächlich deuten Studien von *Grahn* und Kollegen darauf hin, dass das vermeintlich flotierende Madopar® Depot einer klassischen Tablette mit verlängerter Wirkstofffreisetzung pharmakokinetisch nicht überlegen ist [130]. Es muss jedoch beachtet werden, dass es fraglich ist, inwiefern Ergebnisse aus Studien zu telemetrischen Kapseln auf vermeintlich flotierende Systeme übertragbar sind. Es wäre zumindest zu erwarten, dass die höhere Dichte der SmartPill® zu deutlich unterschiedlichen Positionen im Magen führt. Bei niedrigviskosen Medien wird dieser Effekt vermutlich noch ausgeprägter sein.

Die Daten zeigten, dass die dynamischen Bedingungen des Gastrointestinaltrakts bei der Entwicklung gastroretentiver Arzneiformen bereits *in vitro* berücksichtigt werden sollten. Hierbei spielen neben der Temperatur und dem pH-Wert insbesondere mechanische Belastungen während des Magentransits eine enorme Rolle. Die im Arbeitskreis entwickelten *In vitro*-Testmethoden ermöglichen daher eine frühzeitige Evaluierung neuer gastroretentiver Systeme und können einen entscheidenden Beitrag leisten, um die Entwicklung von gastroretentiven Arzneiformen gezielt voranzutreiben.

3 Ausblick

Eine Grundvoraussetzung für gastroretentive Systeme ist die von den bisher beschriebenen Parametern unabhängige Funktionsweise. Das tatsächliche Transitverhalten und damit der zweifelsfreie Nachweis gastroretentiver Eigenschaften muss jedoch abschließend mit Hilfe einer *In vivo*-Studie bestätigt werden. Um einen Hinweis auf das gastroretentive Potential *in vivo* zu bekommen, wurde von Neumann und Kollegen ein Antrummodell entwickelt, welches die gastrale Motilität möglichst realistisch simulieren soll. Mit Hilfe dieses Modells konnten wir antrale Kontraktionswellen *in vitro* nachstellen und den Vorwärtstransport verschiedener Objekte im Modell untersuchen [81]. Mit Hilfe dieses Modells konnten wir zeigen, dass Objekte mit elastischen Eigenschaften weniger gut von simulierten Kontraktionswellen vorwärts transportiert werden. Eine längere Magenverweildauer ist daher wahrscheinlich. Starre Objekte wurden, ebenso wie Objekte mit einer reibungsverminderten Oberfläche, leicht vom Modell vorwärts transportiert, was auf eher schlechte gastroretentive Eigenschaften *in vivo* hindeutet. Die in diversen klinischen Fallberichten beschriebene Retention von Trichobezoaren im menschlichen Magen konnte mit dem Antrummodell ebenfalls bestätigt werden [81]. In einer bisher unveröffentlichten Arbeit haben wir nach dem Vorbild solcher Trichobezoare Polymere mit Arzneistoff beladen und zu haarartigen Filamenten schmelzversponnen. In Zukunft kann auf Basis der vorliegenden Arbeit die Drucksensitivität solcher Filamente überprüft werden. Daneben soll das gastroretentive Potential solcher Filamente in Abhängigkeit vom verwendeten Polymer mithilfe des Antrummodells realistisch eingeschätzt werden. Das Modell sollte zudem unter Nutzung der SmartPill®, ebenso wie die in der vorliegenden Arbeit genutzten *In vitro*-Modelle, umfassend auf seine biorelevante Funktionsweise hin überprüft werden. Eine filamentöse Arzneiform, beispielsweise in eine Kapsel eingebracht, könnte dabei einen neuen Ansatz liefern, um die zuverlässige und reproduzierbare Gastroretention von Darreichungsformen zu ermöglichen.

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Publikationen

Intragastric pH and pressure profiles after intake of the high-caloric, high-fat meal as used for food effect studies

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Intragastric pH and pressure profiles after intake of the high-caloric, high-fat meal as used for food effect studies



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ABSTRACT

The intraluminal conditions of the fed stomach are critical for drug release from solid oral dosage forms and thus, often associated with the occurrence of food effects on oral bioavailability. In this study, intragastric pH and pressure profiles present after the ingestion of the high-caloric, high-fat (964 kcal) FDA standard breakfast were investigated in 19 healthy human subjects by using the telemetric SmartPill® capsule system (26 × 13 mm). Since the gastric emptying of such large non-digestible objects is typically accomplished by the migrating motor complex phase III activity, the time required for recurrence of fasted state motility determined the gastric emptying time (GET). Following the diet recommendations of the FDA guidance on food effect studies, the mean GET of the telemetric motility capsule was 15.3 ± 4.7 h. Thus, the high caloric value of the standard breakfast impeded gastric emptying before lunch in 18 out of 19 subjects. During its gastric transit, the capsule was exposed to highly dynamic conditions in terms of pH and pressure, which were mainly dependent on further meal and liquid intake, as well as the intragastric capsule deposition behavior. Maximum pH values in the stomach were measured immediately after capsule intake. The median pH value of the 5 min period after capsule ingestion ranged between pH 3.3 and 5.3. Subsequently, the pH decreased relatively constantly and reached minimum values of pH 0–1 after approximately 4 h. The maximum pressure within the stomach amounted to 293 ± 109 mbar and was clearly higher than the maximum pressure measured at the ileocaecal junction (60 ± 35 mbar). The physiological data on the intraluminal conditions within the fed stomach generated in this study will hopefully contribute to a better understanding of food effects on oral drug product performance.

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1. Introduction

The comprehension of basic principles of food-drug interactions is of great importance for oral drug delivery, since these may lead to altered pharmacokinetic profiles with serious consequences for efficacy and safety of drug therapy [1]. Kang and Ratain reported that significant food effects on oral drug absorption are reported for about one third of the 99 new orally administered active pharmaceutical ingredients that were approved by the FDA between January 2000 and May 2009 [2]. Clinical studies intended to investigate these food effects are typically conducted by following the "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" released in 2002 by the FDA [3]. This guidance determines important specifications on the study design, since the evaluation of food effects of certain drugs or formulations requires highly standardized study conditions. This includes

the recommendation for a high-caloric (800–1000 kcal) and high-fat (>50% of the calories derived from fat) test meal, which is served after an overnight fast of at least 10 h. The so-called FDA standard breakfast is composed of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk. The meal is served to the subjects 30 min prior to the administration of the drug product to be tested and shall represent a worst-case scenario of drug intake by inducing a maximum physiological response. Since 2012, the EMA recommends the same meal for evaluation of food-drug interactions in its respective guideline [4].

In the last decade, the obligation to evaluate food effects on oral NMEs and certain oral generic drug products (e.g. modified release dosage forms) resulted in significant progress in the comprehension of food-drug interactions. Despite the various *in vitro* and *in silico* tools as well as animal models available, food effects on oral bioavailability cannot be predicted with certainty without performing clinical studies [5–9]. This is partly due to the lack of understanding of GI physiology and digestion processes. However, this knowledge is required for the development and optimization of powerful *in vitro* and *in silico* tools, as well as for the interpretation of clinical study results. For instance,

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little is known about the *in vivo* processing of the FDA standard breakfast. A recent magnetic resonance imaging (MRI) study was the first to investigate the gastrointestinal conditions present in food effects studies. With the aid of MRI, changes of the volume and the fat fraction of the gastric content were determined over time. In comparison to fasted state, both parameters were significantly increased for more than 6 h [10]. Based on these data, it can be assumed that food effects can occur even several hours after food intake as was already demonstrated for different poorly water soluble drugs such as quazepam or bilonanserin [11,12].

Food intake also changes the physicochemical and mechanical conditions inside the lumen of the upper gastrointestinal (GI) tract. Hence, drug release and absorption can be altered if a solid oral dosage form is administered in the fed state [1,13,14]. Particularly in terms of ionizable drugs with poor aqueous solubility, the pH value of the luminal fluids is regarded as one of the main reasons for altered drug release and thus, for the occurrence of food effects [15,16]. Moreover, in case of modified-release dosage forms, different excipients are used to control drug release based on the pH value of the surrounding medium [17]. Therefore, a thorough characterization of pH profiles in the fed stomach is essential for the elucidation of food effects. Gastric pH values are typically measured by the aspiration of luminal contents or by use of catheters or telemetric capsules equipped with pH sensors (e.g. Bravo® pH capsule, IntelliCap® or SmartPill®) [18–21].

A major advantage of the telemetric SmartPill® GI monitoring system is the additional opportunity to measure the pressure within the GI tract in high temporal resolution. The pressure sensor was included to enable the diagnosis of motility disorders such as gastroparesis or constipation [22,23]. In terms of oral drug delivery, the GI motility can affect the transit times within the individual segments of the GI tract and thus, the exposure time of a drug to certain physicochemical conditions and the site of absorption. Moreover, gastrointestinal peristalsis influences the luminal drug distribution and generates shear stresses that may act on solid oral dosage forms. Especially the antro-duodenal region is regarded as a zone of high shear stresses [24].

To the best of our knowledge, intragastric pH and pressure profiles under conditions, which represent the situation of clinical studies investigating the food effect on oral bioavailability, have not been investigated so far. However, these data are highly needed for the comprehension of food effects, as both parameters can affect drug release in the fed state. By using a telemetric motility capsule (TMC), the present study aimed at the characterization of the intragastric transit conditions in terms of pH and pressure as well as the determination of the gastric emptying time of the TMC after intake of the high-caloric, high-fat standard meal recommended by FDA and EMA for food-effect studies. This system was further used to investigate the influence of food and liquid intake on intragastric temperatures.

2. Materials and methods

2.1. Subjects

The study was conducted with 20 healthy human subjects (9 males, 11 females), aged 21–34 years (26.0 ± 4.1 years) and with a body mass index of 19.5–27.9 (22.7 ± 2.2). All subjects were ascertained to be in good health by means of their medical histories, physical examination, and clinical chemical urine analysis. None of the subjects had undergone abdominal surgery, took medication (except oral contraceptives) or suffered from diseases affecting gastrointestinal motility. All subjects gave their written informed consent. The study was approved by the ethics committee of the University Medicine Greifswald (registered no. BB 125/13).

2.2. Study protocol

The study protocol followed the FDA "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" [3]. The subjects

were admitted to the study unit approximately 12 h before administration of the TMC in order to ensure standardized gastrointestinal conditions at the time of TMC intake. After an overnight fast of at least 10 h, the subjects had to ingest the FDA standard breakfast within 30 min. The meal consisted of two strips of bacon (Tulip Bacon, Tulip Food Company, Denmark), two slices of toast (Sammy's Super Sandwich, Harry-Brot GmbH, Germany) with butter (Meggle Alpenbutter, Meggle AG, Germany), two eggs (free range eggs size L, Poseritzer EierHof, Germany) fried with butter, 113 g of hash brown potatoes (Rösti-Ecken, Gut & Günstig EDEKA Group, Germany), and 240 mL of full-fat milk (Domo LangLecker long-life full-fat milk with 3.5% fat, FrieslandCampina, Germany). The total caloric value of the meal amounted to 964 kcal based on the product specifications. Food intake according to the protocol was supervised by the staff members. In analogy to drug administration in food effect studies, 30 min after starting meal ingestion, the subjects swallowed an activated TMC, together with 240 mL of tap water at room temperature. The success of the TMC ingestion was supervised by mouth checking and confirmed by the pH change caused by stomach entry, which was recognized through the data receiver. For the subsequent 5 h, the intake of foods and liquids was standardized. The subjects received 100 mL of water at room temperature 1, 2, 3, and 4 h after swallowing the capsule. A standard lunch consisting of spaghetti bolognese, mixed salad with yoghurt dressing and cream yoghurt was served 4.5 h after TMC intake. The maximum caloric value of this meal was approximately 1000 kcal. The subjects were allowed to leave the study unit at the earliest 5 h after capsule ingestion. From that time, they were allowed to eat and drink without restrictions. They recorded their food and liquid intake as well as all other relevant events (e.g. sleep, activities of all kind, micturition/defecation) in a diary. High physical strain such as sports as well as the intake of alcohol or drugs (except hormonal contraceptives) was not allowed throughout the study. Until capsule excretion, the subjects collected their stool in order to recover the capsule. After return of the excreted capsule, its structural integrity was checked and post-calibration was performed.

2.3. SmartPill® GI monitoring system

The SmartPill® GI monitoring system (Given Imaging Ltd., Yoqneam, Israel) was used to measure gastrointestinal pH (measuring frequency 0.2 Hz), temperature (measuring frequency 0.05 Hz) and pressure (measuring frequency 2.0 Hz). The data receiver needed to be worn close to the body in order to record the data packages sent by the capsule (13 × 26 mm). After capsule excretion, the subjects returned the data receiver to the staff. Before ingestion and after excretion, pH (pH 1–9), pressure (0–400 mbar) and temperature sensors (one point calibration) were calibrated in vitro.

Temperature compensation for pH value and pressure was performed automatically by MotiliGI® software. In the case of pressure, the software also performed a baseline correction. However, we abstained from using the baseline corrected data as these were only relative data, which did not represent the real values measured *in vivo*. Therefore, only the temperature compensated data were used for the analysis.

2.4. Data analysis

Data were analyzed using Origin 8.5.1G (OriginLab Corp., Northampton, USA). As illustrated in Fig. 1, gastric emptying time (GET), small intestinal transit time (SITT) and colonic arrival time (CAT) were determined by consideration of significant pH changes. Gastric emptying was identified by a significant and permanent pH change to values of pH 5 and higher. Colonic entry was registered by a sharp pH decrease of at least 0.5 pH units occurring at least 30 min after gastric emptying. Capsule excretion was identified by a drop in temperature.

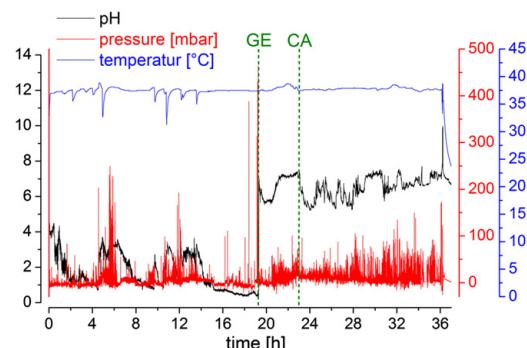


Fig. 1. Exemplary pH (black), pressure (red) and temperature (blue) profiles over time obtained after TMC administration in fed state by subject 9 (GE – gastric emptying, CA – colonic arrival).

Owing to the observed pH drift of the TMC sensors, the pH values were corrected based on the results of the post-calibration. The following equation was used:

$$pH_{corr} = pH_m - \left(\frac{\Delta pH}{WGTT} \cdot t \right) \quad (1)$$

Where pH_m is the pH value measured by the TMC, ΔpH is the mean pH drift calculated from the values determined during pre- and post-calibration, $WGTT$ is the whole gut transit time in hours and t is the time in hours after the TMC intake. The pH profiles of subjects, for whom post-calibration could not be performed, are marked as those in the figures.

Data were characterized by minimum, maximum, interquartile range, median and arithmetic mean \pm standard deviation where appropriate. For the statistical evaluation of the pH profiles and pressure data, only data sets from subjects, for whom the post-calibration procedure was performed successfully, were included.

3. Results

For 19 out of the 20 subjects that were enrolled in this study, transit data were successfully recorded by the data receiver and transferred to the computer. One subject's data could not be analyzed due to capsule deactivation prior or during intake. In three other subjects, the post-calibration of pressure and pH value was not possible owing to empty battery or unsuccessful recovery of the TMC. These subjects were not included into the analysis of pH values, since the pH sensors were prone to a highly variable drift that was in a range of

0.001–0.050 $\Delta pH/h$ (mean: $0.010 \pm 0.013 \Delta pH/h$). However, the pH drift measured in this study was in line with the results of a recent SmartPill® study published by Abbas and colleagues [25]. Significant pH changes could still be identified and thus, these subjects' data could be used for the calculation of transit times. The pressure sensor was not prone to drift and therefore, all 19 subjects were included into the analysis. None of the subjects experienced an adverse event.

3.1. Gastrointestinal transit times

Based on characteristic pH changes, gastric emptying and colon arrival were determined successfully. The comparison of the transit times through stomach, small intestine and colon as well as through the whole gut is given in Fig. 2. It can be seen that all transit times were highly variable with exception of the small intestinal transit time. The GET was between 4.3 h and 20.2 h. However, in 18 subjects the GET was clearly longer than 4.5 h and thus, not before lunch. The

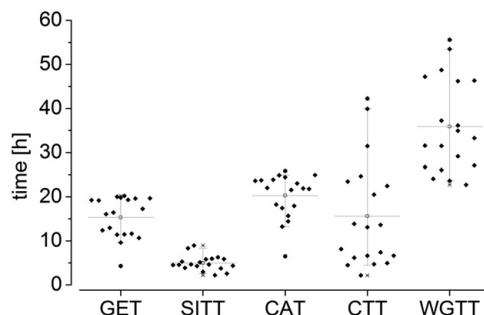


Fig. 2. Gastrointestinal transit times obtained by TMC administration 30 min after starting the ingestion of a high-caloric, high-fat meal. Whisker: 10–90%; square: mean; asterisks: max/min; $n = 19$. (GET – gastric emptying time, SITT – small intestinal transit time, CAT – colon arrival time, CTT – colon transit time, WGTT – whole gut transit time).

mean GET amounted to 15.3 ± 4.7 h. In 12 out of 19 subjects gastric emptying was observed at night. There was clear evidence from the diary entries of the subjects and the pH value prior to emptying that the rigid non-digestible TMC was emptied only in fasted state. On average, the last meal intake was 7.8 ± 2.3 h prior to gastric emptying.

3.2. Gastric pH

As exemplified in Fig. 1, the gastric passage of the TMC was characterized by varying transit conditions. Strong fluctuations of the intragastric pH value were observed in all subjects. In one subject, the TMC was first exposed to a pH value below pH 2 already after 4 min, whereas in another subject the pH was constantly above pH 2 for more than 3 h. Fig. 3 depicts the intragastric pH profile over the first 5 h. It should be noted that although the inter-individual variability was high, the mean gastric pH value decreased fairly consistently until approximately 4 h, when the baseline level of pH 1 was reached. After an average 1.1 ± 1.1 h, the capsule was for the first time exposed to pH values below pH 2, though a constant pH value below pH 2 was

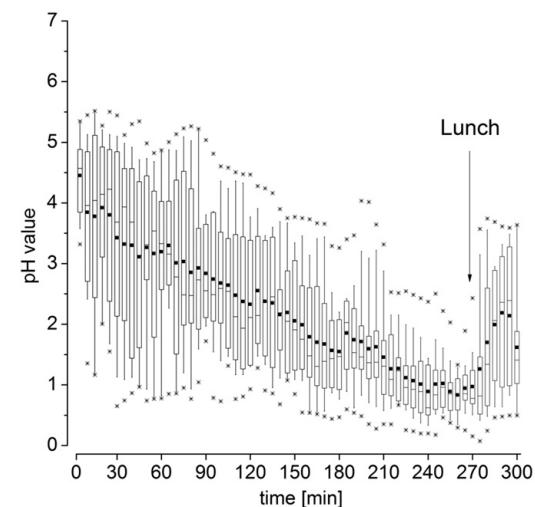


Fig. 3. Gastric pH values for the initial 5 h time frame after TMC administration. Each box represents a 5 min interval. Box: 50%; whisker: 10–90%; square: mean; asterisks: max/min; $n = 16$. The three subjects, for whom post-calibration could not be performed, were excluded from this statistical analysis.

observed only after 3.1 ± 0.6 h. The intake of 100 mL of water after 1, 2, 3 and 4 h only led to slight and short-term increases in pH. For the subjects with gastric transit times longer than 4.5 h, the intake of lunch strongly affected the gastric pH value. The serving of lunch resulted in a momentary increase to a value of $pH 3.6 \pm 0.4$. Since the subjects could eat freely after leaving the study unit, standardization of the dietary regimen was no longer given and thus, the pH profiles were strongly dependent on timing, type and amount of further food and liquid intake. The largest effects were observed after solid foods. In most of the cases, these caused an increase in pH to values of pH 2–4. Interestingly, none of these events led to a value higher than the pH measured immediately after TMC intake.

Fig. 4a shows the initial pH values measured in the first 5 min after capsule ingestion. The median pH value during that period amounted to pH 4.6. However, high inter-individual differences (pH 3.3–5.3) were noted. **Fig. 4b** presents the pH values measured during the hour before gastric emptying of the TMC. For several subjects, short-term pH values above pH 5 were notable in the 1 h interval prior to gastric emptying.

3.3. Temperature

Food and liquid intake mainly affected the intragastric temperature, whereas the effects on the temperature in small intestine and colon were negligible. In general, the effect of food or liquid intake on temperature was greater when the gastric content volumes were supposed to be on lower levels (e.g. before lunch). In particular hot or cold drinks, which were allowed after the standardized dietary regime of 5 h following capsule intake, led to clear temperature changes if the capsule was

still in the stomach. These periods, which can also be seen in **Fig. 1**, lasted in part longer than 30 min. In this study, the intragastric temperature varied between 28.3°C and 41.9°C .

3.4. Pressure

Fig. 5 summarizes the occurrence of pressure events above 100 mbar.

The number of marked pressures events within the stomach was highly individual and ranged from 1 to 62. Interestingly, none of these events were observed during the first 2 h after intake. Although the intake of lunch led to a higher incidence of pressure events, the number of pressure events did not correlate with the gastric emptying time. The amplitude of the pressures was also highly individual and the maximum pressures amounted to values of up to 496 mbar (mean: 293 ± 109 mbar). These highest pressures were typically observed shortly, i.e. 30 min to 5 min, before the pH drop that indicated gastric emptying. Interestingly, as can be seen in **Fig. 6**, the time point of pH increase indicative of gastric emptying was not directly linked to the time point of the highest gastric pressure.

Fig. 7 compares the maximum pressures measured in the antropyloric region and at the ileocaecal junction. It can be seen that at the ileocaecal junction, another sphincter muscle, the maximum pressure events amounted to 60 ± 35 mbar. Thus, these values were significantly lower in comparison to the pressures measured in the antropyloric region.

4. Discussion

In comparison to the short median GET of 30 min that was measured in a recent fasted state study performed with the similarly sized IntelliCap® system, there was a significant prolongation of GET in this study [26]. The striking difference in GET can be explained by different motility patterns in fed and fasted state [27]. In fasted state, the strong peristalsis of the migrating motor complex (MMC) phase III, so-called housekeeper waves, enables the emptying of even large non-digestible objects such as telemetric capsules [28]. However, food intake disrupts the MMC and induces the fed pattern [29,30]. During that pattern, large non-digestible objects are retained in the stomach – a process referred to as gastric sieving [18]. Several studies have demonstrated that the duration of the MMC interruption mainly depends on the caloric value of the ingested content [29,30]. Ewe and co-workers described a close correlation between the caloric values of ingested food and the GET of non-disintegrating tablets with a size of 11×6 mm. When the subjects received main meals and snacks at intervals of 2.5 h, the GET of the tablets was 569 ± 120 min. When the subjects received solely

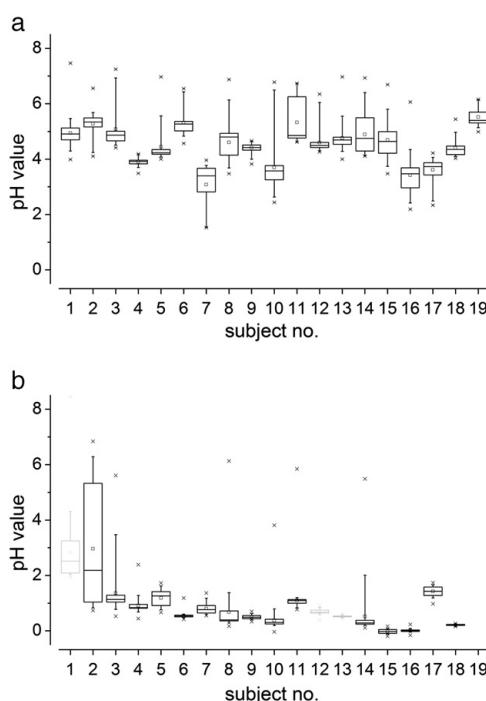


Fig. 4. Comparison of pH values measured over a period of 5 min directly after TMC intake (a) and over a period of 1 h before gastric emptying (b); box: 50%, whisker: 10–90%, square: mean, asterisks: max/min; n = 19. Subjects, for whom post-calibration was not possible are indicated by gray boxes.

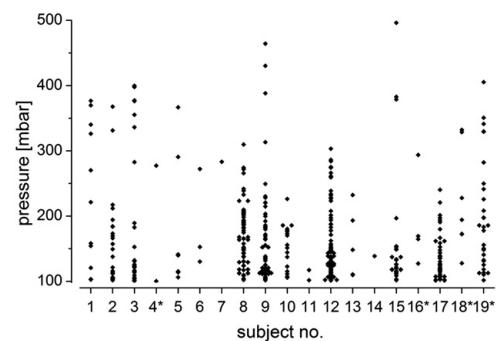


Fig. 5. Intragastric pressure events above 100 mbar (n = 19). The asterisk (*) indicates temporary loss of data during gastric transit of the TMC.

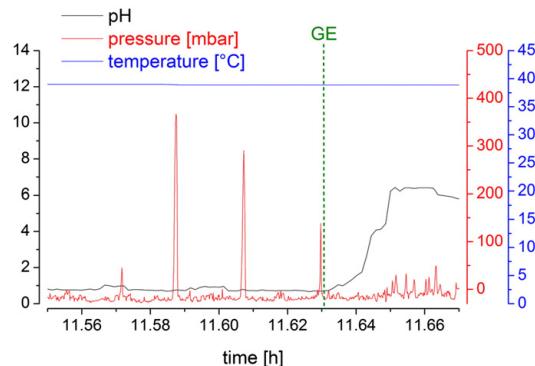


Fig. 6. Gastric emptying (GE) pattern of subject 5.

breakfast, GET was only 201 ± 10 min [31]. A similar effect could be observed in the present study. Following the rule of thumb that the ingestion of 200 kcal inhibits the MMC for one hour, the FDA breakfast (965 kcal) interrupts the MMC theoretically for about 4.8 h and thus, until lunch [27]. Thus, the long gastric residence times observed in this study were the consequence of the ingested calories. This assumption was strengthened by the results of a recent MRI study with 12 healthy human subjects. The gastric content volumes after intake of the FDA standard breakfast are significantly increased compared to fasted state volumes for more than 6 h [10]. In the present work, lunch was served 5 h after breakfast, which led to a further extension of the fed pattern. Similar findings were published by Willis and colleagues, who found a marked increase of GET, if gastric emptying did not happen before an ad libitum lunch buffet [32]. With respect to food effect studies, whether lunch is given after 4 h or 6 h might have strong effect on the study results. However, in this study, the last meal intake was on average 7.8 ± 2.3 h before gastric emptying.

The properties of the tested objects, in particular size and density, are also critical for the GET. But although numerous studies were performed, a clear cut-off diameter that prohibits gastric emptying in fed state could not be defined yet [33]. For instance, Podczeck and Newton showed that non-disintegrating tablets with a diameter of 3 mm are already retained in the stomach by food [33].

During gastric transit, highly dynamic pH values are present within the stomach. These are the result of digestion processes including secretion and emptying on the one hand, and further liquid and food intake on the other hand. The median pH value of pH 4.6 during the initial 5 min interval after TMC intake was clearly lower than the pH value of $pH 6.61 \pm 0.03$ determined in vitro after shredding of the meal [34]. This discrepancy was probably caused by the delay between the start of meal intake and swallowing of the capsule. TMC was ingested 30 min after the start of the meal and thus, gastric acid secretion was already stimulated, when the capsule entered the stomach. It was shown by Malagelada and colleagues that the initial secretion rates after a high-fat meal of 458 kcal can amount to 10 mL/min and higher. This could lead to a fast drop in pH owing to the strongly acidic character of gastric secretions [35]. In the present work, the pH value further decreased within 4 h to strongly acidic baseline levels. These pH values were significantly lower than the fasted state pH values determined recently by use of the IntelliCap® system [26]. After on average 3.1 ± 0.6 h, the pH value was constantly below pH 2. Interestingly, as shown recently by MRI, the stomach still contains a considerable volume of gastric content at this time [10]. Due to simultaneous secretion and emptying processes within the stomach, the pH decreased much faster than the gastric content volume, which can be explained by the dilution of caloric contents in the human stomach [36,37]. Hoad and co-workers demonstrated for a nutrient drink that gastric secretions were responsible for more than 50% of the gastric content volume 75 min after the intake [37]. Besides HCl, gastric secretions also contain enzymes (e.g. pepsinogen or gastric lipase) that are required for the digestion of certain food components such as proteins or lipids. Thus, the rapid pH drop was the physiological response to the high-caloric, high-fat meal in order to enable digestion. The gastric distension, the increase of luminal pH as well as the presence of certain nutrients such as proteins or lipids caused by ingestion of the FDA standard breakfast stimulated the secretion of gastric acid from parietal cells via endocrine, paracrine and Neurocrine pathways [38,39]. The pH values present after the intake of the FDA standard breakfast had not been determined prior to this study, but gastric pH profiles after consumption of other meals had already been investigated. Dressman and colleagues investigated the pH profiles after ingestion of a high caloric standard meal (1000 kcal) by use of the Heidelberg pH capsule [16]. The composition of this meal was comparable to the FDA standard breakfast. Interestingly, the pH profiles recorded during the first 4 h are also comparable with the results of the present work.

The strong variations in gastric pH observed in the present study were probably the consequence of the dynamic deposition behavior of the TMC and the heterogeneity of the gastric content. For instance, if the TMC was located close to the stomach wall, it might have registered lower pH values owing to gastric secretions than amidst the stomach content, where mixing with gastric secretions is weaker. The slow progress of dilution of a highly viscous meal by gastric secretions was demonstrated by Marciani and co-workers in a recent MRI study [40]. Other authors also revealed pH differences between proximal and distal parts of the stomach. Owing to the small volume and intense mixing, the pH value in the antrum is less affected by the buffering capacity of the meal and is hence lower compared to that of the fundus [41,42]. Moreover, Hila and co-workers demonstrated the presence of multiple acid layers within the stomach after ingestion of a solid meal. These layers were persistent in four different body positions [41]. The proximal layer is also known as the acid pocket and results from high secretion, but poor mixing after meal intake [43]. As was shown by MMM, incoming food can push larger objects such as tablets into distal parts of the stomach, where the pH is typically lower [44]. However, the hypothesis that changes in the intragastric capsule position was responsible for the observed pH fluctuations can only be confirmed by combining a TMC system with imaging techniques enabling its exact localization in high temporal resolution such as scintigraphy or magnetic marker monitoring (MMM). Additionally, in some subjects short periods of higher pH

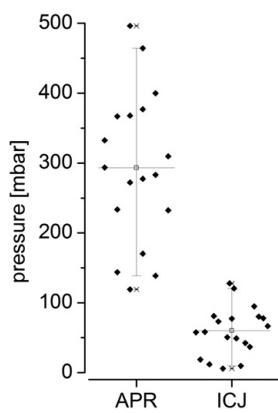


Fig. 7. Comparison of maximum pressures measured in the antropyloric region (APR) and at the ileocaecal junction (ICJ). Whisker: 10–90%, square: mean, asterisks: max/min; n = 19. The maximum pressure of one subject (subject 19) at the pylorus is lacking due to temporary loss of data during gastric emptying.

values could be detected prior to gastric emptying (Fig. 4b). These short episodes were most probably the result of duodenogastric reflux. This physiological phenomenon describes the retropulsion of intestinal contents into the fasted stomach and is typically associated with MMC phase III motility [45].

The effect of elevated gastric pH on the bioavailability of orally administered drugs is currently the subject of intense debate [46,47]. In terms of food effects, the changed gastric pH could also play a role. It seems likely that the meal-induced initial pH increase could alter particularly the drug release from immediate release dosage forms. For weak bases, reduced oral bioavailability is expected, owing to decreased solubility in comparison to the fasted state administration. This effect was also demonstrated for the weak base lapatinib by administering it together with esomeprazole. Due to limited aqueous solubility at $pH > 4$, the oral bioavailability actually drops by about 26% [48]. Interestingly, the intake of lapatinib after a high-caloric, high-fat standard meal leads to a three- to four-fold increase of the oral bioavailability [49]. The rise in pH after a meal is thus not necessarily associated with the extent and direction of the food effect as was also shown for other drugs [47]. In particular the presence of lipids and surface active digestion products will contribute to the occurrence of food effects. We demonstrated recently that the fat share of the gastric content is on a high level for at least 6 h [10]. Thus, the positive food effects observed for the poorly water soluble drugs quazepam and blonanserin, which were present even hours after meal intake, were probably caused by increased solubility due to the presence of lipids and certain digestion products [11,12]. Further parameters critical for food-drug interactions might be the increased gastric content volume, the deceleration of gastric emptying as well as the interaction of food components with drug absorption and metabolism.

Since the TMC was emptied only in fasted state into the duodenum, the pH values in small intestine and colon were consistent with the findings of a previous study, in which the IntelliCap® was ingested by fasted subjects [26]. In terms of biorelevant dissolution testing of large non-digestible ER products, it therefore seems suitable to use fasted state media for the simulation of intestinal conditions as was also proposed by Markopoulos and co-workers [50]. In the present study, an effect of further food or liquid intake on pH, temperature, and pressure in small intestine or colon was not observed.

The pressure sensor of the TMC allowed the generation of pressure data for the GI transit of an orally administered object. Such data are of great interest, since events of high pressures within the gastrointestinal tract were previously shown to affect drug release from solid oral dosage forms. In particular, soft monolithic objects such as hydrogel matrix tablets can be influenced by physiological forces, which may lead to dose dumping [51].

During gastric emptying, a temporal offset of several minutes between maximum pressure and pH shift was observed. Since the transit through the duodenal C is typically very fast, an immediately following increase of pH would be expected after the passage of the pylorus [52]. It can be assumed that the maximum pressures of up to 496 mbar was probably not caused by the pyloric sphincter, but the consequence of forceful peristaltic waves (MMC phase III) in the terminal antrum that pushed the TMC against the stomach wall. During gastric emptying, the TMC was probably transported aborally ahead of these contraction waves through the open pylorus into the duodenum. In that case, the pressure registered by the capsule would be smaller compared to a closed pylorus and the TMC pushed against the stomach wall. Moreover, lunch intake clearly affected the number and amplitude of pressure events as incoming food probably pushed the TMC towards distal areas, where antral contraction waves could act on the capsule. Thus, with respect to clinical studies, the tablet position could again have a considerable effect on the drug plasma profile. It was shown by MMM that the localization in the antrum, which is associated with higher shear stresses, leads to increased drug release rates in comparison to the

fundus [53]. It is likely that the transfer into the antrum as it was observed during lunch intake could cause the same effect. The influence of meal intake on initial intragastric position and drug release was demonstrated for Augmentin XR tablets with the aid of MMM. In comparison to the administration after a test meal, higher drug plasma concentrations were measured when the tablets were ingested at the beginning of meal intake owing to localization within the antrum [44].

The results of this study and a recent MRI study are highly relevant for the comprehension of the *in vivo* conditions present after intake of the highly relevant FDA standard breakfast. The data clearly demonstrated that the typical intake advice for fasted state administration of drugs with undesired food effects – 1 h or 2 h after a meal – for the administration on an empty stomach seems not justified [3]. Based on the present data, it is clear that even 2 h after food intake, highly important parameters like fat content, gastric content volume and gastric motility are different compared to fasted conditions (Table 1) [10].

However, the stomach was clearly acidic after 2 h as the mean gastric pH declined to $pH 2.3 \pm 1.1$. Consequently, pH effects will be less pronounced if a drug is taken 2 h after meal intake. Nonetheless, a recent MRI study showed that large portions of the meal are still inside the stomach and thus, other physicochemical factors such as surface tension, buffer capacity or viscosity, which could not be evaluated by the two techniques, still differ [10]. All parameters mentioned are known to influence drug release within the fed stomach and may contribute to the occurrence of food effects.

4.1. Limitations

The pH sensor of the used TMC is an ion-sensitive field effect transistor (ISFET) [54]. It was shown recently that these sensors are prone to drift over time and that various parameters such as pH, composition or temperature of the surrounding medium contribute to the sensor drift [55]. In the present study, the pH values measured by the TMC were corrected assuming linear drift of the pH sensor. But as the main reason for sensor drift remained unclear, a non-linear drift behavior cannot be excluded. However, as the drift rate was small, the effect of the correction method would be minimal.

Although the study protocol followed the FDA and EMA guidelines, the results must be interpreted with some caution and cannot be transferred from one to one pharmaceutical products. In the present study, the subjects were allowed to leave the study unit after a high-caloric lunch and could follow their normal eating habits. At this point, standardization was no longer prescribed, which contributed to the highly variable GET observed in this study. Owing to the long presence of the fed state motility and the associated disruption of the MMC, the time point of gastric emptying was clearly dependent on further meal and liquid intake of the subjects. Furthermore, it must be noted that the TMC used in this study had a size of 26×13 mm and thus, the capsule is larger than common solid oral dosage forms. Due to its dimensions, it could only be emptied in fasted state by MMC phase III activity or isolated antral contraction waves [18]. In addition, as was observed in a recent IntelliCap® study, such large objects may not be emptied during the first MMC phase III activity after re-initiation of the fasted state motility [26].

The objects' dimensions might also influence the magnitude of the pressure, since this would be the result of an occlusion with a certain diameter that is generated by peristalsis. Hence, the larger the object is, the higher are the forces experienced by the object. The results of this study should therefore be regarded as a worst-case scenario for monolithic solid oral dosage forms. Nonetheless, they provide important information on the magnitude and variability of gastric pH values and pressures present after the intake of the high-caloric, high-fat FDA breakfast recommended for food-effect studies.

Table 1

Comparison of fasted and fed conditions in the stomach after intake of the FDA standard breakfast measured by MRI ($t = 0$ min was the beginning of meal intake), SmartPill® and, IntelliCap® [10,26].

		Fasted	After FDA standard breakfast		
			65 min	105 min	195 min
MRI [10]	Gastric content volume [mL]	31 ± 19	551 ± 57	510 ± 77	358 ± 65
	Fat content [% (v/v)]	3.4 ± 2.6	8.2 ± 0.4	7.5 ± 0.5	6.8 ± 1.0
SmartPill® IntelliCap® [26]	pH value	—	3.3 ± 1.6	3.0 ± 1.4	1.7 ± 1.0
	pH value	2.7 ± 0.8	—	—	—

5. Conclusion

Moreover, gastric transit was characterized by strongly variable conditions in terms of pH and pressure, which were also dependent on further food or liquid intake. Maximum pH values were generally measured directly after swallowing the TMC. Subsequently, the pH value decreased within 4 h to acidic baseline levels of pH 1 and lower. Remarkably, only minor pressure events were registered by the TMC during that period. Maximum pressures of up to 500 mbar were typically observed shortly before gastric emptying and were associated with forceful antral contraction waves.

Despite the high relevance of this standard meal for the comprehension of food-drug interactions, this study was the first of its kind to explore intragastric pH and pressure profiles under conditions representative for studies investigating food effects on oral bioavailability. The data obtained here demonstrate that great care has to be taken with respect to the design of clinical studies investigating the food effect on oral bioavailability. The period between drug administration and lunch, the serving of water during this period as well as the serving of further snacks can have a huge impact on the outcome of such clinical trials. By increasing the degree of standardization it is likely that the variability of such studies can be reduced and thus, their explanatory power may be increased. Furthermore, the pH and pressure profiles measured in this study can be implemented into present *in vitro* and *in silico* tools and hence, contribute to a better understanding and prediction of food effects.

Acknowledgments

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Resolving the physiological conditions in bioavailability and bioequivalence studies: Comparison of fasted and fed state

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Technical note

Resolving the physiological conditions in bioavailability and bioequivalence studies: Comparison of fasted and fed state



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ABSTRACT

In the present study temperature, pH and pressure profiles of nine healthy human volunteers were investigated after ingestion of the SmartPill® under conditions simulating the fasted state treatment in bioavailability and bioequivalence studies. In a previously published study the same subjects received the SmartPill® under fed conditions as recommended by the FDA. Since large non-digestible objects are mainly emptied during phase III of the interdigestive migrating motor complex, the gastric residence time of the SmartPill® was found to be clearly shorter under fasting conditions. Intragastric pH values during the initial 5 min were similar with an identical median value of pH 4.6. Interestingly, the median lowest observed intragastric pH value in fasted state was about one pH unit higher than that under fed conditions. Highest pressure activity was observed within the stomach, in relation to gastric emptying. In fasted state, pressure values upon gastric emptying varied strongly between 30 mbar and 304 mbar, whereas after fed state ingestion values of at least 240 mbar could always be observed. The data showed highly variable gastrointestinal parameters even under fasting conditions which must be considered when evaluating clinical studies and developing biorelevant in vitro test methods especially for large non-disintegrating dosage forms.

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1. Introduction

The physiological conditions of the gastrointestinal (GI) tract can largely affect the in vivo performance of orally administered dosage forms during bioavailability and bioequivalence studies. Besides several techniques that can be used to assess GI conditions, GI transit times as well as pH values can be determined by using radio-telemetric capsules containing a pH sensor (e.g. IntelliCap®, Heidelberg capsule, Bravo® pH Capsule, SmartPill®). The capsules are able to travel along the entire GI tract thereby generating a complete pH profile, which can also be used to determine residence times in the different parts of the GI tract. In addition to pH, the SmartPill® contains a pressure sensor that allows the recording of pressure activity within the GI tract. These data enable the identification of sections of high pressure activity. Such knowledge might be of great relevance for the evaluation of the disinte-

gration behavior especially of large, monolithic modified release dosage forms such as hydrogel matrix tablets.

In bioavailability and bioequivalence studies, dosage forms are administered either in fasted or in fed state. Under fasting conditions, the drug is ingested together with typically 240 mL of water after an overnight fast of at least 8–10 h [1,2]. To achieve fed state conditions, subjects receive a high-caloric, high-fat standard breakfast (approx. 1000 kcal) 30 min before drug intake in order to induce maximum physiological response. Such studies are usually carried out in a cross-over design by administering a dosage form to the same subject under the different conditions to minimize confounding effects between test and control groups. It is obvious that possible food effects are the result of changed GI conditions.

In order to understand the outcome of clinical studies performed under either fasted or fed state conditions, a thorough understanding of GI physiology is needed. Recently, Koziolek and colleagues investigated fed state conditions using magnetic resonance imaging and SmartPill® recording in healthy subjects [3,4]. However, intra-subject data are not available for the repeated administration of the SmartPill® to the same subjects under fasted and fed state conditions according to the "FDA Guidance

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for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies” [1].

With the results of the present study we gained information about the physiological conditions along the GI tract for the transit of large monolithic dosage forms administered under fasting conditions as recommended for bioavailability or bioequivalence studies. Moreover, we provide follow-up data to the already published study in which the identical subjects received the SmartPill® under fed state conditions [3].

2. Materials and methods

The study was performed at the clinical trial unit of the Department of Clinical Pharmacology, University Medicine Greifswald, Center of Drug Absorption and Transport (C_DAT), Greifswald, Germany. The study protocol was approved by the independent Ethics Committee of the Medical Faculty of the University of Greifswald (ethical protocol no. BB 125/13).

2.1. Subjects

All subjects that already participated in the previous study, in which fed state conditions were characterized, were asked to be included in this follow-up study. In total, nine healthy human subjects (three females, six males, age 22–29 years, body mass index 19–28 kg/m²) could be enrolled. They had no history of bowel diseases or GI surgery. During the whole study period, no medications were allowed except for oral contraceptives. All volunteers gave written informed consent prior to inclusion.

2.2. Study protocol

The present study was designed according to the specifications recommended for fasted treatment described in the “FDA Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies”. After an overnight fast of at least 10 h, the healthy subjects swallowed a SmartPill® together with 240 mL tap water of room temperature. The SmartPill® measures 26 mm × 13 mm. Its ingestion represented the administration of the dosage form to be tested in bioequivalence and bioavailability studies. The intake of food and liquids was standardized and strictly supervised for 5 h after SmartPill® ingestion. The subjects drank 100 mL tap water of room temperature 1, 2, 3 and 4 h after capsule ingestion. Lunch (approx. 1000 kcal) was eaten after 4.5 h. The in-house confinement was finished five hours after capsule ingestion. The subjects kept a diary to record all special events after leaving the study unit (e.g. food and fluid intake, sleep behavior, physical activity and micturition/defecation). All subjects were asked to eat and drink as usual. Alcoholic products were not per-

mitted. Sports and other extreme physical exercises were not allowed until excretion of the SmartPill®. The subjects sampled stool until recovery of the SmartPill® for visual examination and post-calibration of the sensors. Fig. 1 shows a scheme of the first 5 h of the first study day for both study arms.

2.3. Data analysis

The collected data were exported and analyzed using OriginPro 8.5.1.G (OriginLab Corporation, Northampton, MA, USA). Gastric emptying was defined as a sharp and permanent rise of the pH to 5 and higher. The colon arrival could be identified by a pH decrease of at least 0.5 units, which occurred at least 30 min after gastric emptying. Capsule excretion could be determined by help of the recorded temperature, which always declined by at least 10 °C. Besides transit times, significant pH values and pressure peaks were analyzed. The initial pH value was determined as the mean pH value during at maximum the first 5 min. Regarding the measured pressures, the integrated software of the SmartPill® performs automatic temperature and baseline corrections in order to calculate a motility index used for diagnostic purposes. We decided to only use the temperature compensated data as possible shifts of the baseline would have been automatically set to a baseline of zero, not displaying the *in vivo* measured values. The results of the present study were compared to those of the previously performed study [3].

3. Results and discussion

All nine volunteers completed the study without experiencing any adverse events. All obtained individual pH, temperature and pressure profiles are shown in Fig. 2.

3.1. Gastrointestinal transit times

In Fig. 3, the transit times through different regions of the GI tract under fasting conditions are shown and compared to the results of the previously published fed state study by Koziolek and co-workers [3]. In all subjects, the gastric emptying time was clearly reduced under fasting conditions. This striking difference is due to the occurrence of the interdigestive motility pattern [3,5]. Recent studies confirmed that just as other large indigestible objects, the SmartPill® is most likely emptied by the fasted state motility during the migrating motor complex (MMC) [5,6]. Food and caloric liquids interrupt this pattern, that again reoccurs when the stomach is nearly completely emptied from the chyme [5].

The mean small bowel transit time of 4.4 h was identical for both study arms and not significantly different ($P < 0.05$, paired Student's *t*-test). However, the translocation of objects into the

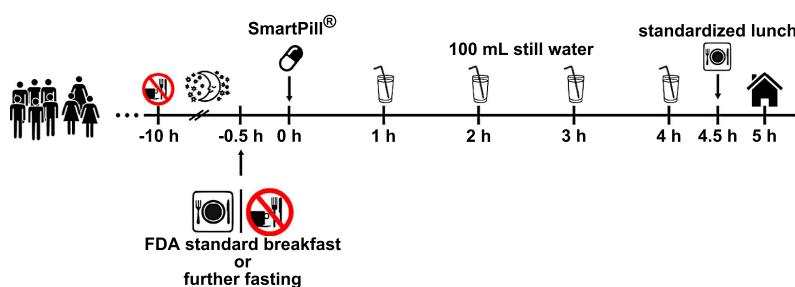


Fig. 1. Time schedule on first study day describing the conditions for fasted and fed treatments.

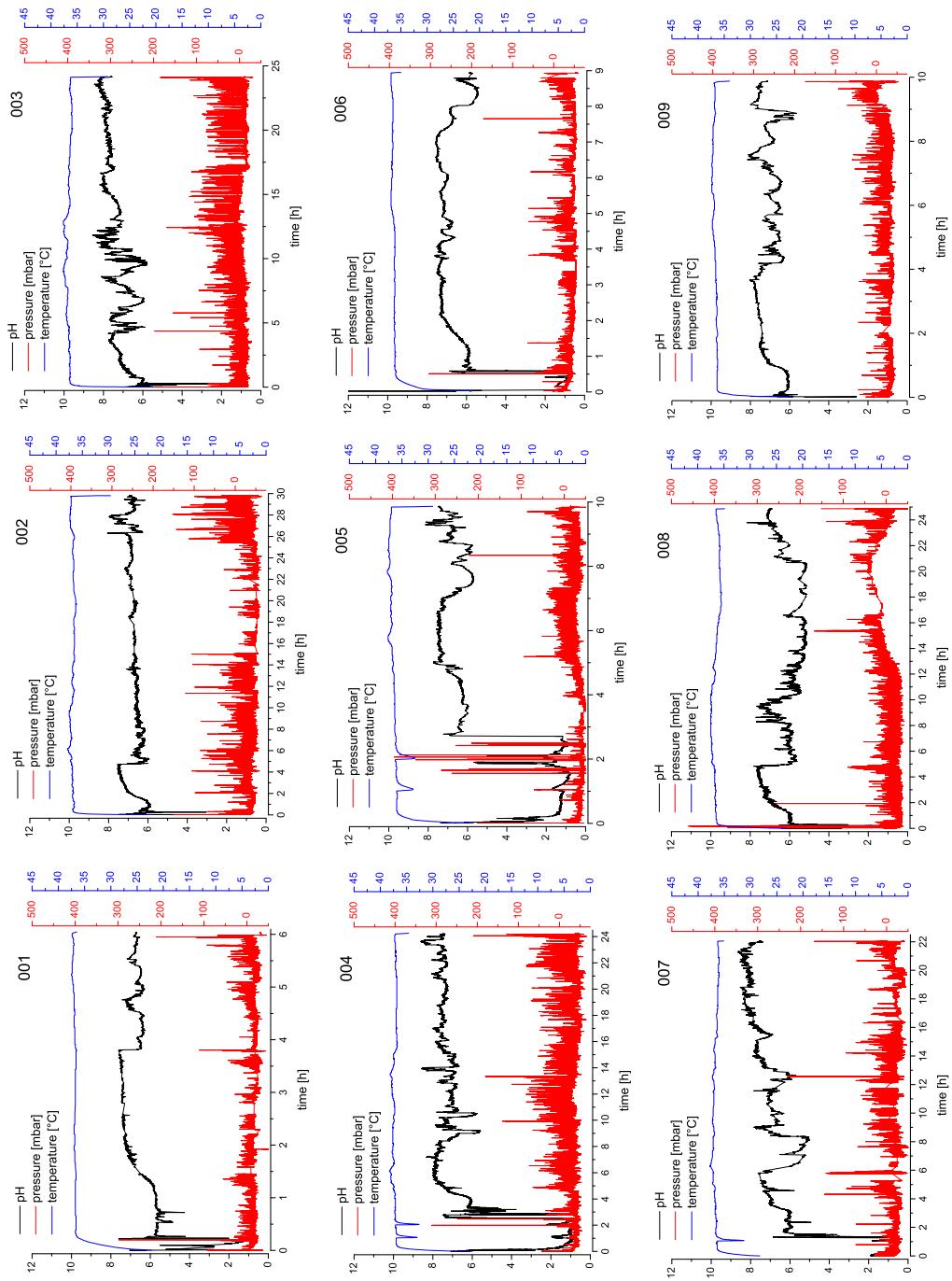


Fig. 2. Pressure, pH and temperature profiles obtained in all nine healthy subjects after fasted state ingestion of the SmartPill®.

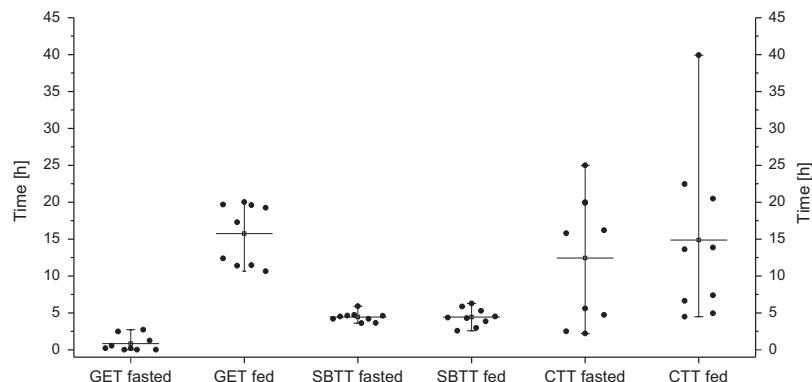


Fig. 3. Gastrointestinal transit times obtained after fasted and fed state ingestion of the SmartPill®. GET – gastric emptying time, SBTT – small bowel transit time, CTT – colon transit time. Whisker: max/min, square: mean; n = 9.

colon is likely associated with food intake (ileocecal reflex), which therefore can affect the small bowel transit time [7]. In most cases after fasted state ingestion, the colon arrival happened shortly before or shortly after standardized lunch, which was given 4.5 h after capsule ingestion. The study design may therefore be highly important.

In both study arms, the colon transit time was highly variable. However, no significant differences ($P < 0.05$, paired Student's *t*-test) between the mean colon transit times were observed with values of $12.4 \text{ h} \pm 8.7 \text{ h}$ for fasted and $14.9 \text{ h} \pm 11.5 \text{ h}$ for fed state ingestion.

3.2. pH values

The pH measurement along the GI passage revealed characteristic patterns in the majority of volunteers. The median initial pH values during the first 5 min after ingestion of the SmartPill® together with 240 mL of water were identical for both study arms (Table 1). The occasionally observed high pH values under fasting conditions can be explained by mixing of the co-ingested water with the residual acidic fluid present in the stomach, which is only about 30–50 mL [7,8].

Interestingly, the median lowest pH value during the gastric passage in the fasted state was about one pH unit higher than in the fed state. The SmartPill® is exposed to increasingly acidic conditions for longer periods in the fed state treatment. This is presumably due to ongoing digestion and finally the reoccurrence of

fasted state. After fasted state ingestion, an occasionally rapid gastric emptying prevents the SmartPill® from getting into contact with highly concentrated acidic fluid but with gastric acid secretion diluted by the remaining co-ingested water.

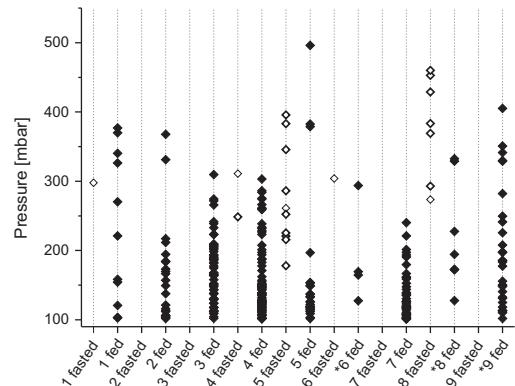


Fig. 4. Individual intragastric pressure events above 100 mbar after fasted and fed state ingestion of the SmartPill®. The asterisks (*) indicate temporary data loss during gastric transit.

Table 1

Selected individual pH values of different sections of the gastrointestinal tract after fasted and fed state ingestion of the SmartPill®.

Subject	Stomach				Small intestine				Colon	
	Initial pH		Lowest pH		pH duodenum		pH ileum		Mean pH	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
1	3.3	4.9	1.2	0.9	5.7	7.1	7.5	8.9	6.6	8.0
2	4.6	5.3	3.0	0.7	6.2	6.0	7.5	7.1	6.7	6.2
3	4.3	4.6	2.0	0.2	5.9	6.0	7.5	7.2	7.4	6.1
4	6.4	4.6	0.8	0.3	5.7	5.2	7.6	7.9	7.3	7.1
5	4.9	4.7	0.7	0.3	6.4	5.2	6.8	6.3	6.5	6.8
6	4.7	3.4	0.6	0.04	5.9	5.1	6.9	6.4	6.9	6.0
7	1.8	3.6	0.5	0.1	5.3	5.6	7.6	7.3	7.3	5.6
8	4.9	4.4	1.4	0.2	5.8	4.3	7.6	7.1	5.9	6.5
9	3.3	5.5	2.6	0.2	6.2	5.7	7.5	7.3	7.0	4.9
Median	4.6	4.6	1.2	0.2	5.9	5.6	7.5	7.2	6.9	6.2

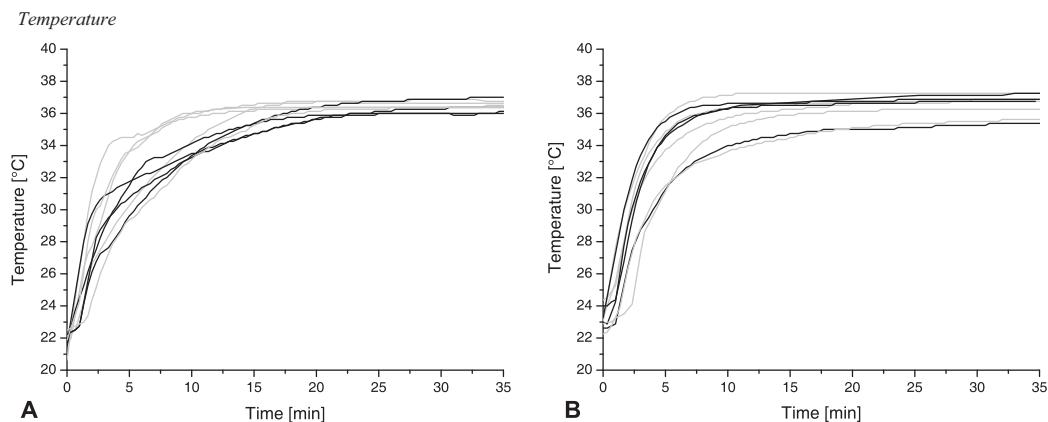


Fig. 5. Temperature profiles obtained by the SmartPill® shortly after ingestion under fasted (A) and fed state conditions (B). Profiles of subjects in whom the SmartPill® reached body temperature during gastric residence after fasted state ingestion are shown in black.

The rise of pH in relation to the entry into the duodenum could always be observed. For both intake conditions, the median pH values during the first 10% of the small intestinal transit were about 1.5 pH units lower than those measured during the last 10%. A characteristic rise along the small intestine could be observed as shown in Fig. 2.

In both study arms, the colonic pH values fluctuated strongly over time. Maximum pH values of pH 8.0 and higher could be observed, whereas the pH also declined to values of about pH 5.5 within short time periods.

3.3. Pressure

The pressure measurement along the GI tract revealed high pressure activity particularly within the stomach. The maximum pressures amounted to 460 mbar. In contrast to the variable pressure activity under fasting conditions, it is shown in Fig. 4, that intragastric pressures of at least 240 mbar were always detected after fed state ingestion of the SmartPill®.

The observed varying pressure values and gastric residence times under fasting conditions can contribute to a variable in vivo performance of large, monolithic dosage forms. Especially for hydrogel matrix tablets a pressure sensitive dissolution behavior was shown [9].

The maximum pressures measured in the small intestine as well as in the large intestine were clearly below those in stomach. The highest pressures during small intestinal passage went up to 103 mbar \pm 65 mbar under fasting conditions. The corresponding pressures in the large intestine were slightly higher and amounted to 140 mbar \pm 75 mbar. Comparable values were measured after fed state ingestion of the SmartPill® during the small intestinal (95 mbar \pm 76 mbar) and colonic transit (164 mbar \pm 29 mbar).

3.4. Temperature

In the fasted state, shorter gastric residence resulted in a faster rise of temperature and, thus, body temperature was reached earlier (Fig. 5A). However, in four subjects the body temperature was reached inside the stomach after fasted state ingestion. Thus, we obtained intragastric temperature profiles after co-ingestion of 240 mL water at room temperature. The resulting mean profile followed an exponential function from 21.9 °C to 36.0 °C for about 20 min ($r^2 = 0.991$). The intragastric temperature profiles under

fed state conditions were found to be more inconsistent with overall shorter times to reach body temperature (Fig. 5B). These data can be especially relevant for gelatin based dosage forms, since their dissolution behavior was shown to be dependent on temperature [10].

A major drawback of the used SmartPill® system was the occasional occurrence of data recording dropouts (especially during night). Furthermore, the pH sensors showed a slight drift during nearly every GI passage. However, the observed drifts were rather small (0.017 pH units per hour) and in line with the previous study. Therefore, a corrective calculation had only minor effects [3].

However, the SmartPill® could successfully be used to obtain important information during its GI transit. Especially its free-floating properties allowed us to estimate the GI conditions experienced by large, monolithic dosage forms under conditions simulating the fasted state treatment in bioavailability and bioequivalence studies.

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In vitro simulation of realistic gastric pressure profiles

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Beiträge der Autoren

Felix Schneider

Erstellung der Arbeitshypothese, Planung und Durchführung der praktischen Arbeiten, Erstellung des Manuskriptes

Regine Beeck

Mitarbeit bei der Durchführung der praktischen Arbeiten zur Simulation intragastraler Druckprofile im *Dynamic Open Flow-Through Test Apparatus*

Melanie Hoppe

Mitarbeit bei der Durchführung der praktischen Arbeiten zur Druckmessung in den kompendialen Apparaturen

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Mitarbeit bei der Diskussion und Korrektur des Manuskriptes

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Anleitung zur Erarbeitung der Fragestellung, Mitarbeit bei der Diskussion und Korrektur des Manuskriptes

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In vitro simulation of realistic gastric pressure profiles



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ABSTRACT

Novel in vitro dissolution tools can aid the development of orally administered drugs by explaining dosage form related in vivo phenomena that are not explainable with standard test apparatuses. Such novel tools are able to mimic various parameters in accordance with gastrointestinal conditions. Hereby, in vivo occurring pressure events were shown to be of major importance since they largely affect dosage form disintegration, drug dissolution and subsequently resulting drug plasma concentration profiles. The aim of the present study was to investigate the feasibility of producing biorelevant pressure events with standard test apparatuses and with the dynamic open flow through test apparatus. For this purpose, we used the SmartPill®, a swallowable capsule that houses a pressure sensor and that was already applied to gather human in vivo data. Among the standard apparatuses, highest pressures were measured in the reciprocating cylinder apparatus and the disintegration tester. No relevant pressure peaks could be detected in the paddle apparatus and the mini paddle apparatus. In contrast, the dynamic open flow through test apparatus enabled the simulation of complete gastric pressure profiles as they occur in vivo. The present work underlines the potential of novel in vitro dissolution models as useful tools during the drug development process as well as for explanatory purposes.

1. Introduction

During gastrointestinal transit, solid oral dosage forms are exposed to a number of different parameters that can affect drug release and absorption. Among these, luminal forces are of major importance for disintegration and dissolution of oral drug products. For instance, hydrogel matrix tablets were shown to be highly sensitive to compressive forces (Garbacz et al., 2008, 2009, 2014a). It is generally assumed that within the human gastrointestinal tract, the shear forces (acting parallel to the surface) are rather low, but the compressive forces (acting perpendicular to the surface) can be high at certain critical points such as the distal stomach and the pylorus. In a recent SmartPill® study that was conducted with fasted healthy volunteers, we could show that high stresses mainly occur in the stomach and thus, gastric residence plays a major role in exerting forces on dosage forms (Schneider et al., 2016). These forces typically facilitate the process of disintegration of immediate release (IR) products and hence, contribute to a fast onset of drug plasma concentrations (Vardakou et al., 2011a). On the other hand, in case of modified-release (MR) dosage forms, these forces can also be a threat to safe pharmacotherapy. It was already shown for various MR products that high compressive forces may be the root for undesired drug release phenomena such as dose dumping (Garbacz et al., 2008, 2009, 2014a; Koziolek et al., 2014).

Information on luminal forces in the human stomach can be assessed in vivo by applying different techniques. Non-invasive imaging techniques such as scintigraphy or magnetic resonance imaging (MRI) can be used to study the gastric distribution of a marker and thus, allow generating information on shear conditions in the stomach. The determination of compression is mainly done by either catheter manometry or capsule manometry. Catheter manometry allows to measure compression along a certain distance of the human gastrointestinal tract, whereas capsule manometry is based on the measurement at a single, often unknown location. However, freely moving capsule manometry systems such as SmartPill® can generate a pressure profile that is representative for the stresses solid oral dosage forms experience in the gastrointestinal tract. After swallowing the SmartPill®, it also generates a pH profile during its transit that can be used to estimate residence times in the different parts of the gastrointestinal tract (Koziolek et al., 2015; Schneider et al., 2016).

In order to study drug release from solid oral dosage forms, numerous compendial as well as novel in vitro test apparatuses were developed. As the stresses in the stomach are mainly important for disintegration and dissolution behavior of oral dosage forms, several biorelevant systems at least partly focus on gastric motility. These devices include highly complex systems such as the TIM-1 system and the Dynamic Gastric Model (DGM), but also simpler systems such as the

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dissolution stress test device (Garbacz et al., 2008, 2009; Minekus et al., 1995; Vardakou et al., 2011b; Vatier et al., 1994). These models were already successfully applied to explain the *in vivo* performance of different orally administered dosage forms (Blanquet et al., 2004; Garbacz et al., 2014a; Vardakou et al., 2011a). Using these models it could be shown that physiologically correct *in vitro* simulation of gastric forces can be of great value for the evaluation of novel formulations before testing them in clinical trials. This allows to specifically design dosage forms that release the drug nearly irrespective of the physiological conditions. In case of MR dosage forms, undesired dose dumping can be foreseen.

On the other hand, the majority of compendial dissolution methods are still based on more or less static test conditions. This does by no means reflect the human gastrointestinal physiology as already been demonstrated by several *in vivo* studies. Even for the investigation of drug release in fasted state, highly variable conditions can be expected influencing the *in vivo* performance of orally administered dosage forms (Kalandzi et al., 2006; Mudie et al., 2014; Schneider et al., 2016). After fasted state administration, the gastric residence time of non-disintegrating solids can be highly variable in the range from few minutes up to 3 h (Schneider et al., 2016). Moreover, the intraluminal pH value as well as the temperature further depend on the amount and temperature of the co-ingested water. These parameters were shown to affect the disintegration behavior and drug dissolution of IR dosage forms (Garbacz et al., 2014b; Van Den Abeele et al., 2015). To adequately simulate the mentioned parameters with respect to the low volumes in fasted state, Garbacz et al. developed the dynamic open flow through test apparatus (Garbacz et al., 2014b). This model is designed to simulate pressure, pH and temperature changes as they also occur *in vivo*. Furthermore, the media flow and the simulated gastric residence time can also be adapted to the conditions described for the fasted state intake of a dosage form. However, the simulation of gastric pressure events with this and comparable novel models is based on artificial test programs that shall cover a broad range of possible cases. Our knowledge from a recent SmartPill® study could significantly increase the correctness of simulation by adapting the test programs to *in vivo* observed pressure profiles.

Therefore, the aim of this study was to assess the stresses occurring in various compendial dissolution test apparatuses under different conditions with the aid of the SmartPill® system. Furthermore, the opportunities of the dynamic open flow through test apparatus in terms of the physiologically relevant simulation of gastric pressure events should be evaluated. For this purpose, the SmartPill® was chosen to serve as a reference system since it was already used to gather *in vivo* data for fasted state conditions (Schneider et al., 2016).

2. Materials & methods

2.1. SmartPill® GI monitoring system

The SmartPill® GI monitoring system (Given Imaging Ltd., Yoqneam, Israel) consists of an ingestible capsule (13 mm × 26 mm), a data receiver to store the data transmitted by the capsule and the MotiliGI® software for transmission and analysis of the data stored on the receiver via a personal computer. The receiver is equipped with a display and an event button. Hereby, the dataset can be marked at special time points whereby different test conditions get assignable during data analysis. The telemetric capsule is able to measure pH, temperature and pressure in the ranges of pH 0.5 to pH 9.0, 25 °C to 49 °C and 0 mbar to 467 mbar, respectively. Its two batteries enable a continuous measurement over a period of at least five days. An integrated energy saving mode gradually reduces the sampling frequency of each sensor beginning after 24 h. For data analysis, we used the baseline compensated pressure data and did all of analysis with aid of OriginPro 8.5.1.G (OriginLab Corporation, Northampton, MA, USA).

2.2. Standard methods

For evaluation of the occurring forces acting on a dosage form during compendial testing, several methods were investigated. The SmartPill® was tested under different conditions and served as a reference system to compare obtained data to *in vivo* measured pressure events.

2.2.1. Disintegration tester

The disintegration tester (ZT 222, ERWEKA GmbH, Heusenstamm, Germany) was used at 30 rpm. The test medium was water at 37 °C. The influences of the SmartPill® orientation within the basket (upright or downright) and the use of disks were investigated. Furthermore, we investigated whether significant pressure events occur if the SmartPill® fully emerges from the water during upward movement.

2.2.2. USP apparatus 2 and mini paddle apparatus

Tests in the paddle apparatus (USP apparatus 2, PT-DT70, Pharma Test Apparatebau AG, Hainburg, Germany) were carried out at 37 °C in water. The rotational speed of the paddle was increased by 25 rpm from 25 rpm up to 250 rpm. Tests in the mini paddle apparatus (modified DT 600, ERWEKA GmbH, Heusenstamm, Germany) were carried out at 37 °C in water. The rotational speed increased by 50 rpm from 50 rpm up to 150 rpm.

2.2.3. USP apparatus 3

To study the effect of up and downward movement of the reciprocating cylinder apparatus (USP apparatus 3, RRT 10, ERWEKA GmbH, Heusenstamm, Germany) on the SmartPill® measurement, tests were carried out at 37 °C. For the tests, a volume of 200 mL or 100 mL and a mesh size of 74 µm up to 840 µm for both sieves were used. The dip rate was increased by 5 dpm from 5 dpm up to 40 dpm. The direction of the pressure sensor remained downwards throughout all tests.

2.3. Dynamic open flow through test apparatus

The dynamic open flow through test apparatus was used to simulate the pressure profiles obtained *in vivo* for three healthy subjects. These subjects swallowed the SmartPill® together with 240 mL of water after an overnight fast of 10 h. A thorough description of the *in vivo* study is given elsewhere (Schneider et al., 2016).

2.3.1. Setup

Fig. 1 shows a schematic of the dynamic open flow through test apparatus as used in this study. This *in vitro* dissolution device was developed by Garbacz et al. in order to mimic gastric conditions arising after fasted state administration of solid oral dosage forms.

The main vessel can contain about 80 mL of dissolution media and is designed to guide the probe chamber, a spherical steel mesh, during its movement. The spherical probe chamber contains the dosage form and is able to perform pendulum motions within the main vessel. These motions are enabled by a stepping motor on one side of the central axis that is linked to the probe chamber. The other side of the hollow central axis contains a connection for compressed air supply. This allows to inflate a balloon inside the probe chamber via a nozzle that is connected with the central axis. The pressure to be exerted on a dosage form is regulated by a valve. The performed motions of the motor as well as balloon inflation are programmable and automated via a personal computer. Furthermore, two channels enable the perfusion of the main vessel with liquid media in horizontal direction. The media flow is enabled by an external programmable peristaltic pump (Ismatec IPC 16, Cole-Parmer GmbH, Wertheim, Germany). A water bath ensures correct temperature regulation.

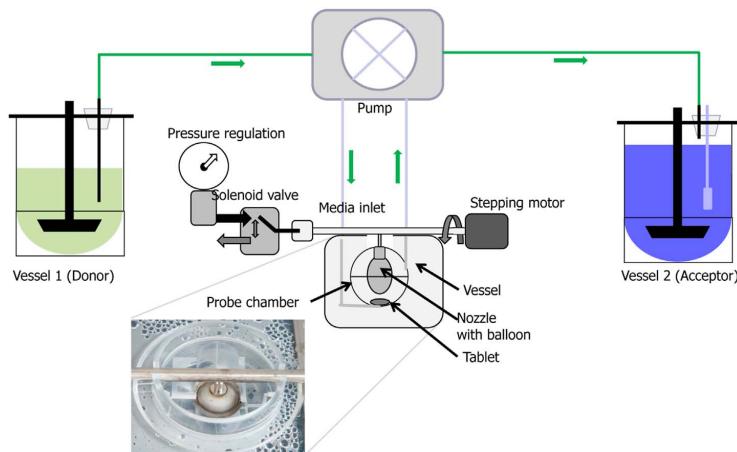


Fig. 1. Schematic of the dynamic open flow through test apparatus.

2.3.2. Simulation of gastric pressure profiles

For the simulation of realistic gastric pressure profiles we used *in vivo* data of a previously performed study, in which nine healthy human subjects swallowed the SmartPill® together with 240 mL of table water after an overnight fast of 10 h (Schneider et al., 2016). For three out of these nine subjects the data were analyzed with focus on gastric pressure data. For these three subjects, the pressure events during gastric transit of the SmartPill® were counted, classified into five ranges (50–100 mbar, 100–200 mbar, 200–300 mbar, 300–400 mbar and 400–500 mbar) and translated into pressure programs, which could be executed by the dynamic open flow through test apparatus. The chosen *in vivo* data should reflect different types of possible gastric pressure profiles after fasted state ingestion. Subject 1 had a fast transit time of about 12 min with two pressure events above 50 mbar. Subject 2 had a comparable transit time with eight pressure events above 50 mbar. This subject represented an upper maximum of possible gastric stress. Subject 3 had an extremely long gastric residence time of 165 min with frequent pressure events above 50 mbar. For the characterization of the test device as well as for the validation of the successful execution of the programs, an activated SmartPill® was placed inside the probe chamber and tested using the different programs.

3. Results

3.1. Standard methods

The pressure profiles obtained by application of the SmartPill® in standard methods revealed generally low exerted pressures. The up and downward movement of the disintegration tester and reciprocating cylinder apparatus resulted in highest pressure activity.

3.1.1. Disintegration tester

As can be seen in Fig. 2, the highest measured pressure peaks obtained with the disintegration tester were about 7 mbar. The orientation of the SmartPill® during the tests had only slight effects on the measured pressure peaks. The use of disks resulted in more irregular pressure patterns. Smaller pressure peaks resulted when the SmartPill® emerged from the media during upward movement of the basket.

3.1.2. USP apparatus 2 (paddle apparatus) and mini paddle apparatus

No relevant pressure peaks could be detected in the paddle apparatus and the mini paddle apparatus (data not shown). This effect was independent of the test conditions and even extreme rotational movement of the SmartPill® at the vessel bottom did not lead to significant

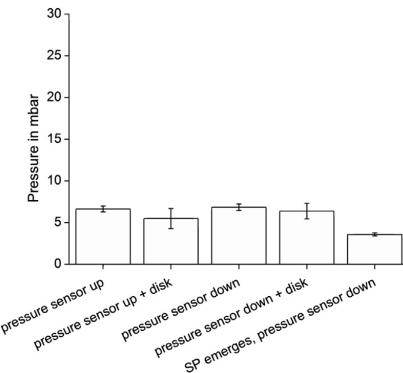


Fig. 2. Pressures measured by the SmartPill® using the disintegration tester under different test conditions. SP – SmartPill®. Means \pm SD, $n = 30$.

pressures.

3.1.3. USP apparatus 3 (reciprocating cylinder apparatus)

The reciprocating cylinder apparatus produced the highest pressures among the four standard test methods. The maximum pressures had a magnitude of about 14 mbar, which were nearly independent of the used mesh size or the applied dip rate (Fig. 3). Decreasing the media volume resulted in clearly lower pressure values.

3.2. Dynamic open flow through test apparatus

The results obtained using the dynamic open flow through test apparatus clearly showed that the different gastric pressure profiles obtained *in vivo* with the aid of the SmartPill® can be simulated *in vitro* (Fig. 4). The simulation of all *in vivo* gastric pressure profiles using the dynamic open flow through test apparatus was successfully performed. The measured pressures were in good approximation to the *in vivo* data. However, slight deviations could be observed especially for lower pressure values. For instance, some pressure peaks in the range of 50–100 mbar were not correctly simulated during *in vitro* testing (Fig. 4). In particular for subject 3, the values in the dynamic open flow through test apparatus were on a lower level throughout the whole test. Furthermore, the reproduction of the applied pressures showed small deviations between the same values. The maximum differences between

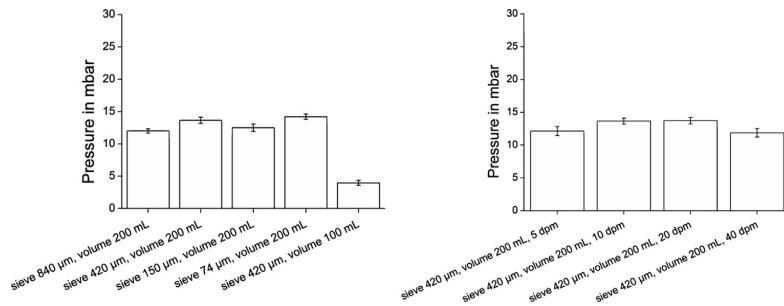


Fig. 3. Pressures measured by the SmartPill® using the reciprocating cylinder apparatus under different test conditions. Means \pm SD, $n = 10$.

same applied pressure values were observed in the range of 200–300 mbar and amounted to 33 mbar. However, most values were within the initially specified range (cf. Section 2.3.2. Simulation of gastric pressure profiles).

4. Discussion

It is generally accepted that the stomach accelerates disintegration and drug release of dosage forms by contributing the highest stresses

among the different sections of the gastrointestinal tract. Therefore, it is not surprising that several novel in vitro dissolution models at least partly account for the complex gastric motility (Bellmann et al., 2016; Kostewicz et al., 2014; Koziolka et al., 2013). These physiologically relevant dissolution tools can aid the development of oral dosage forms as they can potentially explain in vivo drug release profiles that cannot be understood by using compendial methods. An example to be mentioned within this context is the sensitivity of hydrogel matrix tablets to biorelevant compression. Garbacz and colleagues investigated the drug

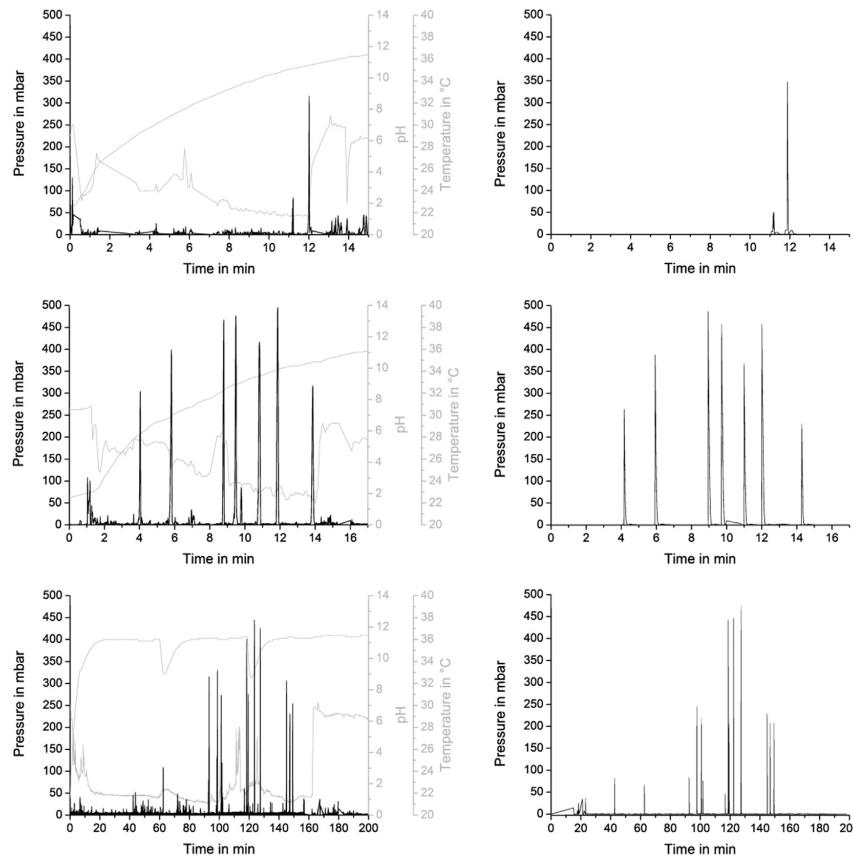


Fig. 4. Gastric pressure profiles measured *in vivo* after fasted state ingestion of the SmartPill® (left) and pressure profiles obtained using the dynamic open flow through test apparatus (right).

release from such tablets with the aid of the dissolution stress test apparatus. This study indicated that observed variability in plasma concentration profiles most likely arise from varying stresses during gastrointestinal transit (Garbacz et al., 2008). The compendial paddle apparatus was not able to identify this drug release behavior. The feasibility of simulating a broad range of possible pressure profiles in vitro may aid to explore the roots of possible in vivo variability of drug plasma concentration profiles. Differences in drug release behavior between edge conditions then are an indicator for the sensitivity of oral dosage forms towards certain parameters. A dosage form that exhibits a stable drug release behavior under different edge programs most likely exhibits less variable plasma profiles in vivo. This could be shown in another study by Garbacz and colleagues, who investigated nifedipine hydrogel matrix tablets. The variability of plasma concentration that was observed in vivo could be explained in vitro by the lack of mechanical robustness. On the other hand, the dissolution behavior of nifedipine OROS tablets showed no significant pressure sensitivity, which leads to reproducible plasma profiles (Garbacz et al., 2009). A similar approach was followed in a recent study by Koziolek and colleagues, in which three different pressure programs were applied with the aid of the Fed Stomach Model to simulate the edge conditions of gastric transit (Koziolek et al., 2014). This study showed highly variable dissolution data for diclofenac sodium MR tablets under the different conditions.

Although the mentioned studies offer a good estimation of the in vivo behavior of the tested dosage forms, the applied pressure programs are artificial and run the risk of over- or underestimating edge conditions. Furthermore, the mentioned in vitro models simulate gastric motility in a simplified and abstract way in order to ensure full control over critical parameters. It seems logical then to verify the correct transfer of applied pressures in vitro with the aid of a reference system like the SmartPill®, since deviations between in vitro applied and in vivo measured values are likely to occur.

In contrast to the mentioned novel dissolution models, compendial methods lack the possibility of simulating physiologically relevant stresses. In the present study, we examined the mechanical conditions in various standard test apparatuses. We could show that none of the devices was able to replicate the in vivo conditions with respect to compressive forces. Interestingly, the reciprocating cylinder apparatus was primarily designed for testing of MR dosage forms and the higher stresses caused by increased dip rates shall better depict gastrointestinal motility compared to the standard paddle apparatus (Dressman and Krämer, 2005; Yu et al., 2002). In the present study, we observed periodic pressure peaks in the reciprocating cylinder apparatus and disintegration tester (Fig. 5). Their frequency matched the set dip rate and maximum pressure values occurred only once during a whole cycle including upward and downward movement. A possible explanation for the origin of measured peaks could be the acceleration due to the turn of the cylinder at the deepest point of the vessel. On the other hand, literature data for the USP apparatus 3 and the disintegration tester suggest maximum velocities at midway positions during the downward and upward stroke of the cylinder, which could also be a source of stress (Kamba et al., 2003; Perivilli et al., 2015). However, after calculating the height of the water column that is needed to produce the measured pressure values, it became clear that the peaks most likely derived solely from the hydrostatic pressure at the deepest point of the cylinder. This assumption was supported by decreased pressure values in experiments with reduced volumes. Furthermore, these data indicated that shear forces were not sufficiently detected by the SmartPill®.

Similar observations could be made in the paddle apparatus. Despite extreme rotational movement of the SmartPill® at 250 rpm, significant pressure peaks could be detected neither in the standard paddle apparatus nor the mini paddle apparatus. This is also partly explainable by hydrodynamics inside the vessel, due to which the SmartPill® was forced to the bottom. At this point, the velocities and subsequently stresses are minimal according to computational fluid dynamics and

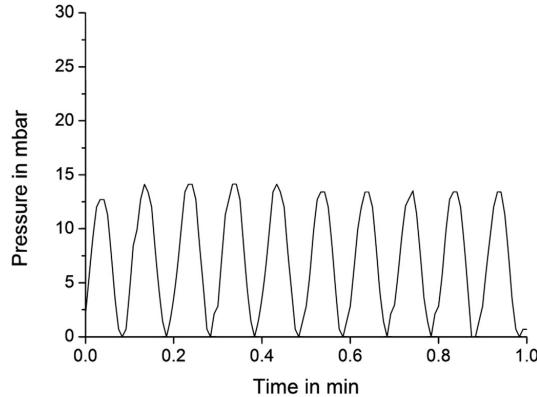


Fig. 5. Exemplary SmartPill® profile showing periodic fluctuations observed in the reciprocating cylinder apparatus at 10 dpm. A sieve size of 420 µm and a volume of 200 mL were applied.

laser-Doppler velocimetry data (Bai et al., 2007; Baxter et al., 2005).

Since significant compression forces were not measured by the SmartPill®, these data indicated that shear stresses at high rates must be the main reason for dosage form disintegration in the standard apparatuses. This explanation is in line with literature data (Vardakou et al., 2011a), but it is also supported by comparing dissolution data from paddle apparatus and reciprocating cylinder apparatus for hydrogel matrix tablets. As already mentioned, such tablets are sensitive to biorelevant pressure events leading to increased dissolution rates (Garbacz et al., 2009, 2014a). If the compression forces in the reciprocating cylinder apparatus would be significantly higher than in the paddle apparatus, clearly increased dissolution rates should result in comparison to the paddle apparatus. However, several authors demonstrated comparable dissolution data for different hydrogel matrix tablets that were tested in both apparatuses at 100 rpm versus 5–10 dpm, respectively (Klein and Dressman, 2006; Missagh and Fassihi, 2005). These data indicate that the compressive forces in both devices have to be more or less comparable. Simply increasing the rotational speed or dip rate does also not lead to a better simulation of gastric motility. In a recent study by Vardakou et al., the grinding forces achieved by the Dynamic Gastric Model and the paddle apparatus were compared (Vardakou et al., 2011b). Even at high rotational speed of the impeller, it was shown that the paddle apparatus is not able to generate forces of physiological relevance. Similar observations were also made by other authors (Aoki et al., 1993; Souliman et al., 2007). Our data suggested that this is true for each of the investigated standard methods. In standard apparatuses usually high shear stresses at higher rates occur than to be expected in vivo (Kong and Singh, 2008; Vardakou et al., 2011a).

Novel biorelevant dissolution models try to overcome the limitations of compendial methods by using different techniques to simulate gastrointestinal motility (Garbacz et al., 2008; Koziolek et al., 2014; Minekus et al., 1995; Vardakou et al., 2011b; Vatier et al., 1994). The dissolution model that was used in the present study transfers forces to dosage forms via the inflation of a balloon (Garbacz et al., 2008, 2014b). For this purpose, the tested object is placed in a spherical steel mesh that houses the balloon and defines its maximum expansion. In this way, individual in vivo pressure profiles from clinical trials could be accurately simulated in vitro. As already demonstrated in previous studies, the increase of in vitro drug release rate of dosage forms can strongly depend on frequency and strength of simulated pressure events (Garbacz et al., 2008, 2009, 2014a; Koziolek et al., 2014). Therefore, a thorough knowledge of possible pressure profiles as well as the feasibility of their correct simulation seems mandatory during in vitro

testing. By this, we believe the explanatory power of the model to increase, since applied test programs can now cover real *in vivo* observed edge conditions. Furthermore, the artificial test programs that shall simulate these edge conditions can also be optimized. The necessity for this is indicated by comparing the previously applied artificial test programs from recent studies with the simulated *in vivo* data from the present work. Especially the upper edge conditions regarding high frequent pressure activity were drastically underestimated in previous studies (Garbacz et al., 2008, 2009). For their simulation, previous investigations included three pressure peaks above 200 mbar after 20 min. In the present work we simulated 7 pressure peaks within 14 min with three of them above 400 mbar. Therefore, the already observed accelerated drug release *in vitro* is considered to be significantly higher.

The value of the dynamic open flow through test apparatus for the simulation of such profiles could be shown. However, some limitations have to be mentioned. The major drawback of the model is the inability to exert pressures below 50 mbar, since the balloons need a minimum pressure for expansion. The use of the SmartPill® for the measurement of pressure events *in vitro* can also be debated. The pressure sensor of the SmartPill® measures the forces transmitted by an outer flexible coat. In the case of the dynamic open flow through test apparatus, the applied pressures may be transferred incorrectly. During inflation of the balloon the SmartPill® was pressed against the spherical steel mesh which may result in a gap below the pressure sensor. In this case the measured forces originate solely from the part of the sensor that is heading in the direction of the balloon, which results in overestimation of the pressures that are necessary to simulate *in vivo* conditions. In this context, the size of a tested dosage form may affect the transmitted forces *in vitro*. But also *in vivo* this is assumed to affect the occurring stresses. Larger dosage forms are then considered to experience an early and sharply rising compression whereas very small dosage forms (e.g. pellets) may experience nearly no compression during the concentric occlusion of the antrum. Furthermore, the transferability of SmartPill® data is most likely restricted to larger indigestible objects since they are mainly emptied during phase III of the interdigestive motility complex, where strongest contraction waves occur (Cassilly et al., 2008). Smaller dosage forms may not be retained to this extent, thus the presented upper edge conditions may not be applicable.

However, the data showed that the novel *in vitro* model was able to simulate a wide range of pressures and the use of the SmartPill® for the first time enabled the direct comparison with human *in vivo* data. Although, the SmartPill® was recently used by Bellmann and colleagues to link *in vivo* occurring pressures with data from the TImage, the reproduction of exact time points and extent was only shown for pressure events up to 25 mbar, which are considered to be equal to gastrointestinal baseline pressures measured by SmartPill® (Bellmann et al., 2016). For many problems, new biorelevant *in vitro* dissolution tools are superior to compendial methods. However, it has to be kept in mind that compendial methods were developed as easy and reproducible standards in order to compare dissolution data of different batches or laboratories. Their use for biorelevant dissolution experiments in order to explain *in vivo* phenomena is restricted to special cases and parameters (e.g. pH-dependent drug dissolution). Therefore, novel *in vitro* dissolution models are able to better explain certain *in vivo* phenomena. However, their use is restricted to explanatory purposes as reproducible testing of product quality is hardly possible or economic yet.

5. Conclusion

We successfully used the SmartPill® GI monitoring system to characterize occurring pressure events in standard test apparatuses and the dynamic open flow through test apparatus. By this, we were able to compare the obtained data with *in vivo* pressure profiles. Our results showed that none of the investigated standard test apparatuses was able

to produce pressure peaks of biorelevant extent. Among the standard test apparatuses, the disintegration tester and the reciprocating cylinder apparatus produced highest values that most likely derived from hydrostatic pressure. In contrast, the dynamic open flow through test apparatus enabled the simulation of complete gastric pressure profiles as they occur *in vivo*. By this, the explanatory power of novel *in vitro* dissolution tools may significantly increase.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Influence of postprandial intragastric pressures on drug release from gastroretentive dosage forms

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Beiträge der Autoren

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Erstellung der Arbeitshypothese, Planung und Durchführung der praktischen Arbeiten, Erstellung des Manuskriptes

Melanie Hoppe

Mitarbeit bei der Durchführung der praktischen Arbeiten

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Influence of postprandial intragastric pressures on drug release from gastroretentive dosage forms

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Manuscript Body

1 **ABSTRACT**

2 Despite extensive research in the field of gastroretentive dosage forms, this “holy grail” of
3 oral drug delivery yet remained an unmet goal. Especially under fasting conditions, the
4 reproducible retention of dosage forms in the stomach seems to be an impossible task. This is
5 why such systems are often advised to be taken together with food. But also the postprandial
6 motility can contribute significantly to the failure of gastroretentive dosage forms. To
7 investigate the influence of postprandial pressure conditions on drug release from such
8 systems, we used a novel in vitro dissolution tool, the dissolution stress test device. With the
9 aid of this device, we simulated three different **intragastric** pressure profiles that may occur
10 after postprandial intake. These transit scenarios were based on recently obtained,
11 postprandial SmartPill® data. The tested systems, Glumetza® 1000 and Madopar® HBS 125,
12 are marketed dosage forms that are based on different approaches to achieve proper gastric
13 retention. All three transit scenarios revealed a highly pressure sensitive drug release
14 behavior, for both drugs. For Madopar® HBS 125, nearly complete drug release was
15 observed even after early occurring pressures. Glumetza® 1000 seemed to be more resistant
16 to these, most likely due to incomplete wetting of the system. On the contrary to these
17 findings, data from standard dissolution tests using the paddle apparatus displayed controlled
18 drug release for both systems for about 6 h. Based on these results, it can be doubted that
19 established gastroretentive systems stay intact over a longer period of time, even under
20 postprandial conditions.

21 **KEY WORDS**

22 SmartPill, Gastric pressure, Dissolution stress test device, In vitro model, Gastroretentive
23 dosage forms

24 INTRODUCTION

25 Despite decades of extensive research in the field of gastroretentive dosage forms, very few
26 concepts were at best partly satisfactory *in vivo*. Although some dosage forms on the market
27 are termed gastroretentive, the goal of a clearly prolonged gastric residence time under
28 different prandial conditions has not been demonstrated yet. But still, gastroretention of solid
29 oral dosage forms remains highly desired for certain drug substances in order to **reduce**
30 stability issues, to improve bioavailability and to reduce dosing intervals (1,2).

31 In general, the three main approaches to achieve prolonged gastric residence time include (I)
32 mucoadhesion to the stomach wall, (II) floating on top of gastric contents and (III)
33 **swelling**/expansion at best beyond the size of the pyloric resting diameter (2,3). However, the
34 outcome of *in vivo* studies, in which these concepts were tested, and the increased
35 understanding of gastrointestinal physiology revealed that there are still considerable hurdles
36 to overcome. Mucoadhesive systems mainly suffer from the high, stimulated gastric secretion
37 rate, which can amount to values of about 10 mL/min (4-6). The basic requirement for
38 floating systems is the presence of gastric contents. Contrary to this, the residual gastric
39 volume in fasted state is only about 50 mL and the 240 mL water that are usually co-ingested
40 together with the dosage form, were shown to be emptied within about 30 minutes (7-9). Not
41 only for expandable systems but for all approaches, the gastric motility is the major challenge,
42 especially during the fasted state. In phase III of the interdigestive migrating motor complex
43 (MMC) strong propulsive contraction waves, able to empty even large objects, clean the
44 stomach from indigestible material (10). However, this fasted state motility can be interrupted
45 by the intake of food or caloric liquids, which results in a change of the motility pattern
46 (11,12). Large and expandable objects have been demonstrated to be retained in the stomach
47 during postprandial motility and also floating systems could exhibit prolonged residence time
48 under fed conditions (13). However, these systems offer only limited therapeutic advantages
49 over conventional extended release dosage forms (1,13). A putative proof of functionality of
50 gastric retention principles may also arise from the choice of improper animal models. For
51 example, ruminant animals like cattle, sheep and goats will not empty larger particles from
52 their stomach. But also pigs show very long gastric retention times for large objects (14).

53 Apart from the physiological factors mentioned above, no or little attention has been paid to
54 intragastric forces acting on gastroretentive dosage forms. High gastric pressures have been
55 shown to increase drug release rate of specific dosage forms and are considered to be **highest**

56 during phase III of the MMC (10,15). Moreover, postprandial intake may lead to similar
57 stresses on dosage forms (16,17). With the dissolution stress test device Garbacz and
58 colleagues could demonstrate in vitro that especially hydrogel matrix tablets are
59 sensitive towards intragastric pressures (15,18). As a result of such stresses, the drug
60 release rate is significantly increased which explains dose dumping or irregular plasma
61 profiles of such dosage forms in vivo (15,18). Based on those findings, it is likely that the
62 in vivo performance of sustained releasing gastroretentive systems is also affected by
63 intragastric pressure events and hence, a thorough understanding of gastric motility is
64 mandatory to comprehend their in vivo drug release behavior. In recent years, data from
65 freely movable telemetric capsules that are able to measure luminal pressures (SmartPill®),
66 expanded our knowledge of the gastrointestinal conditions that large non-disintegrating
67 dosage forms experience (10,17,19). Besides providing deeper insights into gastric motility in
68 health and disease, the pressure data can be used to improve novel in vitro dissolution tools,
69 such as the dissolution stress test device (20). Owing to the lack of predictive and
70 explanatory power of the current in vitro tools with respect to the in vivo performance of
71 gastroretentive dosage forms, there is an increased need for the implementation of these
72 physiological data (1). It seems obvious that usual tests for parameters such as floating time
73 or swelling ratio along with standard dissolution test methods are not able to fully characterize
74 novel gastroretentive dosage forms with respect to their drug release behavior in vivo.

75 The aim of the present study was to investigate the influence of in vivo occurring intragastric
76 pressure events on the drug release behavior of two products that are marketed as
77 gastroretentive systems (Glumetza® 1000, Madopar® HBS 125). For this purpose,
78 intragastric pressure data, obtained by using the SmartPill® in healthy volunteers (17), were
79 considered during in vitro dissolution testing. First, we defined test scenarios as basis for in
80 vitro simulation of realistic gastric conditions experienced by gastroretentive dosage forms. In
81 a next step, we used the dissolution stress test device that was developed by Garbacz and
82 colleagues (15) and applied these scenarios during in vitro dissolution testing of the
83 mentioned products. **Madopar® HBS and Glumetza® 1000 represent the most promising**
84 **and most marketed gastroretentive concepts (i.e. floating and large in size).** Thereby, the
85 **broad applicability of the dissolution stress test device regarding the in vitro testing of**
86 **gastroretentive systems should be demonstrated.**

87 MATERIALS AND METHODS

88 Materials

89 Hydrochloric acid (Merck, Darmstadt, Germany) and sodium chloride (Carl Roth, Karlsruhe,
90 Germany) were used for preparation of the dissolution medium (Simulated Gastric Fluid *sine*
91 *pepsin*). For the preparation of standards, metformin hydrochloride and levodopa were
92 purchased in form of powder from Alfa Aesar (Karlsruhe, Germany). **Investigated products**
93 **were Glumetza® 1000 (Valeant, Laval, Canada) and Madopar® HBS 125 (F. Hoffmann-**
94 **La Roche, Basel, Switzerland).** Glumetza® 1000 is a large, oval shaped tablet (12 mm
95 [w] x 20 mm [l] x 10 mm [h]) containing metformin hydrochloride, a BCS class III
96 compound which occurs in its highly soluble cationic form (pKa 11.5) in GI fluids (21).
97 The sustained release is achieved via diffusion controlling coating (22,23). Amongst
98 others, the tablet contains polyvinyl alcohol, hypromellose, polyethylene glycol,
99 polyacrylate dispersion and crospovidone. Madopar® HBS consists of a hard gelatin
100 capsule containing levodopa (BCS class III) and benserazide hydrochloride (24).
101 Amongst others, it contains povidone, hypromellose and hydrogenated vegetable oil. The
102 contents are considered to form a sustained releasing, mucous body that floats on top of
103 the gastric contents by exhibiting a density below 1 g/cm³ (25).

104 SmartPill® GI monitoring system

105 The SmartPill® GI monitoring system (Medtronic plc, Dublin, Ireland) consists of a
106 telemetric capsule (13 mm x 26 mm), a data receiver and the MotiliGI® software. The
107 receiver is equipped with an event button that allows registering any events relevant for data
108 analysis and interpretation. The telemetric capsule is able to measure pressure, pH and
109 temperature. In **the present** study, the baseline **corrected** pressure data were used for data
110 analysis (**cfr. reference 20**). The data were analyzed by OriginPro 8.5.1.G (OriginLab
111 Corporation, Northampton, MA, USA).

112 Dissolution stress test device

113 The dissolution stress test device was used to simulate physiologically relevant **pressure**
114 **profiles** during in vitro testing of the two drug products. The device allowed us to exert
115 pressure events of different magnitudes on the dosage forms and to simulate dosage form
116 movement as occurring in vivo. A detailed description of the device is given elsewhere (15).
117 In brief, the central part of the device is a pipe-like bar with probe chambers attached. The

118 spherical probe chambers consist of steel netting wire and hold the dosage form during
119 dissolution testing. Balloons inside the probe chambers can be inflated via compressed air
120 supply which results in an exerted pressure event. Moreover, a stepping motor can rotate the
121 bar with subsequent movement of the dosage forms within the probe chambers. The probe
122 chambers are submerged in standard vessels containing dissolution medium, which is
123 adequately stirred by an impeller.

124 *Simulation of gastric pressure profiles*

125 For the simulation of realistic pressure profiles, we used data from a previously published
126 study in which the SmartPill® was administered to 19 healthy human subjects **under**
127 **postprandial conditions according to the FDA guidance on food-effect bioavailability**
128 **and fed bioequivalence studies. Detailed information is given elsewhere (17).**

129 We analyzed all 19 pressure profiles with focus on characteristic intragastric pressure events.
130 If possible, we checked a connection of these events with information recorded by the
131 subjects via event button. Interestingly, in some cases food intake and drinking seemed to
132 favor the occurrence of pressure events. In most of the subjects, the administered standard
133 breakfast, water and lunch led to few and only slight pressure events. However, in five
134 subjects, the intake of a standardized lunch caused pressure events of more than 200 mbar at
135 high frequency. In between the meals, only smaller pressure events were observed. In three
136 subjects, a small dinner resulted in an increased pressure activity with amplitudes of more
137 than 100 mbar. In most cases, the highest pressures (up to 500 mbar) were recorded during
138 gastric emptying of the SmartPill®.

139 Based on the in vivo data for the different subjects, we defined three exemplary transit
140 profiles for each case that was mentioned above, i.e. pressure events after lunch, after dinner
141 and upon gastric emptying. Based on the amplitude, the pressure events from the in vivo study
142 were classified into five ranges (50-100 mbar, 100-200 mbar, 200-300 mbar, 300-400 mbar,
143 400-500 mbar). Together with the corresponding time points, these classes formed the basis
144 for the in vitro simulation of the pressure profiles in the dissolution stress test device. In order
145 to simplify the test programs, the following pressures were used to represent the five classes:
146 50, 150, 250, 350 and 450 mbar. To assure comparability between the in vitro pressures with
147 the ones determined in vivo, an activated SmartPill® was placed inside a probe chamber on a
148 silicone inlay and used to calibrate the dissolution stress test device.

149 Based on the pressure profiles observed in vivo, we defined three realistic transit profiles that
150 should simulate the borderline conditions and the “average” profile (Fig 1). Thereby,
151 **program 1** (P1) was the low stress program with no pressure events occurring during gastric
152 transit except for gastric emptying. Program 2 (P2) was regarded as the average profile.
153 Program 3 (P3) displayed the high stress program, with the maximum number of pressure
154 events. In particular early occurring pressures were considered. For all test programs, we
155 assumed a considerable prolongation of gastric residence time for the investigated
156 gastroretentive dosage forms and thus, the time point of simulated gastric emptying in all test
157 programs was set to 24 h.

158 *Test conditions*

159 **Other important parameters (e.g. pH, temperature) were kept constant throughout the**
160 **experiments in order to correctly interpret the dissolution data regarding the possible**
161 **influence of intragastric pressures on drug release. Therefore,** the dissolution stress test
162 investigations were performed at a rotational speed of the impeller of 75 rpm. Simulated
163 gastric fluid *sine pepsin* (SGF sp) pH 1.2 at 37 °C was used as a dissolution medium. The
164 media volume was 1100 mL. All tests were performed in triplicate. For the correct exertion of
165 pressure, the spherical probe chambers contained silicone inlays on which the dosage forms
166 were placed during dissolution testing. Slight intragastric movement of the dosage form was
167 simulated by the rotation of the central bar at 10 rpm every 5 min during each program.

168 *Analytics*

169 Measurements were performed with fiber optics at least every 5 min for a period of 24 h.
170 During phases of high frequency pressure events the measurement intervals were decreased to
171 every 3 min. Sample analysis was done with an UV/Vis spectrophotometer (Varian Cary® 50
172 Bio UV-Vis Spectrophotometer, Agilent Technologies, USA). For this purpose, levodopa and
173 metformin hydrochloride were measured at 279 nm (5 mm probe tips) and 235 nm (1 mm
174 probe tips), respectively. Data acquisition was performed with Cary WinUV software.
175 Volume loss over time due to evaporation was assumed linear and calculated based on the
176 initial volume and the volume at the end of each test.

177 **Standard dissolution testing**

178 Compendial dissolution tests were carried out in USP apparatus 2 (paddle apparatus, PT-
179 DT70, Pharma Test Apparatebau AG, Hainburg, Germany) at a rotational speed of 75 rpm.

180 Simulated gastric fluid *sine pepsin* (SGF sp) pH 1.2 at 37 °C was used as a dissolution
181 medium. The media volume was 1000 mL. Due to the floating of Madopar® HBS 125, the
182 capsules were placed in a sinker during dissolution testing. All tests were carried out in
183 triplicate. Drug release was measured with the aid of fiber optics every 5 min for 24 h. Sample
184 analysis was done with an UV/Vis spectrophotometer (Varian Cary® 50 Tablet UV-Vis
185 Spectrophotometer, Agilent Technologies, USA). The measurement parameters are consistent
186 with the ones described above (see *Test conditions*). Data acquisition was performed with
187 Cary WinUV software. Volume loss was considered as described above.

188 **RESULTS**

189 **Dissolution experiments with Madopar® HBS 125**

190 The dissolution data of Madopar® HBS 125 revealed a decreased levodopa release rate for
191 the dissolution stress test device running program 1 (P1) compared to compendial dissolution
192 testing. Around 80% of the drug was released after about 5 h in the paddle apparatus (Fig 2).
193 The results obtained with programs P1 and P2 showed that Madopar® HBS 125 is highly
194 pressure sensitive. In P2 the pressure sequence after 6 h resulted in a complete release of the
195 drug after around 8 h. In case of P3, drug release was even faster and complete drug release
196 was reached after around 6 h. Even the low amplitude pressure events during the first 90 min
197 led to 80% drug release after about 3 hours. In this case sampling was stopped after about
198 14 h due to complete drug release.

199 **Dissolution experiments with Glumetza® 1000**

200 In comparison to Madopar® HBS 125, the drug release from Glumetza® 1000 was slightly
201 slower. In the paddle apparatus, 80% of the drug was released after about 6.5 h (Fig 3).

202 Regarding the different programs in the dissolution stress test device, the slowest drug release
203 was again observed in P1. This can be attributed to the lack of pressure events except for
204 simulated gastric emptying at the end of the test. Under these conditions, 80% of the drug
205 were released after about 18 h. In contrast to what was seen for Madopar® HBS 125, the last
206 pressure sequence after 23.5 h increased drug release by about 20% within a short period of
207 time.

208 With respect to P2 and P3, it can be seen that during phases of highly frequent pressure events
209 a rapid increase of metformin release rate occurred. In both programs complete drug release

210 was reached already at the beginning of the pressure sequence at 6 h. Thus, the sequence of
211 smaller pressure events at about 12 h had no further effect. During the first 6 h of P3, in which
212 smaller pressure events were included at the beginning of the tests, the metformin release rate
213 was comparable to the data from the paddle apparatus. Sampling was stopped in P3 after 19 h
214 due to completed drug release. The results clearly indicated the pressure sensitivity of the
215 dosage form in terms of its drug release behavior.

216 DISCUSSION

217 Gastroretentive dosage forms remain a “holy grail” of oral drug delivery due to the various
218 potential benefits for oral pharmacotherapy, but also due to the fact that none of the dosage
219 forms developed in the last decades sufficiently demonstrated gastroretention especially in
220 fasted state. Thus, the total number of marketed dosage forms termed gastroretentive remains
221 limited so far (26).

222 At the moment, the most descriptive way to test potentially gastroretentive dosage forms is
223 via extensive in vivo investigations. In this connection, data from animal models such as the
224 pig or the dog have to be interpreted carefully, since anatomy and physiology of the human
225 gastrointestinal tract is significantly different. Even between animal species, great differences
226 are present (26,27). Consequently, time- and cost-intensive human in vivo studies remain the
227 gold standard for the evaluation of gastroretentive dosage forms. But here, several aspects
228 have to be considered. In particular, the study design and the nutritional regime are critical. It
229 was shown in recent studies that the intake of caloric food and liquids significantly prolongs
230 the gastric residence time of large non-digestible objects (10,19,28). For instance, Ewe and
231 co-workers could prolong the gastric residence time of non-disintegrating tablets for up to 10
232 hours by administering several meals and snacks (28). With respect to gastroretentive dosage
233 forms, this may lead to biased results in favor of the tested system (3,13). For example, the
234 gastroretention of Glumetza® 500 was nicely demonstrated under fed conditions, i.e. drug
235 administration after a heavy meal of approximately 1000 kcal, with 50% of the calories
236 coming from fat. In contrast, after fasted state intake the gastroretention of Glumetza® 500
237 remained limited (29,30). Berner and Cowles have further shown that a reduction of the fat
238 content of the co-administered meal from 50% to 30% already results in **a decrease of mean**
239 **gastric residence time of 5 h** (30).

240 In order to improve the success rate of the development of gastroretentive dosage forms,
241 powerful in vitro tools are needed that allow an early and descriptive evaluation. Owing to the

242 expected long gastric residence time of gastroretentive dosage forms, the biorelevant
243 simulation of physiological stresses arising during gastric transit seems to be highly important
244 for the in vitro testing of such **systems**. This was already noticed by Nakagawa and
245 colleagues, who developed a novel floating system and applied the paddle-beads method
246 proposed by Aoki et al. for drug release testing (31). In this setup, polystyrene beads within
247 the vessel of a standard paddle apparatus should lead to increased stress on the dosage form
248 (32,33). However, occurring collisions and additional stress due to the beads are evenly
249 distributed over the whole test duration, whereas this is clearly not the case *in vivo* (33-35).

250 A recent SmartPill® study showed that significant, single gastric pressure sequences can
251 occur after concomitant intake of the high-caloric, high-fat FDA standard meal and during the
252 following gastric transit (17). **Comparable** pressure events were already shown to affect drug
253 release from hydrogel matrix tablets *in vitro* and also hard gelatin capsules are influenced by
254 simulated intragastric pressures (18,36).

255 In order to detect possible drug release problems associated with **such** pressure events, we
256 developed an in vitro test setup that mimicked realistic gastric **pressure profiles**. The results
257 of **the present** study showed that both products, Glumetza® 1000 and Madopar® HBS, do
258 not stay intact under simulated gastric conditions for a longer period of time. Both
259 investigated dosage forms showed a drug release behavior that was sensitive to pressure
260 events as they occur in the human stomach under postprandial conditions. According to **our**
261 results, this may even lead to intragastric dose dumping. However, this does not necessarily
262 translate into a sharp plasma peak. **Drug that** is released in the stomach is likely mixed with
263 gastric contents **due to postprandial peristalsis**. Since gastric emptying under postprandial
264 conditions is significantly prolonged compared to fasted state, **gastric emptying and not the**
265 **drug delivery system itself will control the onset of drug concentration in plasma** (37).

266 Our data for Madopar® HBS indicated a high sensitivity towards pressures that are realistic
267 for the human stomach. The simulation of early pressure events of low amplitude already
268 caused a significant increase of drug release. Moreover, the experiments in the dissolution
269 stress test device revealed that the capsule contents were easily dispersed during the pressure
270 sequences (Fig 4). An *in vivo* study by Grahenen and colleagues with Madopar® HBS
271 suggests that **the gastroretentive properties of the drug are likely negligible**. **Comparable**
272 **pharmacokinetic profiles** after postprandial intake **can also be achieved by administering**
273 **a conventional, non-floating sustained release tablet** (38). Furthermore, based on the
274 results from **the present** study, the prolonged drug release from the intact system **is also**

275 **unlikely** under fasted conditions. Even if the dosage form is able to float in the fasted
276 stomach, it will most likely be destroyed by the intense peristalsis occurring during MMC
277 phase III (“**housekeeper** waves”).

278 In case of Glumetza® 1000, metformin release is controlled by a coating. Increased gastric
279 residence time is mainly enabled by the size but, as already mentioned, the success of this
280 principle is most likely restricted to postprandial conditions. In comparison to Madopar®
281 HBS, the dosage form was less affected by early pressure events of low amplitude. In
282 contrast, events of higher pressure at later time points resulted in complete drug release within
283 short periods of time, which indicates that the tablet was highly sensitive towards pressures in
284 the swollen stage. Figure 5 shows a photograph of one tablet during dissolution testing in the
285 dissolution stress test device. The disrupted coating (white) can be optically delimited from
286 the yellow balloon.

287 **The demonstrated in vitro** drug release behavior suggests that the oral bioavailability **may**
288 **be decreased significantly when gastric emptying happens early, e.g. after fasted state**
289 **intake of the drug.** Since early pressure events **during gastric emptying will have only**
290 **minor effects on drug release and intestinal pressure events were shown to be clearly**
291 **lower, the drug may stay intact during the whole gastrointestinal transit. A rapid gastric**
292 **emptying under fasting conditions could then lead to fecal excretion of a large portion of**
293 **the drug. For Glumetza® 500,** Schwartz and colleagues could **indeed** show that the **relative**
294 **oral** bioavailability drops to about 58% **when administered under fasting instead of**
295 **postprandial conditions** (29,30).

296 In the present study, physiological in vivo data on pressure events were implemented into the
297 biorelevant dissolution stress test device. By considering a broad range of possible transit
298 scenarios, we were able to simulate the extremes in terms of gastric stresses. However, some
299 limitations have to be mentioned. Assuming actual gastroretentive properties for the two
300 tested dosage forms, we defined a test duration of 24 h, which was based on maximum transit
301 times determined in the previous SmartPill® study. In **that** study, gastric residence times
302 were highly variable and ranged from 4.3 h to 20.2 h, mainly depending on the individual
303 eating habits of the subjects (17). Since the SmartPill® transit times are considered to be
304 comparable to the expected transit times of large monolithic dosage forms, it is likely that the
305 gastroretentive properties of the tested systems were overestimated. Furthermore, it is also
306 unclear whether the intragastric localization and thus, the pressure profile of the SmartPill® is
307 applicable to floating dosage forms. However, by applying three different pressure profiles,

308 the extremes of gastric transit were considered and pressure sensitivity for both systems could
309 be verified. These data further indicate high variability of drug release in vivo.

310 Our study demonstrated the value of simulating realistic gastrointestinal pressure events
311 during drug dissolution testing of gastroretentive dosage forms. Besides established methods
312 for the characterization of such dosage forms, a test investigating the sensitivity towards
313 physiologically relevant pressures can significantly improve the drug development process.

314 **CONCLUSION**

315 In the present study, we could show the value of considering realistic, intragastric transit data
316 during in vitro dissolution testing of gastroretentive dosage forms. By defining edge profiles
317 of gastric pressure events, the resulting data suggest high variability of plasma concentration
318 in vivo. The simulation of relevant gastric pressures was crucial for the drug release profiles
319 of the two tested dosage forms, which are marketed as gastroretentive systems. Besides the
320 well-known physiologic hurdles for gastroretentive systems to overcome, we could
321 demonstrate that intragastric pressure events are an additional factor that should be taken into
322 account during in vitro testing. Our results showed that appropriate in vitro tests to foresee the
323 mentioned problems could be highly valuable and may aid the drug development process of
324 novel gastroretentive systems.

325

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- 463

Figure Captions

1 **LEGEND TO FIGURES**

2

3 **Fig 1.** Pressure programs performed using the dissolution stress test device. Program 1 (P1), program
4 2 (P2) and program 3 (P3).

5

6 **Fig 2.** Levodopa release from Madopar® HBS 125 under different test conditions: P1 (top left, black),
7 P2 (top right, black), P3 (bottom, black) and in paddle apparatus (grey). Pressure events are indicated
8 by red lines. Mean \pm SD, n = 3.

9

10 **Fig 3.** Metformin release from Glumetza® 1000 under different test conditions: P1 (top left, black), P2
11 (top right, black), P3 (bottom, black) and paddle apparatus (grey). Pressure events are indicated by red
12 lines. Mean \pm SD, n = 3.

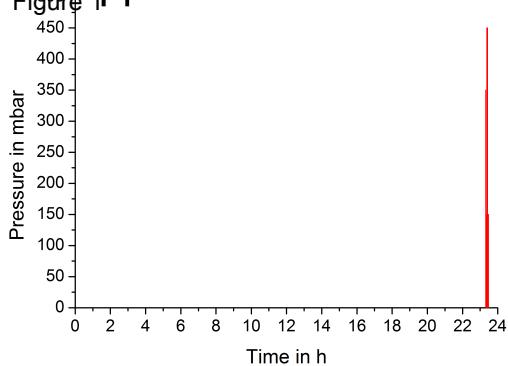
13

14 **Fig 4.** Photograph of Madopar® HBS after a pressure sequence.

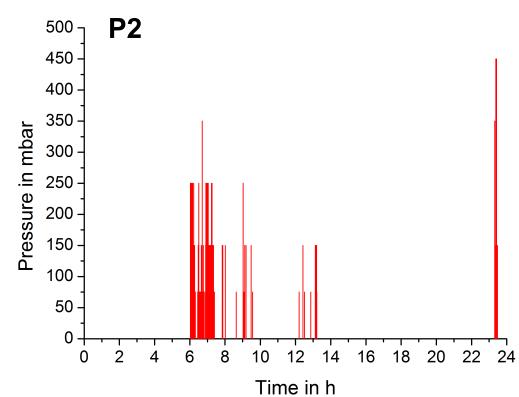
15

16 **Fig 5.** Photograph of Glumetza® 1000 after a pressure sequence. The red circle highlights the
17 disrupted coating (white).

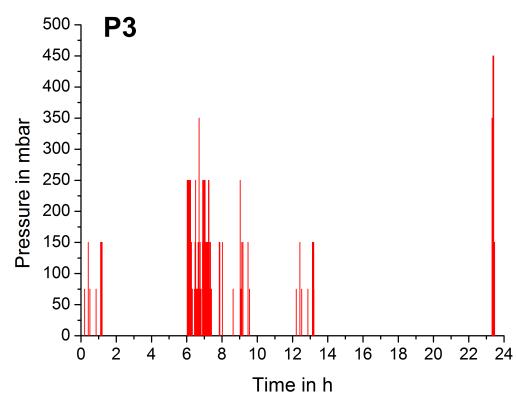
Figure 1P1



P2



P3



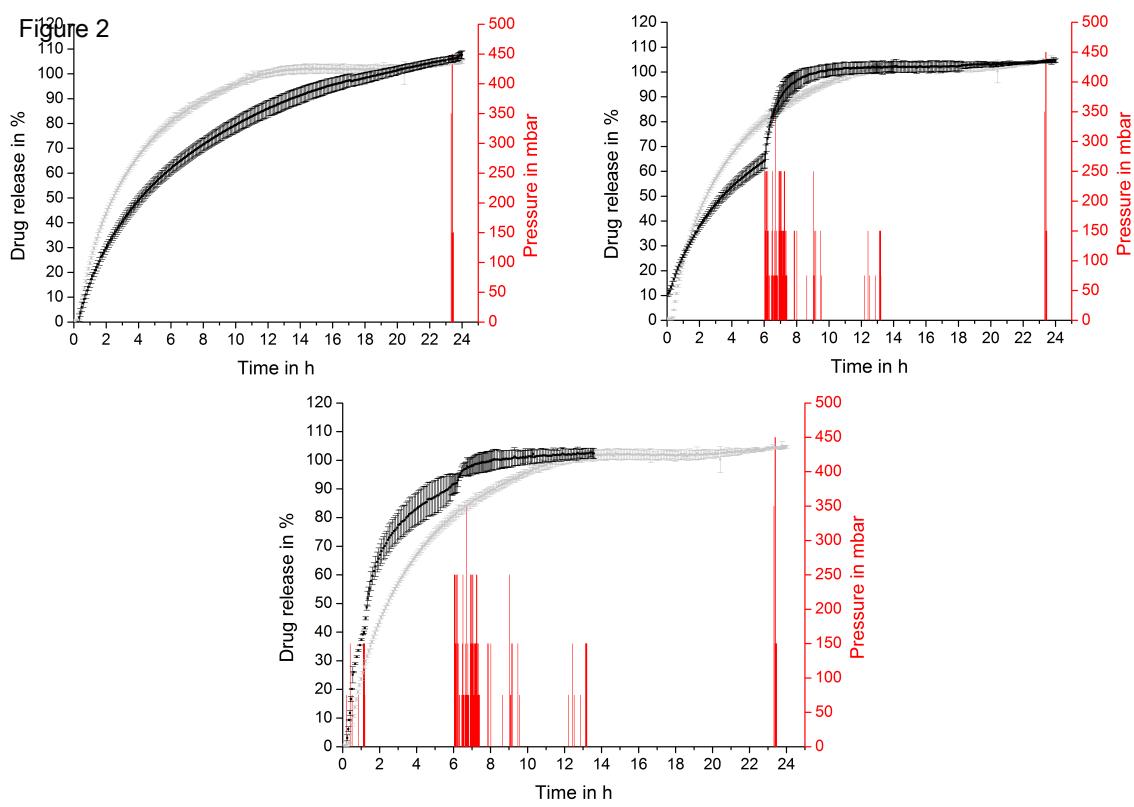


Figure 3

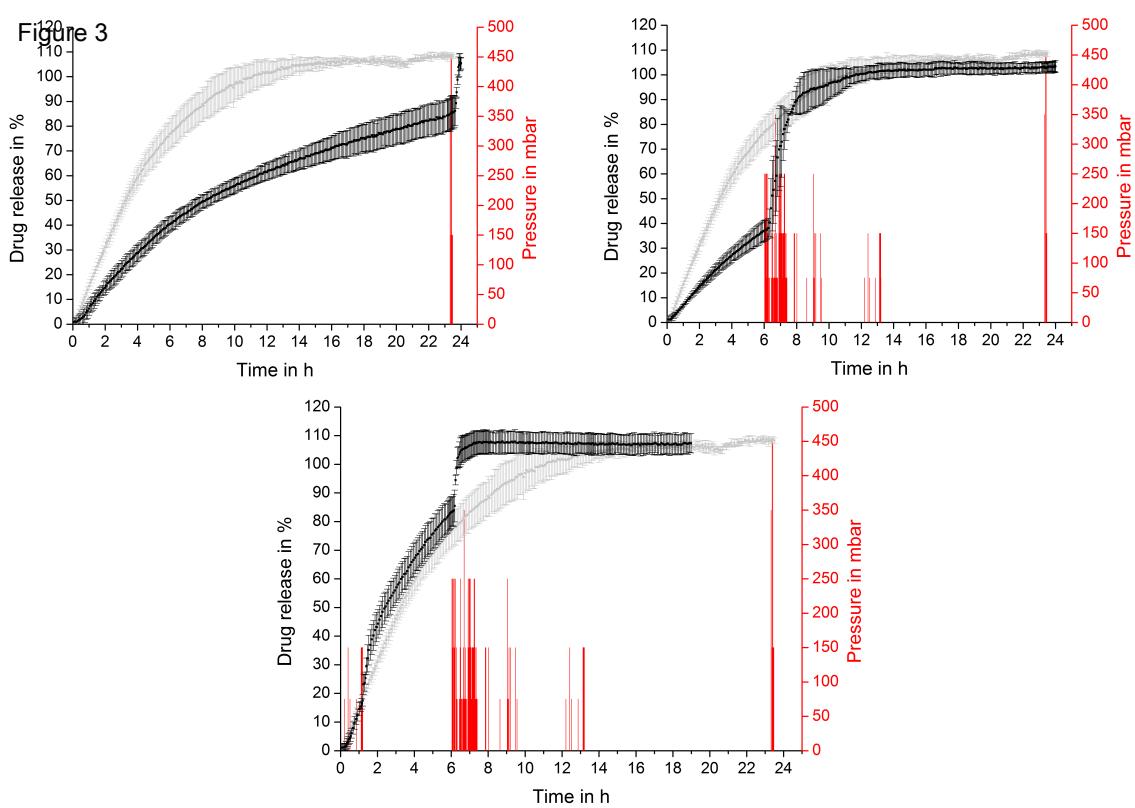


Figure 4

[Click here to download Figure fig 4.jpg](#) 

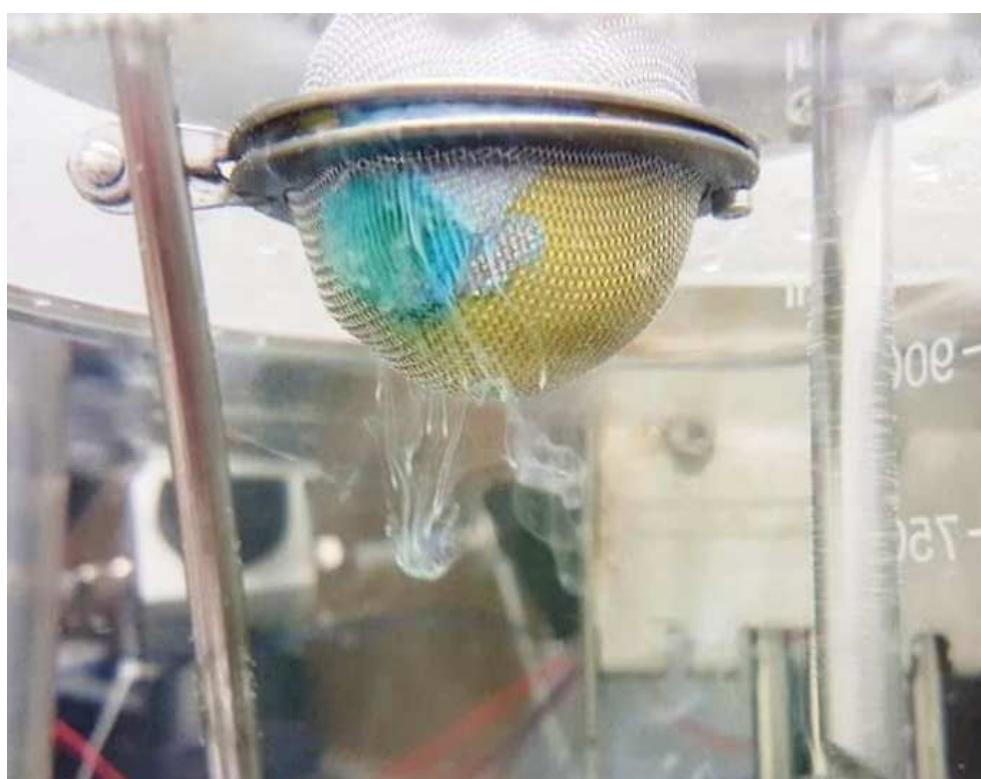


Figure 5

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Veröffentlichungsverzeichnis

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M. Koziolek, F. Schneider, M. Grimm, C. Modeß, A. Seekamp, T. Roustom, W. Siegmund, W. Weitschies. Intragastric pH and pressure profiles after intake of the high-caloric, high-fat meal as used for food effect studies. *Journal of Controlled Release* **2015**, 220, 71–78.

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