Strategies to design push-pull osmotic systems for delivering low and pH-dependent soluble drugs

Malaterre, Vincent

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Thèse de *Monsieur Vincent MALATERRE*

intitulée :

"Strategies to Design Push-Pull Osmotic Systems for Delivering Low and pH-Dependent Soluble Drugs"

La Faculté des sciences, sur le préavis de Monsieur R. GURNY, professeur ordinaire et directeur de thèse (Section des sciences pharmaceutiques – Laboratoire de pharmacie galénique), Madame N. LOGGIA, docteur et codirectrice de thèse (Novartis Pharma AG – Pharmaceutical Development – Life Cycle Management & Drug Delivery Technologies – Basel, Switzerland), Messieurs P. KLEINEBUDDE, professeur (University of Duesseldorf – Institute for Pharmaceutical Technology – Duesseldorf, Deutschland), et J.-C. LEROUX, professeur (Eidgenössische Technische Hochschule Zürich – Institut Pharmazeutische Wissenschaften – Galenische Pharmazie – Zürich, Swcheiz), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

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A ma famille

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TABLE OF CONTENTS

Chapter I

Introduction

INTRODUCTION

In the recent years, novel oral drug delivery systems have been recognized as an attractive niche for pharmaceutical industry. Among these systems, controlled-release formulations have been developed based on their significant advantages over conventional immediate release dosage forms, such as the decrease of dosing frequency, the increase of patient compliance, better dosing patterns, the reduction of side effects, or the maintenance of the drug concentration within a desired range, i.e, an overall improved therapeutic benefit. However, oral controlled release formulations are exposed to changing environment during transit through the GI-tract which may affect their performances e.g. physiological factors such as patient age or food-intake. Reported as releasing drug independently of these factors, oral osmotically-driven systems (OODS) have taken an increasing place in the MR field. Using osmotic pressure as driving force, various OODS designs and compositions have been developed and launched.

After more than 30 years clinical use, *Chapter II* of this thesis reviews the different OODS types and their role in drug delivery. The current situation is described through an extensive patent and publication review. Marketed products and technologies are detailed in terms of composition, applicability and benefits. Clinical benefits and risk are subsequently discussed highlighting the importance of consolidating the choice of the OODS technology and the expected benefit. This chapter introduces the push-pull osmotic system (PPOS) technology among the OODS showing that this technology is mainly used for delivering poorly and pH-dependent drugs.

In the subsequent *Chapter III*, the drug release mechanism of PPOS is investigated by magnetic resonance imaging (MRI). Hypothesized as dependent of the tablet hydration, this novel approach allows to monitor the hydration kinetics and thereby, investigate its influence on the drug delivery. This investigation highlights the key role played by the drug dispersion into the drug layer. Based on these results, the tablet core composition is optimized on *Chapter IV*, in order to modulate the drug release kinetics and increase the tablet drug load.

The two last chapters are dedicated to broaden the expertise in formulation and processing parameters. *Chapter V* is a systematic investigation of the PPOS

formulation. Results on a practically insoluble drug (isradipine) and a freely soluble drug (chlorpheniramine maleate) are given showing that the drug properties do not significantly influence the drug release. A modeling approach for dissolution profile is described highlighting the key role of the membrane composition for controlling the drug delivery. *Chapter VI* describes finally the development of an imaging method to characterize the membrane thickness. Two properties of Pulsed-TeraHertz signal are used to map the coating thickness distribution around the tablet and detect physical alterations in the membrane structure impacting the dissolution performances.

Chapter II

Oral osmotically-driven systems, an overview over 30-years development and clinical use

Review

Oral osmotically-driven systems: 30-years of development and clinical use

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Abstract

The number of marketed oral osmotically-driven systems (OODS) has doubled in the last ten years. The main clinical benefits of OODS are their ability to improve treatment tolerability and patient compliance. These advantages are mainly driven by the capacity to deliver drugs in a sustained manner, independent of the drug chemical properties, of the patient's physiological factors or concomitant food intake. However, access to these technologies has been restricted by the crowded patent landscape and manufacturing challenges. In this review article, we intend to give an overview of the last 30-years of OODS development, detailing the technologies, specific products and their clinical use. General guidance on technology selection is described in light of the recent advances in the field. The clinical performance of these technologies is also discussed, with a focus on food-effects and the *in-vivo in-vitro* correlation. Special attention is paid to safety given the controversial case study of Osmosin®. Overall, oral osmotically-driven systems appear to be a promising technology for product life-cycle strategies.

Keywords: osmotic pumps ; oral osmotic systems; GITS; OROS; controlled drug delivery; review; life cycle management

Table of contents

Abbreviations

ADHD: Attention deficit hyperactivity disorder
CPOP: Controlled porosity osmotic pump
COER: Controlled-onset extended-release
DDS: Drug delivery system
DOEOP: Drug overcoated elementary osmotic pump
EOP: Elementary osmotic pump
GI: Gastrointestinal
GITS: Gastrointestinal therapeutic system
IP: Intellectual property
IVIVC: *In-vivo in-vitro* correlation
MOTS: Muco-adhesive osmotic therapeutic system
OODS: Oral osmotically-driven systems
OROS: Oral osmotic systems
PPOP: Push-pull osmotic pump
PSOP: Push-stick osmotic pump
SCOT: Single composition osmotic tablet
SEOP: Self-emulsified elementary osmotic pump

1. Overview on 30-years of OODS development

Controlled drug delivery has taken an important place in pharmaceutical development, improving the tolerability and patient compliance with prescribed dosing regimens (1-3). Despite the predominant use of polymer-based systems, alternatives have been developed to decrease the influence of the various physiological factors that occur following food-intake or that are dependent on patient age (2-4). One of the most promising technologies is the oral osmotically-driven system (OODS) (4-6). Nevertheless, over the past 30 years the development of OODS technologies has been accompanied by controversies around product safety and concerns regarding the benefit /cost-of-good ratio. It is, therefore, interesting to begin this paper by reviewing the key milestones in OODS development.
Oral osmotically-driven systems have evolved from being device-concepts primarily for the delivery of veterinary medicines, namely Rose-Nelson (7), Higuchi-Leeper (8) and Higuchi-Theeuwes pumps (9). Using osmotic pressure as the energy source, the semipermeable membrane controls water inflow, generating hydrodynamic pressure inside the device and, thereby, controlling drug delivery. All of these technologies have in common the 'semipermeable' membrane controlling the drug delivery rate (Fig.1). Relatively complex and scalable with technical difficulties, a major milestone was achieved in 1974 with the description by Theeuwes and Alza's co-workers of a tablet design (9,10) composed of a compressed tablet-core surrounded by a semipermeable membrane with a single passageway (orifice), a so-called elementary osmotic pump (EOP). This design adaptation for human use was conveniently processable using standard tabletting and coating procedures and equipment (11). The first two products indomethacin, Osmosin®, (12) and phenylpropanolamine, Acutrim™, (13), were launched in the 1980s. In contrast to the originally anticipated business success (14-16), Osmosin® had to be withdrawn from the market due to severe side-effects such as GI irritation and perforation of the intestinal wall (17-19). This opened a crucial debate on (i) the safety of administering non-degradable systems such as OODS *per-os*, (ii) the prolonged delivery of irritating drug substances from delivery systems that are somewhat hindered in their transit through the GI tract and thereby delivering the drug to one small region of the gut wall (i.e. area of the GI mucosa directly facing the delivery system orifice) over extended periods of time and (iii) the importance of adapting the drug delivery system to the drug properties and risks.

Due to these adverse events seen with the OODS formulations of indomethacin, a well-known anti-inflammatory drug since the 50s (20-23), the use of OODS has for many years been associated with the amplified risk of stagnation of the dosage form in the GI tract.
Despite these events negatively affecting the reputation of these drug delivery systems, OODS development continued with two new OODS designs, the controlled-porosity osmotic pumps (CPOP) and the push-pull osmotic pumps (PPOP). The first of these was the CPOP, which was designed to decrease the risk of extremely localised drug-induced irritation at the site close to the orifice, as seen in the case of Osmosin®. The applicability of the OODS to poorly soluble drugs was targeted by using PPOP. Thus, nifedipine PPOP (Procardia XL®) was one of the most successful drug delivery systems of the last century, marking the revival of the OODS. This system was the gold-standard treatment for the management of hypertension (24-26) from 1990 to 1995. Despite the relatively low incidence of safety events (6) seen with Procardia XL®, there were continuous clinical controversies surrounding the risk of GI occlusions of this dosage form in patients with a certain disposition (27,28). In the 2000s, a new drug product based on OODS technology was formulated to deliver methylphenidate to children (above the age of 6 years) with attention-deficit hyperactivity disorder (ADHD). These delivery systems were based on a new design, the push-stick osmotic pumps (PSOP), which combined immediate and sustained drug release phases. This system, Concerta™,

seemed to mark the end of the controversies concerning good treatment compliance with the technology and demonstrated tolerability in children (29).
The history of the OODS reflects the difficulty in developing an innovative technology in the pharmaceutical field. Often times, the return on the initial investment made to develop the technology was delayed after several set backs during development. Currently, OODSs are becoming attractive technologies because of their abilities to enhance the clinical profile of certain therapeutic agents and to positively differentiate a drug product from others on the market. However, a systematic approach is needed in order to apply a coherent development strategy to future OODS products. Such a strategy should address the three fundamental questions, which are as follows:
- is the OODS technology safe for administering a specific drug?
- does the drug release profile over time match the target (desired) pharmacokinetics in the patient?
-to what extent is it beneficial in terms of the patient's compliance ?

Some elements needed to answer these questions are discussed in the following paragraphs, giving hints on the technology and clinical achievements reported in the scientific literature.

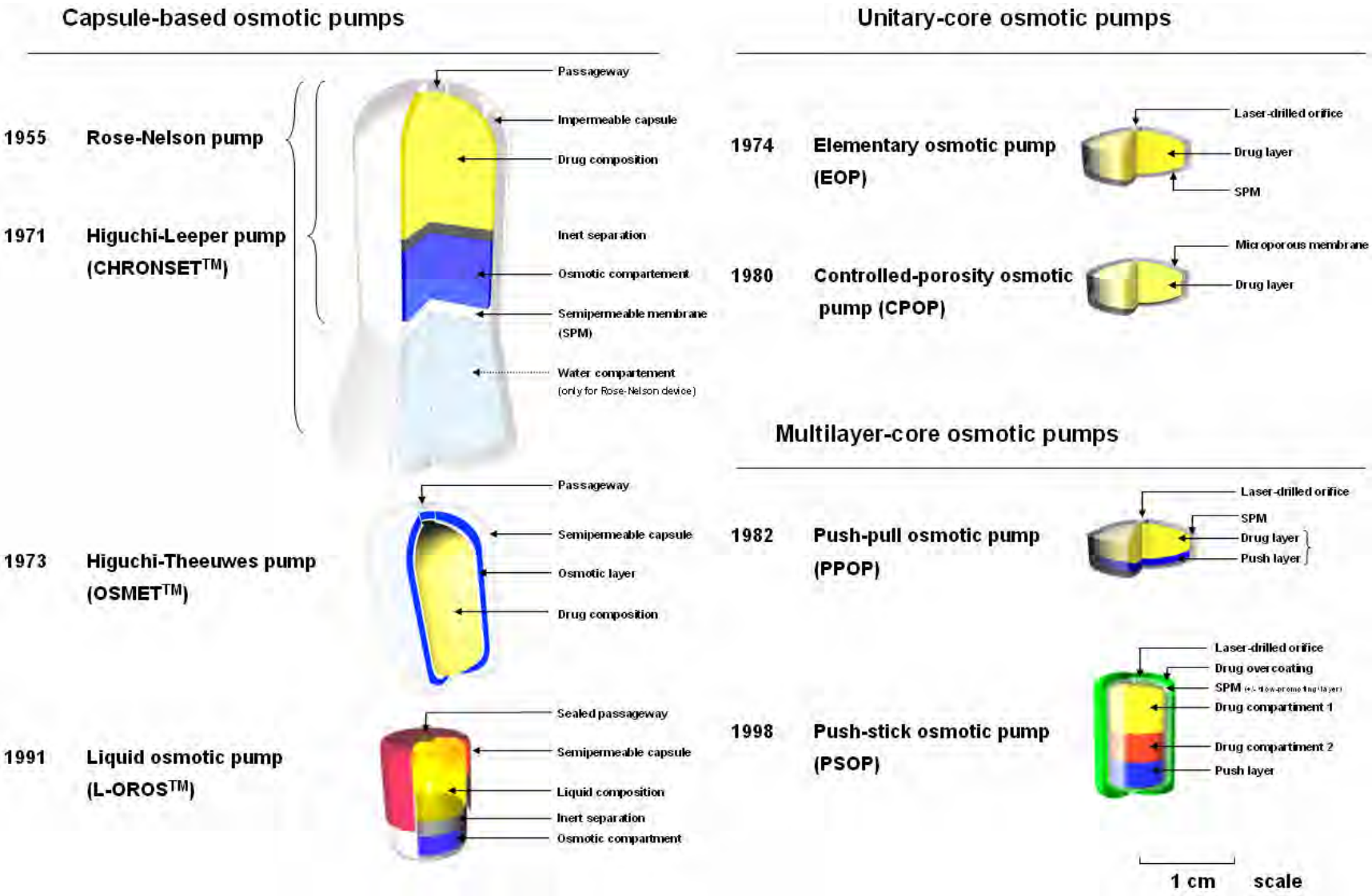

Fig. 1. Design evolution of the oral osmotically-driven systems

2. Current place of OODS

2.1. Literature review

The information sources dealing with OODS are relatively restricted and are often limited with respect to full retrieval of all technical details. As described in Fig. 2, information has been mainly obtained through intellectual property (IP) publications, which to some extent, are difficult to analyze and judge (30). Only 14 research papers were published on the formulation aspects of osmotic systems *versus* 161 patents on the same topic until the year 2000. In 90%, of these, Alza Corp co-authored these publications. In contrast, clinical results on nifedipine OODS are well documented in the literature with about 120 articles published in the 1990s. The situation changed in the 2000s with the expiration of the primary patents. After this time, there was a large entrance of competitors in the field with a subsequent increase in the number of new patents being filed. A growing field of IP covering various drug specific applications has been recorded over the last ten years, followed by more than 200 publications of clinical studies on bioequivalence, tolerability, safety and efficacy of generic formulations.
Some of these articles are very informative and disclose background on the formulation, clinical data and safety of OODS as summarized in Table 1. The excellent patent review written by Santus and Baker (30) describes the patent landscape and the evolution of the OODS design from the 1950s to the 2000s. Recent patent review updates were published in 2003 and 2007 (31, 32). Formulation and manufacturing aspects of oral osmotic systems were described in three reviews by Verma and Garg (11, 32, 33). Many clinical results were reviewed in two publications (4, 35) and the safety aspects were more specifically covered by Bass (6).

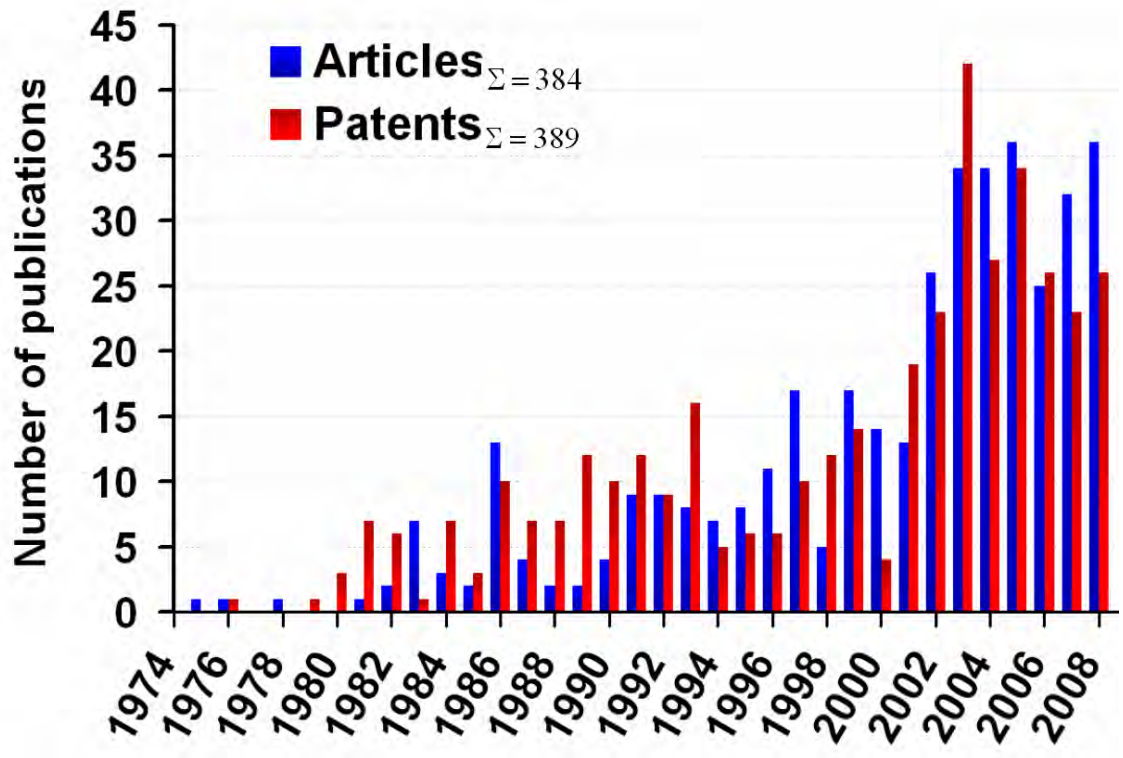

Fig. 2: Publications related to oral osmotically-driven systems
(Source: ISIweb of Sciences, Pubmed & EMBASE; micropatent, espacenet ; End date, Dec08)

Table 1. Leading articles focusing on OODS

Review on	First author	Year	Description	Ref.
Formulation	Theeuwes	1975	First article on the formulation of elementary osmotic pumps	(10)
	Theeuwes	1983	Formulation strategy to design EOP	(36)
	Verma	2000	Review on the OODS technologies	(33)
	Verma	2002	Review of formulation factors affecting the OODS drug delivery	(11)
	Verma	2004	Description of the OODS technologies and products	(34)
Patents	Santus	1995	Patent review of 240 patents dealing with osmotic systems	(30)
	Kaushal	2003	Update on the OODS patent review up to 2003	(31)
	Kumar	2007	Patent review up to 2006	(32)
Clinics	Conley	2006	Review of the OODS clinical use	(4)
	Meredith	2007	Comparison of the nifedipine controlled-release formulations	(35)
Safety	Bass	2002	Retrospective review on the gastrointestinal safety of OODS	(6)

2.2. Marketed products

Thirty-one products have been developed and marketed based on OODS technology. These products cover primarily the four following therapeutic areas: cardiovascular (35%), neurological (25%), seasonal (25%) and metabolic disorders (15%). These products have been mainly developed by two companies, the former Alza Corp., which was later acquired by Johnson & Johnson and is the historical inventor of the technologies, with 20 products (53%), and Osmotica Pharmaceutical Corp., which was a spin-off company of Phoenix Inc., with 10 products (26%). Seven products are currently in the late development stage, from which 3 compounds are for pain management (1). The increasing number of marketed products has translated into a two-fold increase in the OODS revenues in the past 5 years, reaching about 3 billion dollars worldwide annual sales. Thus, OODS products represented 6.2% of the total sales volume of oral drug delivery systems in 2007 *versus* only 3.0% in 2002.

To further understand the interest in OODS, the pharmacokinetic properties of the formulated drugs, e.g., half-life and bioavailability, were studied as shown in Table 2. It appears that about 30% of the formulated drugs have a half-life longer than 12 hours and 50% longer than 6 hours. This shows that the half-life is not the dominant criterion for OODS selection. Interestingly, most of the products (80%) show a stable or increased relative bioavailability in comparison to the immediate-release form (see Table 2) (37-39).

Table 2: Marketed oral osmotically-driven products classified according to therapeutic indication

Product	Active	Form	Strength (mg)	F (%)[a]	Rel. F (%)[b] CR/IR	$t_{1/2}$ (hrs)	Developer / Marketer	Status/Approval (Market)
Cardiovascular disorders								
UT-15C	Treprostinil diethanolamine	SEOP	1	100%	n.p.	4	United Therapeutics.	Phase II
LCP-Lerc	Lercanidipine	DOEOP	20	44%	140-270%	3	Osmotica / Recordati	Phase III
Cardura CR	Doxazosin mesylate	PPOP	4-8	50-70%	~ 60%	15-22	Alza / Pfizer	2005 (WO)
Concerta	Methylphenidate HCl	PSOP	18-54	11-52%	~ 100%	2-4	Alza / McNeil	2000 (WO)
Ditropan XL Ditropan UD / Tavor	Oxybutynin chloride	PPOP SEOP	5-15	6%	~ 150%	12-16	Alza / UCB Pharma Osmotica / Phoenix	1998 (US) 1998 (South Am)
Teczem	Enalapril Diltiazem	CPOP	280 5	60% 40-60%	n.p.	11 4-6	Merck / Aventis	1996 (WO)
Tiamate Dilacor XR	Diltiazem HCl	CPOP SCOT	120-240	40%	n.p.	3-4.5	Merck / Aventis Andrx	1996 (WO) 1997 (US)
Covera HS	Verapamil HCl	COER	180-240	20-35%	n.p.	2-5	Alza / Pfizer	1996 (WO)
DynaCirc CR	Isradipine	PPOP	5-10	15-24%	n.p.	8	Alza / Novartis	1994 (US)
Minipress XL or Alpress LP	Prazosin	PPOP	2.5-5	40-80%	~ 50%	2-4	Alza / Pfizer	1992 (WO)
Procardia XL / Adalat CC Nifed Sol	Nifedipine	PPOP DOEOP	30-90	60-75%	75-85%	2-5	Alza / Pfizer - Bayer Osmotica / Phoenix	1989 (WO) 2000 (South Am)
Metabolic disorders								
Topamax	Topiramate	PSOP	25-175	80%	n.p.	21	Alza	phase II
AltoPlus XR	Metformin HCl Pioglitazone HCl	SCOT	500-850 15	50-60%	n.p.	5.2	Andrx / Takeda	Phase III
Fortamet	Metformin HCl	SCOT	500-1000	50-60%	~100%	5.2	Andrx	2004 (US)
Altoprev	Lovastatin	EOP	10-60	<5%	156%	1.1-1.7	Andrx	2002 (US)
Glucotrol XL	Glipizide	PPOP	2.5-10	90%	90%	2-4	Alza / Pfizer	1994 (US)
Nervous and neuronal disorders								
Flexeril XL	Cyclobenzaprine	EOP	15-30	33-55%	n.p.	18	Alza	Phase III
Oxycontin	Oxycodone	PPOP	10	5%	~100%	~ 3	Alza	Phase III
Jusnista	Hydromorphone	PPOP	8-64	30-35%	~ 100%	2-3	Alza / J&J	phase III
Invega	Paliperidone	PPOP	3-12	28%	32-45%	23	Xian-Janssen	2007 (US)
Elafax XR	Venlafaxine HCl	EOP	37.5-150	45%	n.p.	3-7	Osmotica / Phoenix	1999 (South Am)
Tegretol XL	Carbamazepine	SEOP	100-400	80%	~ 100%	25	Alza / Novartis	1996 (WO)
Osmosin	Indomethacin	EOP	75	~100%	n.p.	2.6-11.2	Alza / Merck	1982 (WO) withd. in 1983
Respiratory & Seasonal disorders								
Teosona Sol	Theophylline	DOEOP	400	100%	n.p.	5-8	Osmotica / Phoenix	1997 (South Am)
Allegra D 24 hrs	Pseudoephedrine HCl Fexofenadine HCl	DOEOP	240 180	85% ~ 33%	~ 100% ~ 100%	9-15 14.4	Osmotica / Aventis	2004 (US)
Loremex	Pseudoephedrine HCl Loratadine	DOEOP	240 10	85% 84%	n.p.	5-8	Osmotica / Phoenix	1997 (South Am)
Mildugen D	Pseudoephedrine HCl Astemizole	DOEOP	240 10	85% ~ 3%	n.p.	5-8 26	Osmotica / Phoenix	1997 (South Am) withd. in 1999
Efidac 24 brompheniramine	Pseudoephedrine HCl Brompheniramine	EOP	240 16	85% -	98% 101%	5-8 -	Alza / Novartis OTC	1996 (US)
Efidac 24 chlorpheniramine	Pseudoephedrine HCl Chlorpheniramine	EOP	240 16	85% 25-50%	n.p.	5-8 21-27	Alza / Novartis OTC	1994 (US)
Efidac 24 Sudafed 24 hour Mex:24	Pseudoephedrine HCl	EOP EOP DOEOP	240	85%	~ 100%	9-16	Alza / Novartis OTC Alza / J&J Osmotica / Phoenix	1993 (US) 1992 (US) 1995 (South Am)
Volmax	Albuterol	EOP	4-8	50%	~ 100%	2.7-6	GSK / Muro Pharmaceuticals	1987 (GB)
Acu System C	Vitamine C	CPOP	n.p.	n.p.	n.p.	n.p.	Alza	1986 (US)
Acutrim	Phenylpropanolamine	DOEOP	75	n.p.	n.p.	3-5	Alza	1983 (US) withdrawn 2000
Gastrointestinal disorders								
Osmoran 300	Ranitidine HCl	DOEOP	300	50%	n.p.	2-4	Osmotica / Phoenix	1999 (WO)

[a] Oral absolute bioavailability of the compound basically determined as an immediate-release form, information from Goodman & Gilman / PDR / Product notice.
[b] Relative bioavailability controlled-release *vs* immediate release calculate as ratio between two dose exposures after the same dose administration with a immediate-or controlled-release pattern (n.p., not published).

3. Technology panel and selection

Ideally, the selection of the OODS technology needs to be done with consideration for the desired pharmacokinetic profile of the drug product. The approach is to control the drug plasma profile by managing the drug release kinetics from the OODS as shown in Fig. 3. To a large extent, the formulation strategy is based on the biopharmaceutical classification (BCS) of a particular drug substance, as proposed by Corrigan and Amidon (40-42) and illustrated in Fig. 4: Only drugs with a high permeability, no absorption window and no marked first-pass metabolism (ideally showing dose-proportional and linear pharmaco-kinetic profiles) have high likelihood of success when formulated as extended-release i.e., BCS class Ia, IIa and Va. For BCS class Ia, the solubilization step is usually rapid and not rate-limiting and the drug release needs to be adjusted in function of the permeability. In the case of BCS class IIa & Va (i.e., either low or variable solubility and high or variable permeability), the drug needs to be delivered in an oversaturated solution in the GI lumen otherwise the solubility could limit the absorption. To the best of the author's knowledge, no OODS have been developed to deliver BCS class Iva drugs. In this particular case, both the solubility and absorption limit the absorption and oral bioavailability. As for BCS class IIa, drug delivery in oversaturated solutions may be beneficial for these drugs if the drug is relatively consistently absorbed through the entire GI tract. Otherwise the use of OODS may impact the drug bioavailability. Consideration regarding saturation of the first-pass liver metabolism may also require special attention.

Thus, the drug release kinetics from OODS might ideally control the amount of drug systemically absorbed per time leading to a good *in-vitro in-vivo* correlation (43), independent of food-intake (44). The importance of adequately defining the dose was described, for example, with oxprenolol (45). Different release kinetics were tested to determine the optimal dosage strength and release rate. Thus, Alza Corp. developed an interesting classification of OODS describing, respectively, the release rate and dosage strength e.g. "metroprolol OROS 14/190" delivers 190 mg metroprolol at a release rate of 14 mg/h.

Further approaches were also proposed, generally grouping them under the generic nomination of chronotherapy (46-48), e.g., to target sufficient plasma concentrations overnight or covering the periods in which children suffering from ADHD are in school.

Fig. 3: Influence of the drug release kinetics to control the drug distribution

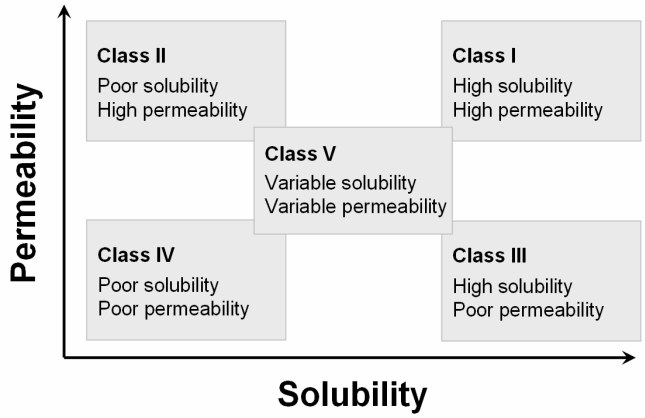

Fig. 4: BCS classification; BCS class I to IV described for immediate- or extended-release dosage forms such as in the FDA guidelines; BCS class V was introduced by Corrigan and Amidon (40-42) for extended-release dosage forms because of the high proportion of basic or acid compounds formulated as controlled-release dosage forms

An important subsidiary issue is the adequate selection of the technology and design. Various oral osmotic tablet and capsule designs have been developed during the past thirty years, giving several opportunities to adapt technology to drug properties. OODS technologies could be classified as unitary-core, multi-layer core or capsule-based oral osmotic systems. This classification has the advantage of reflecting the increasing complexity of the different systems and helps with the selection of the appropriate OODS.
The two main criteria that should be taken into account in technology selection are the drug solubility and dosage strength (Fig. 5 & Fig. 6). Through the review of 66 patents and articles, it is interesting to note that 75% of drugs formulated as OODS were either freely soluble or practically insoluble (Fig. 5), showing that OODS is mainly used to overcome the technical challenges of formulating such drugs. Unitary-core technologies (EOP, CPOP or SCOT) were mainly used to deliver freely soluble drugs. However, the recent development of self-emulsifying technologies (SEOP) has further extended the applicability to practically insoluble drugs. Multi-layer core (PPOP and PSOP) drugs were indiscriminately used to deliver soluble and insoluble drugs. The development of capsule-based OODS, mainly developed as exploratory tools (49), was quite restricted mainly due to the complex scale-up.

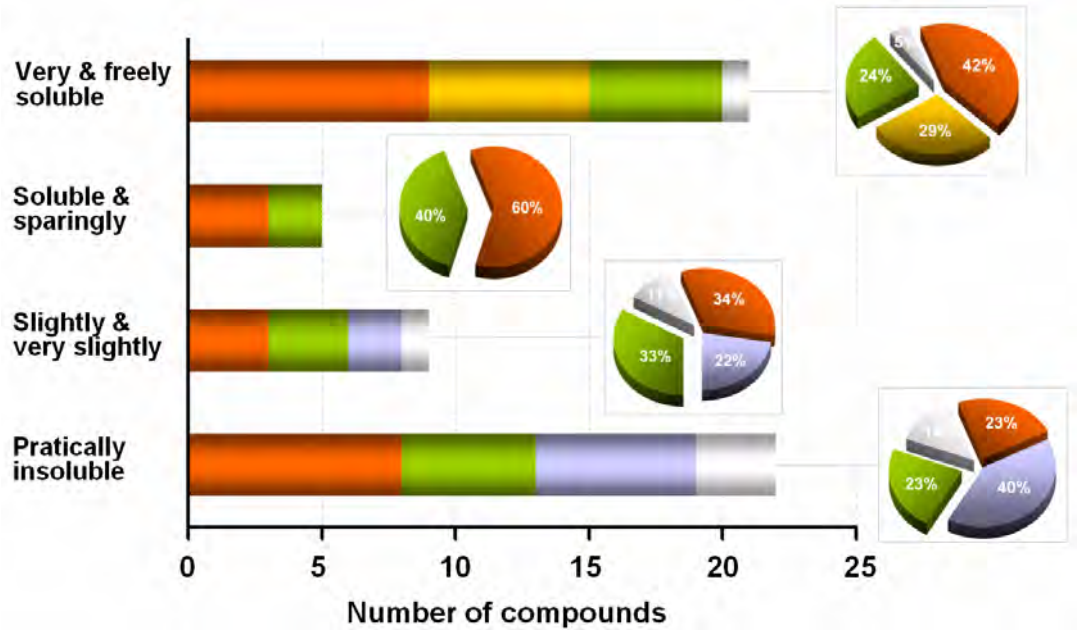

Fig. 5: Number of compounds sorted by USP solubility criteria based on a selection of 57 drugs reported in the literature and formulated as EOP/SCOT ( ), CPOP ( ), PPOP ( ), SEOP/SCPOP ( ) or capsule-devices ( ).

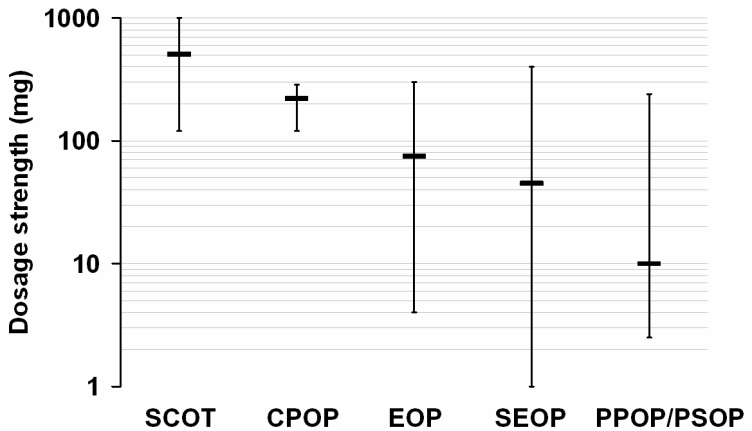

Fig. 6: Dosage strength of the marketed products using OODS (median and range).

3.1. Unitary-core osmotic systems

Unitary-core osmotic systems represent two-thirds of marketed OODS products (Table 2). Four technologies were developed using this concept, as summarized in Table 3,

- the elementary osmotic pump (EOP)
- the single composition osmotic pumps (SCOT)
- the controlled porosity osmotic pump (CPOP)
- the self-emulsified unitary-core (SEOP / SCPOP)

EOP, CPOP and SCOT have all been used primarily to deliver freely soluble drugs, representing 71% of formulated freely soluble drugs (Fig. 5), whereas slightly soluble or practically insoluble drugs were formulated as SEOP.

The design of the unitary-core osmotic system was described by Theeuwes (9,10). Composed of a tablet-core surrounded by a semipermeable membrane, EOP and CPOP differ only in the way by which the drug is delivered. For the EOP, drug is delivered through a laser-drilled passageway, while for the CPOP the drug is given through pores in the membrane (Fig. 1). The objective in formulating such a system is to deliver under zero-order kinetics, the maximum drug fraction over a fixed duration, varying mostly from 4 to 24 hours. The tablet-core composition has been considered to be the primary influencer of the drug delivery fraction in a zero-order, whereas the membrane characteristics are thought to control the drug release rate. Thus, the tablet-core composition may be formulated in such a way that both core osmotic pressure and density are maximized (10). If the drug has sufficient osmotic pressure, such as metformin hydrochloride, single composition osmotic tablets (SCOT) could be used, delivering drug loadings from 75% to 90% in a constant manner (50-52). Even in this case, single osmotic agents (53) or a sugar-mixture (54) may be added to the tablet-core composition to obtain a zero-order delivery pattern, which is independent of the external osmolarity (12, 55). Additional tableting and bulk excipients may be needed to simplify the tableting process, but soluble and finely-milled grade are preferred (56). Furthermore, drug release retardant effects may be obtained by adding polymers (57-59) or solubility modulators (56, 60, 61). This approach presents the additional advantage of preventing burst effects observed in the case of membrane rupture. In the case of slightly soluble or practically insoluble drugs, self-emulsifying agents have been added to the tablet-core composition. For example, a strategy to formulate different drugs as SCPOP using a cyclodextrin complex has been described (62). Similar results have been reported for the use of surfactants (63, 64) or pH-modifiers (65, 66). Using this approach, 3- to 4-fold oversaturated drug concentrations were measured *in-vitro* (67).

Independent of the tablet-core, the drug release kinetics from these systems can be modulated by varying the membrane thickness (68, 69) or composition (57, 68, 70-72). All osmotic systems are coated at any production-scale using film-coating spray equipment mainly with organic solvents such as an acetone-water mixture for generating cellulosed-based membranes, e.g. cellulose acetate or ethylcellulose, with high mechanical resistances (73, 74). In production scale, the high amount of solvent required may become problematic and costly. Therefore, aqueous coatings such as metacrylic polymers in aqueous dispersion have been proposed as an alternative to organic coatings, in order to avoid the solvent recycling seen in large-scale product manufacturing (75-77). Plasticizers are added to improve the membrane physical properties (74), independent of the polymer selected. The water-soluble plasticizers (PEG, HPMC) may be preferred for rapidly creating a porous structure (73, 75, 77), thus, reducing the latency time to drug delivery. Water-insoluble plasticizers, such as castor oil, were also reported as allowing a more constant drug delivery (69) for single-core systems.

Finally, an orifice can be drilled on the coated table. The passageway size should be estimated based on Pouiseuille's law (10) depending on the tablet-core composition and the coating property. In the calculated range, the drug delivery remained as independent of the

passageway size (78-80), except in the case of highly viscous compositions (70, 81, 82). Various drilling techniques were developed depending the scale using either manual-drilling (12, 83), laser-drilling (84), or modified punches, so-called indentation (85, 86).

Further technologies were developed to modulate the drug delivery pattern, increasing or decreasing the lag time, i.e., the latency before the drug delivery of 30 min to 1 hour. Immediate-release drug layers around the semipermeable membrane were sprayed, for example, around EOP, so-called Osmodex™ technology. Releasing an initial burst of drug (87), this technology avoids the lag time of two hours generally observed before drug absorption. This technique was also used to deliver a combination of two drugs, one in an immediate release pattern and the other in controlled-manner (88). Enteric coated EOP, so called OROS-CT™, has also been proposed to target colonic absorption (89).

Table 3: Principal oral osmotially-driven technologies and designs

Technology	Developer	Description	Ref.
(I) Unitary-core osmotic pumps			
(a) Elementary osmotic pumps (EOP)			
'Standard' EOP	Alza Corp., USA	Single drug composition compressed as a core surrounded by a semipermeable membrane with a drilled orifice	(9,10,12,90)
	ADD Technology, CH	EOP containing agents modifying the drug kinetics, such as	
	Sun Pharm., India	(i) a polymer or wax	(58,82,91,92)
	Alza Corp., USA	(ii) saltz e.g. sodium chloride for salbutamol	(53,60,61)
Single composition osmotic tablet (SCOT)	Watson Pharm. / Andrx, USA	EOP with highly porous membrane allowing high drug loading (> 75%)	(50-52)
Self-emulsified EOP	Novartis Pharma, CH Ranbaxy, India	EOP with incorporated agent for modifying the drug thermodynamic properties(e.g. solubility), such as	
	Shire, USA	(i) crystal-habit modifying agents, e.g. polymers	(93-95)
	Alza Corp., USA	(ii) complexing agent, e.g. β-cyclodextrin	(62,80)
	Supernus Pharm., India	(iii) surfactants e.g. Sodium laurylsulfate	(63,64)
	Alza Corp., USA	(iv) pH-modifying agents e.g. acid or basic agent	(65,66)
Over-coated EOP	Osmodica, Arg.	EOP surrounded by	
	Alza Corp, USA	(i) an immediate-release drug layer (DOEOP)	(87,88,96,97)
	Merck & Co, USA	(ii) enteric coating (OROS-CT™)	(89,98,99)
Effervescent EOP	Alza Corp., USA	EOP containing sodium bicarbonate to promote the drug release	(100-103)
(b) Controlled porosity osmotic pump (CPOP)			
'Standard' CPOP	Alza Corp., USA Merck&Co, USA	Tablet-core surrounded by a membrane which allows the diffusion of the drug	(53,56,104,105)
Self-emulsified CPOP	Merck & Co, USA	CPOP containing agents to modified the drug thermodynamics i.e.	
		(i) complexing agent e.g. cyclodextrines	(62,80,106)
		(ii) pH-modifying agents	(95,107,108)
(II) Multi-layer osmotic pumps			
Push-pull osmotic pump (PPOP)	Alza Corp., USA	Bi- or tri-layer tablet core composed by a drug layer to disperse the drug and a push-layer which generates a hydrodynamic pressure pushing the drug through one or more passageways.	(109-116)
Push-Stick osmotic pump (PSOP)	Alza Corp., USA	PPOP improved to deliver high dose with both a sub-coating the semipermeable membrane to avoid drug adhesion and an immediate-release drug over-coating	(117-120)
Over-coated PPOP	Alza Corp., USA	PPOP coated with enteric coating delivering either the drug without (OROS-CT™) or with a special onset (COER-24™)	(54,121-125)
Muco-adhesive osmotic system (MOTS)	Alza Corp., USA	PPOP specially designed for buccal administration of drugs	(124-126)
(III) Capsule-based osmotic pumps			
CHRONSET™	Alza Corp., USA	System specially designed to deliver a bolus (>80% drug within 15min) for intestinal or colonic absorption of protein or muco-adhesive particles	(127,128)
OSMET™	Alza Corp., USA	Device design to study the colonic absorption of drugs delivering the drug as bolus or over a prolong period up to 8 hours.	(129-132)
Assymetric-membrane osmotic pump	Pfizer, USA	Systems coated subsequently with a semipermeable membrane and a highly porous membrane allowing higher water inflow	(133-136)
Liquid osmotic system (L-OROS™)	Alza Corp., USA	Osmotic system delivering either liquids, lipid-lipid emulsion or solid dispersion.	(137,138)

3.2. Multilayer-core osmotic systems

Two main multilayer designs have been developed and marketed by Alza, namely the push-pull and push-stick osmotic pumps (PPOP and PSOP, Table 3). The multilayer-core osmotic systems are composed of a bi-or tri-layer tablet-core, surrounded by a semipermeable membrane with a laser-drilled orifice (Fig. 5). Developed to deliver drugs independently of their solubility, the tablet-core composition contains mainly polymers and drugs. It allows drug delivery through the orifice as either a solution or dispersion (11) under the hydrodynamic pressure generated by the swelling of the so-called 'push-layer'. As for the unitary-core systems, the drug release composition needs to be optimized for delivering the maximum drug load, whereas the kinetics are controlled mainly by the membrane characteristics. However, the formulation strategy differs from the unitary-core, due to the polymeric nature of the composition, leading to a viscous microenvironment. Therefore, the strategy to formulate the tablet-core may be handled as an approach to balance the hydration kinetics of both layers, while also controlling the polymer viscosity & swelling kinetics (139). Osmotic agent amounts and polymer grades may be selected to enhance the drug dispersion (113). Water-soluble excipients would be preferable especially in the drug layer avoiding drug agglomeration (112). Under these conditions, loadings of up to 30% may deliver in a zero-order manner (109,113,114) over a prolonged period, i.e., from 4 to 24 hours, by varying the membrane characteristics (112,114,115). Because of the drug dispersion delivery, a larger passageway size should be preferably drilled using manual (113), laser (112) or indentation (111) drilling techniques.

More complex designs, such as the COER-24 or push-stick osmotic pumps, were recently developed to deliver higher dosage strengths in a more complex pattern. The COER-24 design was specially design to deliver verapamil, Covera HS™ (140). Delivering the drug constantly after a delay of 2 hours, COER-24 has a special interest for overnight drug administration. More versatile than PPOP or COER-24, PSOP has been specially designed for delivering high loadings of water-insoluble drugs. A hydrophilic polymer layer, the so-called 'flow-promoting layer', was sprayed between the tablet-core and the semi-permeable membrane, avoiding internal drug adhesion (118). Surrounded by an immediate-release drug layer, the trilayer tablet-core (Fig. 1) gives additional flexibility to adapt the drug delivery to an optimal plasma profile (117). Adapted for methylphenidate (Concerta™), an extremely controlled plasma profile was monitored, allowing drug delivery over the school hours for children with attention-deficit hyperactivity disorder (ADHD) and also avoiding tachyphylaxis (120, 141).

3.3. Capsule-based osmotic systems

Mainly used as exploratory tools, capsule-based osmotic pumps are developed for site-specific drug delivery to investigate drug pharmacokinetics (128,142,143). For example, Chronset™ osmotic pumps were designed as a pulse-delivery system, releasing muco-adhesive particles containing peptides or proteins (127,128). The Osmet™ design was developed as a miniature osmotic pump to deliver a drug as bolus or over 8 hours in the colon (129,142). Osmet™ devices are available as an empty module ready to be filled by researchers with simple drug compositions and used in clinical trials to deliver a drug over 8, 12 or 24 hours (36). Site-specific deliveries of oxprenolol (131), nitrendipine enantiomers (132) or lidocain (144) were tested using the Osmet™ device. To validate the effective rectal drug delivery, GI transit time of Osmet™ was studied under fasted and fed states using gamma-scintigraphy (145,146). Results show that the retention time in the stomach was

drastically increased (5.3 hrs *vs.* > 12 hrs) by concomitant food-intake, probably due to the large non-degradable Osmet™ device.
Another capsule-based system, the so-called L-OROS™, was developed to deliver non-aqueous liquid formulations suitable for either poorly soluble actives or polypeptides (147). This design offers continuous delivery of the liquid or semisolid composition, improving the bioavailability of the drug. Depending on the formulation viscosity, soft- and hard-capsule L-OROS design may be preferred (148).

4. Clinical aspects of OODS, risk and benefits

4.1. Safety and precautions

In discussing the development of the OODS, one main safety aspect must be addressed as a prerequisite—the drug substance irritant property to the target site. Thus, in case of the delivery of irritating drug substances, the concern is the local delivery of the drug from an OODS with impaired transit through the GI tract, which might lead to gut wall irritations. In the worst case, it can result in gut wall perforations, as has been reported from patients receiving the indomethacin OODS, Osmosin®. Thus, Osmosin® was withdrawn from the market after 18 patients had died and more than 400 severe intestinal ulcerations (19, 21, 23, 149) had been reported. Since the 1950s, indomethacin has been a drug known to be irritating to the GI system (20, 21, 23). The risk of irritation was probably amplified by local drug delivery through the orifice and the potentially prolonged transit time observed with non-degradable systems (145, 150). Therefore, *in-vitro* evaluation of the drug irritation potential on GI mucosa was proposed as a standard procedure before human studies.
Two precautions must also be addressed by the physician before treatment instauration due to the non-degradable nature of OODS. The first precaution is to detect pre-existing GI injury in the patient history that might increase the likelihood of GI narrowing. Thus, the potential hazard of GI occlusion was reported in about one case for > 76 million units (6). Possible difficulties in swallowing OODS should also be taken into account. Second, physicians must inform the patient that the empty shell may be excreted in the feces, which can disturb fragile patients, such as in the treatment of schizophrenia using paliperidone (Invega®).

4.2. Gastrointestinal (GI) transit and drug absorption

Due to non-uniform transit throughout the GI tract, drug absorption is a key element in the design of the extended-release dosage form. Thus, the residence time of the ER form along the gut might strongly influence the drug absorption, as shown in two clinical studies by scintigraphy on oxprenolol EOP (151) and carbamazepine SEOP (152). Results showed that drug absorption varied from 40% to 80% depending on the transit time, which was due mainly to prolonged residence time in the stomach. In a few patients, the OODS were excreted before complete drug delivery, as shown by the good correlation between the residual drug substance remaining in the excreted OODS shell and the extrapolated residue from in-vitro data (153). However, an extensive investigation on overall transit time showed that the excretion of incompletely depleted systems only occurred in a minority of patients (150). Further studies on non-disintegrating tablets have been carried out to compare the gastrointestinal transit of OODS to other modified release forms, such as erodible matrix or pellets. It appears that the size of the system plays a minor role in the fasted state, as is illustrated by the comparison of pellets versus large non-disintegrable capsule (145, 146). However, concomitant administration of food may change the situation. While no significant difference in GI transit was observed for systems with a size lower than 7-mm (154), large non-disintegrable systems, like Osmet® capsules (145, 146) or 9-mm round tablets (155), remained for > 10 hrs in the stomach. Contradictory results for larger round tablets with

diameters up to 10-mm, carbamazepine SEOP (152) and indomethacin EOP, were reported, (156) with lower gastric retention times of about 3 to 5 hrs depending the meal composition. Despite these controversial results, there is great evidence that the patient-to-patient variability increases with the OODS size. Therefore, efforts to decrease the size of the system should generally pay off. Furthermore, systematic studies on the gastrointestinal transit of non-disintegrating systems may also help to optimize both the drug release rate and the OODS design to the expected drug absorption.

4.3. Food-effect

As previously described, food-intake may influence the GI transit time and, thereby, the drug absorption of drugs delivered from OODS. In addition to the longer gastric residence time, the shear forces applied on the stomach's bowl are duplicated leading to a faster disintegration of the erodible dosage forms, e.g., matrix tablets. Furthermore, the higher fat concentration in the bowl might increase drug solubility. Thus, the food effect is of special interest for drugs with a narrow therapeutic index. For example, a drastic increase in drug absorption following administration of nifedipine erodible matrix tablets with food was reported to increase the side-effect proportion (157). However, a critical review of the literature shows that food effects were mainly reported for practically insoluble drugs when formulated in surface erodible drug delivery systems, like matrix tablets. In contrast, when studies were carried out on osmotic pumps delivering nifedipine or oxybutinin, results showed that neither the totally absorbed drug amount (as expressed by AUC) nor the maximum plasma concentration (Cmax) were significantly influenced by concomitant food intake (158, 159). On the other hand, erodible matrix tablets (158), coated minitablets (158) or pellets (160), when administered under fasted and fed conditions, resulted in maximum plasma concentrations (Cmax) that were at least doubled and in most cases, the dose exposures were doubled as well when these same preparations were given together with food. One publication on a nifedipine formulation, Slofedipine XL®, was reported as not being affected by food, but its drug bioavailability was reported as 3-fold lower than the OODS, Adalat™ (159). No significant food effects were reported on freely soluble drugs for both immediate- or modified-release systems.

Table 4: Food-effect on pharmacokinetics

Drug	Drug delivery systems	n*	Dose (mg)	Variations Fed vs Fasted		Ref.
				$AUC_{(0\text{-inf})}$	Cmax	
Practically insoluble						
Nifedipine	Push-pull osmotic pump	28	30	6%	29%	(158)
		22	60	17%	11%	(159)
		24	60	9%	23%	(159)
		24	60	6%	18%	(162)
	Erodible matrix					
	- Sandoz Retards ™	28	30	29%	209%	(158)
	- Hydrophilic matrix	18	90	76%	303%	(163)
	- Coral™	22	60	44%	217%	(161)
	Enteric-coated erodible matrix (Slofedipine™)**	24	60	-12%	6%	(159)
	Encapsulated minitablets (Nifedicron ™)	24	60	23%	151%	(159)
	Multiparticulate systems filled in capsule	9	60	120%	180%	(160)
Oxybutinin	Push-pull osmotic pump	50	15	-11%	-9%	(164)
		35	20	-27%	-31%	(165)
	Enteric-coated erodible matrix	35	20	-21%	-17%	(166)
	Hydrophilic matrix (Cystrin ™)	23	10	6%	121%	(167)
		29	10	-10%	72%	(165)
Slightly soluble						
Doxazosin	Push-pull osmotic pump	24	4	18%	31%	(168)
Freely soluble						
Methylphenidate	Push-stick osmotic pump	24	18	20%	33%	(170)
		31	36	17%	11%	(170)
		35	36	22%	18%	(171)
	Multiparticulate pump (Ritalin LA™)	18	40	5%	-5%	(172)
		24	40	31%	17%	(169)
	Immediate-release form (Ritalin™)	24	40	15%	23%	(169)
		15	10	1%	-14%	(173)
Pseudoephedrine	Elementary osmotic pump	12	240	-9%	-10%	(174)
	Drug overcoated EOP	24	240	1%	5%	(175)
Hydromorphone	Push-pull osmotic pump	27	16	-7%	22%	(176)
	Melt-extruded multiparticulate system	22	24	-3%	17%	(177)
Oxprenolol	Elementary osmotic pump	6	160	-9%	-23%	(178)
	Immediate-release	6	160	17%	8%	(178)
Metoprolol	Elementary osmotic pump	8	190	-2%	-5%	(179)
		12	190	13%	11%	(180)
	Immediate-release form	12	50	14%	15%	(181)

* n: number of patients studied

4.4. *In-vivo In-vitro* correlations (*IVIVC*)

The IVIVC of controlled-release forms are of strong industrial interest due to their ability to (*i*) surrogate at least some of the bioequivalence studies required during scale-up and any process changes (SUPAC) and (*ii*) validate and justify dissolution specifications based on the *in-vivo* relevance of the in-vitro data (182). Table 5 summarizes the IVIVC reporting for OODS. Good 'level A' IVIVC was reported in dogs (183) or healthy volunteers (183). That is to say, *in-vitro* drug release and *in-vivo* deconvoluted drug 'input' were directly superimposable (184). Interestingly, good IVIVC was investigated on drugs of BCS class-I

(metoprolol or nifedipine), class-II (indomethacin or oxybutinin), class-III (salbutamol or metformin), and class-V (tenidap or WAG994). Of interest, IVIVC was also shown on technologies delivering concomitantly two drugs, one in an immediate-release fashion and the other in a controlled-release pattern (185). *IVIVC* was also reported as being independent from food-intake for oxybutinin PPOP (186).

Table 5: Literature showing *in-vitro in-vivo* correlations

Drug	formulated as	Dose (mg)	Model	References
Nifedipine	PPOP	30, 60	Fasted human	(183)
Oxybutinin	PPOP	10, 20	Fasted human	(186)
Salbutamol	EOP	8	Fasted human	(187)
Metoprolol	EOP	190 & 285	Fasted human	(188,189)
Melatonin	PPOP	0.11	Fasted human	(47)
Indomethacin	EOP	85	Fasted Mongrel	(12)
NVS WAG994	EOP	5	Fasted beagle	(190)
Tenidap	PPOP	50	Fasted beagle	(114)
Pseudoephedrine / Brompheniramine	DOEOP	240 / 16	Fasted beagle	(174)
Metformin / Glipizide	EOP	500 / 5	Fasted beagle	(185)
Carvedilol	SEOP	12.5	Fasted beagle	(191)
Prednisolone	SEOP	20	Fasted/Fed beagle	(44)

5. Conclusion

Development efforts of oral osmotically-driven systems (OODS) during recent years have been very dynamic with the emergence of new technologies and products. With the expiration of the OODS primary patents and the increasing demand of health authorities for improved patient treatment compliance and tolerability, the OODS is primed to increase their market within oral modified-release dosage forms. Developed as a drug delivery platform for delivering drugs regardless of their physico-chemical properties, oral osmotically-driven systems (OODS) have several applications (i) in early clinical phases (including early stage exploration of pharmaco-kinetics), (ii) in novel dosage form development and (iii) in product life-cycle management. The clinical benefits of OODS mainly reside in their capacity to deliver a drug at a pre-determined rate, independent of physiological parameters such as food-intake or patient age. Nowadays, the large variety of OODS technologies available allows an interesting adaptation of the system to the drug properties and dosage strength. Despite the controversy concerning the safety in the administration of non-disintegrable tablets, the reported clinical benefits have opened up new perspectives to the future development of drugs as oral osmotically-driven systems.

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Chapter III

Benchtop-magnetic resonance imaging (BT-MRI) characterization of push-pull osmotic systems

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Benchtop-magnetic resonance imaging (BT-MRI) characterization of push–pull osmotic controlled release systems

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ABSTRACT

The mechanism of drug release from push–pull osmotic systems (PPOS) has been investigated by Magnetic Resonance Imaging (MRI) using a new benchtop apparatus. The signal intensity profiles of both PPOS layers were monitored non-invasively over time to characterize the hydration and swelling kinetics. The drug release performance was well-correlated to the hydration kinetics. The results show that (i) hydration and swelling critically depend on the tablet core composition, (ii) high osmotic pressure developed by the push layer may lead to bypassing the drug layer and incomplete drug release and (iii) the hydration of both the drug and the push layers needs to be properly balanced to efficiently deliver the drug. MRI is therefore a powerful tool to get insights on the drug delivery mechanism of push–pull osmotic systems, which enable a more efficient optimization of such formulations.

1. Introduction

Controlled drug delivery systems for oral applications are widely used clinically to decrease the frequency of administration or to reduce side effects that are related to peak plasma concentrations (C_{max}). Many of them are based on matrix tablets. In many cases, their drug release rates are either dependent on pH and / or on shear forces of the local environment leading to a so-called food effect and *in vivo* variability [1]. A reproducible zero-order release profile of poorly and pH-dependently soluble drugs is a challenge. Osmotic [2,3], multiparticulate [4,5] and, more recently, special erosion controlled delivery systems (Egalet™) [6] have been developed to overcome these limitations.

Osmotic pumps also known as oral osmotic systems (OROS™) were reported as suitable to deliver poorly soluble compounds such as nifedipine, isradipine or doxazosin [7]. This controlled release technology was initially developed by Theeuwes and associates in the 1970s as a result of an ultimate simplification of Higuchi–Leeper pump design [8]. Two delivery systems based on OROS technology were mainly developed and marketed [9]. The elementary osmotic pump is based on a single tablet core and suitable for highly soluble drugs. The second type is the push–pull osmotic system (PPOS) based on a bilayer tablet core for poorly soluble compounds (Fig. 1).

The delivery principle of all osmotic systems involves controlled water diffusion through a semipermeable membrane and the drug release through a laser-drilled orifice [2]. Several mathematical hydration models were proposed for single core systems [2,9] as well as for bilayer PPOS [10]. These approaches were based on the Starling equation (Eq. (1)) describing the flow rate (dV/dt) through a semipermeable membrane as:

$$\frac{dV}{dt} = \frac{A \cdot L_p}{h}(\sigma \cdot \Delta\pi - \Delta P) \quad (1)$$

with the membrane thickness (h) and surface (A), the water permeability (L_p), the difference of hydraulic pressure (ΔP) and the osmotic gradient ($\sigma \cdot \Delta\pi$). Eq. (2) was adapted to bilayer PPOS by Wong et al. [11]:

$$\frac{dV}{dt} = \frac{\sigma \cdot L_p}{h}\left[A_P(H) \cdot \pi_p + (A - A_P(H)) \cdot \pi_D - \Delta P(H)\right] \quad (2)$$

with the degree of hydration (H), the layer surfaces (A_x) and the osmotic pressure (π_x) of the push and the drug layers indexed with P and D respectively. These models were used to explain the effect of some parameters from a qualitative point of view. However, knowledge of the detailed mechanisms underlying the release process from PPOS is still limited due to a lack of experimental data despite the clinical value and long history of oral osmotically driven drug delivery systems. Therefore, the aim of the present study was to investigate the hydration kinetics of push–pull osmotic systems in more detail. For this purpose, a marketed formulation was compared to several laboratory formulations. The drug layer composition was modified with respect to drug load and polymer

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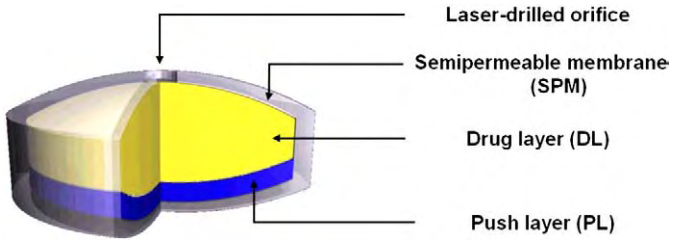

Fig. 1. Design of a push–pull osmotic system with a bilayer tablet core.

grade. The osmotic agent proportion in the push layer and the drug layer/push layer ratio were also varied.

The PPOS hydration behaviour and kinetics was monitored using nuclear magnetic resonance imaging. This non-destructive technique is a well established and powerful method to investigate drug delivery systems in vitro and in vivo [12]. The hydration of various drug delivery systems has been investigated by MRI [12]. Examples include hydrophilic matrix tablets based on hydroxypropylmethylcellulose (HPMC) [13], amylose starch [14] and polyethylene oxide (PEO) [15], film coated tablets [16], Egalet systems [17,18] and pulsatile systems [19]. However, to the best of our knowledge, only two papers describe MRI measurements on osmotic systems. Fyfe and Blazek-Welsh proposed a technique to follow the hydration kinetics of an elementary osmotic pump during a dissolution test in a flow through cell [13]. The second publication was focused on Dynacirc CR tablets, a marketed PPOS tablet system for the delivery of Isradipine [20]. Unfortunately, the authors of this study performed the whole study with bidistilled water at room temperature within a NMR test tube of 10 or 15 mm diameter. No specification of the water volume was given, but it is clear that the small volume within an unstirred NMR test tube is very artificial and neither reflects USP nor physiological conditions. Compared to standard conditions, a change of the hydration and release kinetics can be expected due to the undefined and changing osmotic pressure of the release medium. At the beginning, the osmotic pressure gradient will be high due to the use of bidistilled water. With time, released material will increase the pressure within the NMR tube. Furthermore, no differentiation of the internal tablet structure such as the push or pull layers was achieved. In addition, no quantitative treatment of the MRI data was done. The authors observed, however, differences in the MRI images between slow and fast releasing tablets.

Until now, superconducting NMR machines have been used as standard MRI equipment. Very recently, benchtop-MRI (BT-MRI) systems have been developed which overcome the main limitation of the MRI applications, namely high installation and running costs of superconducting systems. Working with a permanent magnet which does not require liquid helium, makes such a system more affordable (installation costs are around 1/5 to 1/10). However, the question remains whether or not, BT-MRI can provide sufficient resolution on "standard"-MRI applications, including the monitoring of the hydration of oral dosage forms. Very recently, BT-MRI has been used successfully to characterize floating tablets, including CO_2 developing coated [16] and matrix tablets [21]. It was therefore the aim of the current study to obtain new, more detailed and quantitative information on the hydration and release processes of osmotic controlled tablets by means of proton BT-MRI. For this purpose, a commercialized formulation of Isradipine, Dynacirc CR, was compared to four modified formulations with various compositions containing isradipine, a poorly soluble calcium channel blocker drug.

2. Materials and methods

2.1. Preparation of the tablets

DynaCirc CR 5-mg tablets (Reliant Pharmaceuticals, United States) were purchased on the US market.

The laboratory formulations were prepared according to the following procedure: A 500 μm mesh sieve was primarily used to sieve the ingredients Isradipine, PEO 200 k, 600 k and 7000 k (Polyox WSR N-80, WSR 205 and WSR 303, Dow Chemical, Midland United States), Natrium Chloride (NaCl, VSR AG, Pratteln Switzerland), indigo blue (FD&C n°2, Univar Ltd, Bradford UK) and magnesium stearate (FACI SRL, Carasco Italy). The ingredients of both drug layer and push layers were separately blended except the amount of magnesium stearate which was added only at the final blending step as external phase as summarized in Table 1. After a 1 kN pre-compression of the drug layer, the push layer was added and a final compression of 6 kN was performed using a single press (EK0, Korsch AG, Berlin Germany). The tablets were coated in a pan coater (BFC5, Bohle AG, Haan Germany) with 25 mg of Cellulose acetate (75%, Mw 30 000 g/mol, Eastman Chem. Prod., Kingsport United States) and polyethylene glycol (PEG, 25%, Macrogol 3350, Clariant GmbH, Sultzbach Germany) previously dissolved in a 95:5 solution of acetone/water. Finally, a 1 mm size orifice was manually drilled on the drug layer face. Each tablet as well as Dynacirc CR 5 mg had the same dimension: 8.3 mm in diameter and 4.4 mm in height.

2.2. Dissolution test and NMR imaging

Dissolution experiments were carried out according to the USP pharmacopoeia XXVII (basket-apparatus 100 rpm, 37 °C, Varian, Palo Alto US). The dissolution media were 1000 mL of USP monobasic potassium phosphate buffer pH6.8 with 0.1% and 0.8% lauryldodecylamine-*N*,*N*-oxide for 5 mg and 50 mg formulations respectively. Samples were collected at 0.5, 1, 2, 3, 4 h and every 2 h over 24 h. Drug detection was performed by high pressure liquid chromatography with a UV-detection at 328 nm (Waters, Milford USA) accordingly to isradipine USP monograph.

For the MRI measurements, tablets were withdrawn from the dissolution vessel at defined time points and analysed by MRI. For every measurement, a new tablet incubated in the buffer at the dedicated time was used. A 20 MHz NMR benchtop system Maran DRX2 (Oxford Instruments Molecular Biotools, Oxfordshire UK) was used. This benchtop system is equipped with 18 mm diameter sample access and variable sample temperature control. The system is capable of T1- and T2-relaxation measurements, the determination of diffusion coefficients and 3D imaging. 64 averages with a receiver band frequency of 10 kHz and 9.8 ms echo time (TE), were used. The repetition time (TR) was set by optimizing the image contrast. TR was varied between 200 and 1500 ms in steps of 100 ms setting an optimum at 300 ms which leads to T1-weighted images. The field-of-view (FOV) was 20*20 mm with a resolution of 128*128 points. The slice thickness was 2 mm (for intensity profiling) or 10 mm. Each

Table 1
Composition of investigated laboratory formulations

	Formulation			
	#1	#2	#3	#4
Drug layer	187.5 mg	187.5 mg	187.5 mg	150 mg
Isradipine	5 mg	50 mg	50 mg	5 mg
PEO (200 kDa)	168 mg	123 mg		
PEO (600 kDa)			123 mg	143 mg
NaCl	12.5 mg	12.5 mg	12.5 mg	
Magnesium stearate	2 mg	2 mg	2 mg	2 mg
Push layer	63 mg	63 mg	63 mg	100 mg
PEO (Mw: 7000 kDa)	60 mg	60 mg	60 mg	84.5 mg
NaCl				12.5 mg
Indigo carmine	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Magnesium stearate	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Coating layer	25 mg	25 mg	25 mg	25 mg
Cellulose acetate	18.8 mg	18.8 mg	18.8 mg	18.8 mg
PEG (3.35 kDa)	6.2 mg	6.2 mg	6.2 mg	6.2 mg

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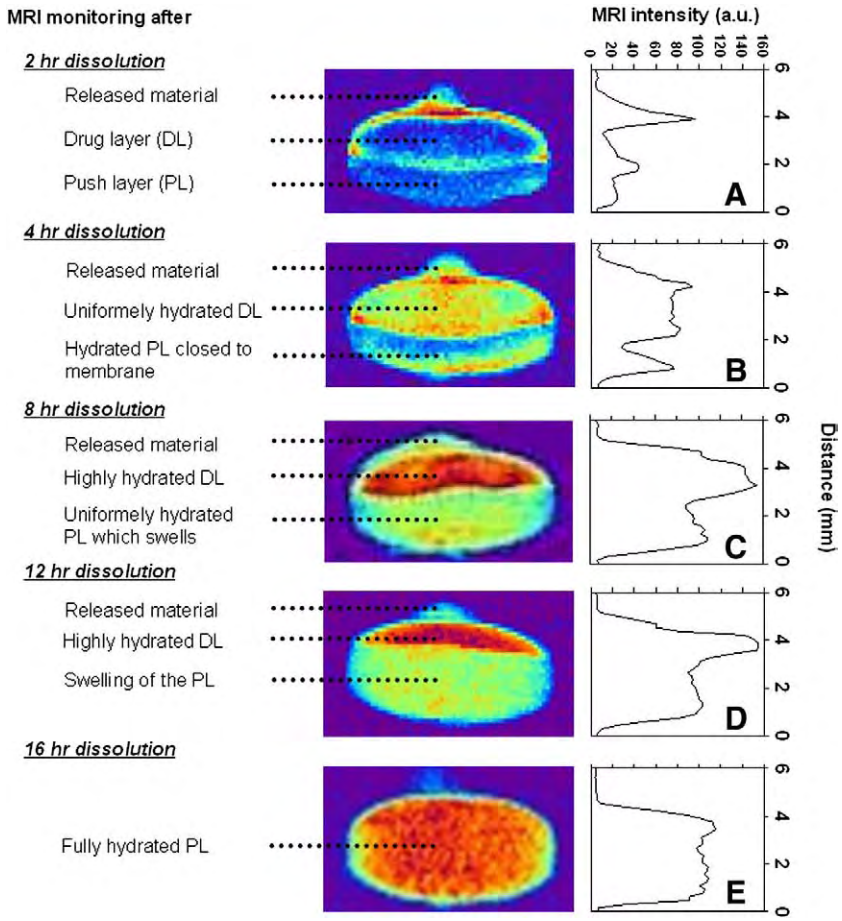

Fig. 2. T1-weighted 1H-NMR images and signal intensity profiles of DynaCirc CR tablets after exposure to the dissolution buffer: Tablets were measured after 2 h (A), 4 h (B), 8 h (C), 12 h (D) and 16 h (E).

image was measured at 37 °C in a moisture regulated chamber with an acquisition time of 40 min.

MRI measurements were also performed on all tablet core compositions in the dry state. No significant differences were observed between the MRI intensity profiles and pictures of the various compositions indicating that the MRI signal intensity mainly reflects the extent of hydration (local water concentration) without being affected by the different compositions (e.g. the percentage or molecular weight of the PEO).

3. Results and discussion

3.1. Investigation of hydration mechanism

3.1.1. Dynacirc CR hydration kinetics

The hydration kinetics of Dynacirc CR was monitored over time. The signal intensity profiles were calculated on the central cross-section of the Dynacirc CR tablet. Fig. 2 shows that the T1-weighted signal intensity of both the drug and the push layers increased up to 8 h until a uniform hydration plateau with different intensity levels

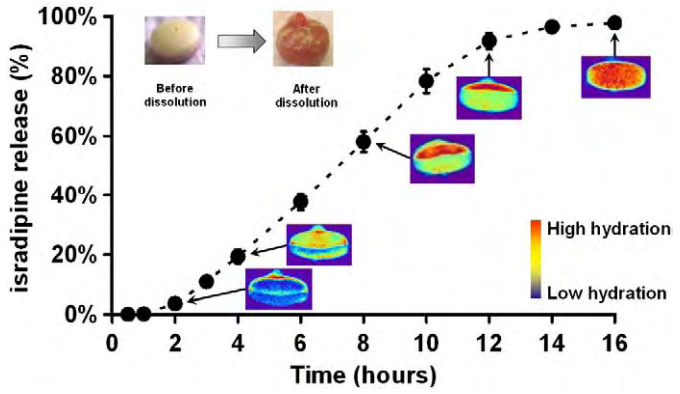

Fig. 3. Dissolution kinetics and corresponding T1-weighted ^{1}H-NMR images of DynaCirc CR 5 mg tablets.

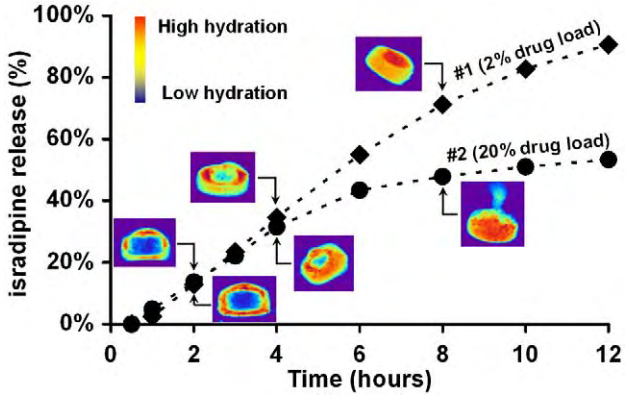

Fig. 4. Dissolution kinetics and corresponding T1-weighted ^{1}H-NMR images of formulations #1 and #2.

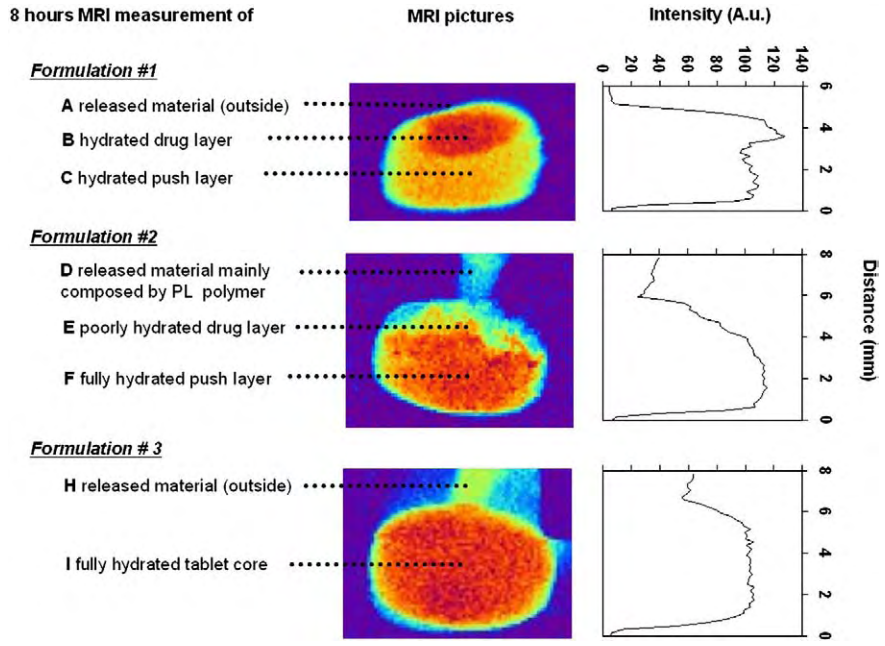

Fig. 5. T1-weighted 1H-NMR images and signal intensity profiles of three formulations after 8 h dissolution: A: the drug layer was more intensively hydrated for the formulation #1 (5 mg), B: the increase of the drug loading for the formulation #2 (50 mg) led to an insufficient hydration of the drug layer which disturbed the drug delivery, C: this insufficient hydration behavior was resolved by increasing the drug layer PEO Mw (formulation #3, 50 mg) and thereby, better disperse the drug within the viscous polymer.

was reached. However, the signal enhancement was higher in the drug layer. The preferential accumulation of water within the drug layer is caused by the presence of sodium chloride, which is only located in the drug layer. Besides the changes of the intensity, BT-MRI provides also the information that the overall size of the Dynacirc tablet remains unchanged during the experiment, showing that the polymer shell of the tablet withstands the osmotic pressure of the tablet. The images also clearly show the decrease of the drug layer thickness and the corresponding increase of the push layer thickness. After 16 h, only the full hydrated push layer is left within the tablet (Fig. 2E). Material which passes the orifice of the tablet dissolves quickly and only a small amount or no material is observed outside the tablet, which indicates that the drug release and dissolution are controlled by the velocity of passing the tablet orifice. To get a link between the hydration and drug release kinetics, an in vitro drug release test was carried out in parallel with the MRI experiments. Fig. 3 shows that the core hydration starts around the orifice causing a local swelling of a small drug layer proportion and thereby, the release of the very first drug fraction (2 h). Subsequently, water enters the tablet core following its permeation through the semi permeable membrane leading to a gradually progressing wetting of the entire tablet core. The constant swelling of the push layer was correlated with the linear drug release from 4 h to 12 h. After 16 h, drug release was completed and the tablet appeared uniformly hydrated.

3.1.2. Effect of the core formulation on the PPOS wetting behaviour

In order to understand the influence of the hydration kinetics on the drug release, three different core formulations were subsequently tested. The effect of the drug loading was investigated comparing two formulations containing 2% and 20% drug loads (formulations #1 and #2 respectively). In a further experimental setup, the 200 kDa PEO of the drug layer was replaced by 600 kDa PEO. It was expected that the 600 kDa PEO could better disperse the drug and thereby help achieving a more uniform hydration of the high loaded drug layer (formulation #3). Finally, an investigation of the hydration kinetics was conducted using a 2% loaded drug formulation #4 designed to have a preferential push layer hydration, i.e. in which the osmotic agent NaCl was only located in the push layer.

3.1.2.1. Influence of the drug load on hydration kinetics. The effect of the drug load on the tablet hydration was studied by increasing the drug load of the formulation #1 from 2% to 20% keeping the rest of the composition constant. Fig. 4 shows that the release and hydration profiles of #1 and #2 were similar at early time points (up to 4 h), but different at later times. An almost complete release (>90%) was observed for the 2% drug load formulation #1. In contrast, an incomplete release (60%) was noticed for #2 which has a high drug load of 20%. The MRI images of formulations #1 and #2 after 4 h indicated a strong heterogeneity of the hydration degree of the upper parts of the tablet (Fig. 4). It suggests that the water which penetrated through the membrane is not able to distribute within the layer within short time. This pattern is in contrast to the commercial Dynacirc formulation, which shows a homogeneous hydration (Figs. 2 and 3). After 8 h, the formulation #1 shows higher signal intensity of the drug layer in contrast to formulation #2, where the drug layer appeared insufficiently hydrated (Fig. 5). The incomplete drug release from #2 could be caused by the rupture of the poorly hydrated drug layer under the push layer pressure and / or aggregation of the drug (due to segregation from the PEO) inside the drug layer. Interestingly, an almost complete drug release

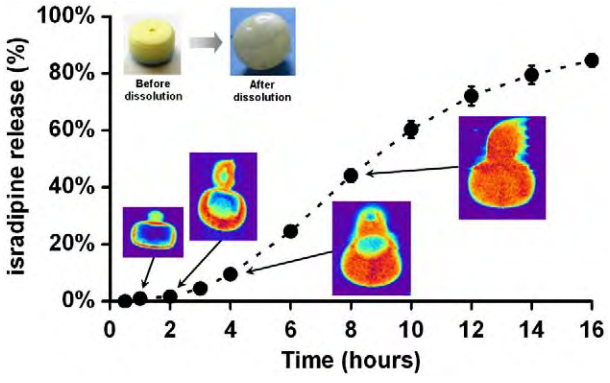

Fig. 6. Dissolution kinetics and corresponding T1-weighted ^{1}H-NMR images of formulation #4.

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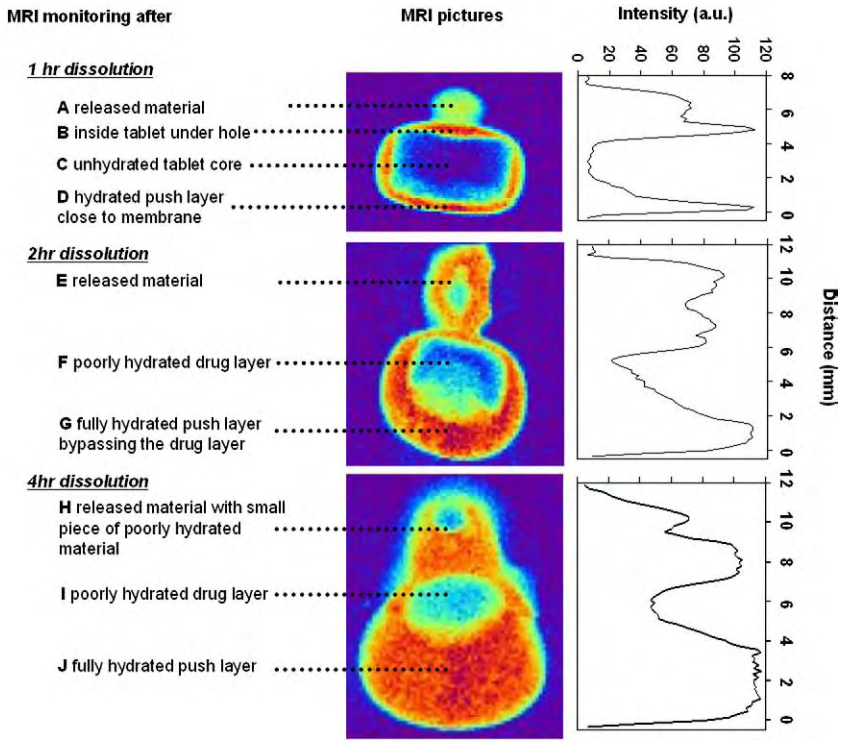

Fig. 7. T1-weighted ^{1}H-NMR images and signal intensity profiles of formulation #4 (5 mg dose) after 1, 2 and 4 h dissolution.

(>90%) at high drug load could be achieved by replacing the PEO 200 k (#2) by PEO 600 k (#3). The MRI image shows a more homogeneous hydration in #3 compared to #2 (Fig. 5). Most likely, the increase of the PEO Mw leads to an improvement of the drug dispersion within the drug layer.

3.1.2.2. Influence of the hydration kinetics balance between the layers. To evaluate the usefulness of MRI for the PPOS development, an investigation was carried out on the formulation #4 (see Fig. 6) which displayed an extremely delayed drug release profile i.e. 10% of the drug were dissolved after 3 h, 50% after 9 h and 85% after 16 h. The T1-weighted imaging gave valuable insights on the behaviour of this formulation. Fig. 7 shows that after one hour the region near the hole (B) and the layers close to the polymer membrane (D) are very well hydrated. The tablet core (C) has a very low signal intensity and is unhydrated. Already some material has been released (A), but not dissolved. It means that dissolution outside the tablet contributes to the overall release kinetics, which is not intended for such delivery systems. After 2 h, the amount of released, but undissolved material increased (E). In contrast to the previous time point (1 h), it shows heterogeneity of the MRI signal intensity with less signal intensity in the "core" of the released material. The drug layer is still poorly hydrated (F). In contrast, the push layer is highly hydrated and bypasses the drug layer (G). Compared to the first hour, the thickness of the tablet has been increased and the shape has been changed to a more spherical form. A further increase in size is visible after 4 h. The push layer is extremely thick and well hydrated (J). The drug layer has a higher intensity compared to earlier time points, but only around 50% compared to the push layer (I, intensity profile). A large amount of material has been released, but remains undissolved. A part of the material (H) shows lower signal intensities which are comparable to the signal intensities of the drug layer inside the tablet. (I). The MRI image therefore suggest that pieces of the drug layer have been pushed through the orifice despite their incomplete hydration due to the very high osmotic pressure within the tablet. The high osmotic pressure leads a large deformation of the tablet shape and increase of the overall dimensions (Fig. 7). This behaviour is in sharp contrast to either the commercial Dynacirc or the other formulations, where the outer dimensions and the shape remained constant throughout the release study (Fig. 2). The NaCl content and location are therefore important parameters to properly balance the hydration kinetics between both the drug and the push layers and thereby, efficiently deliver the drug.

4. Conclusion

The findings of this study lead to a deeper mechanistic understanding of drug delivery from PPOS. The hydration and swelling behaviours of both layers were non-invasively studied using BT-MRI. The hydration balance between both the drug and the push layers appeared as a key parameter influencing the drug delivery. Incomplete delivery linked to high drug load was observed and linked with an inhomogeneous hydration. Based on MRI, the core formulation was optimized to achieve balanced hydration kinetics between the drug and the push layers. Critical parameters for the hydration and drug release process are the drug load, the presence of osmotic active agents and the molecular weight of the matrix PEO. The use of MRI gives unique insights into the tablet which lead to a better understanding of the drug release mechanism and thereby open new perspectives for fast and adequate development of push–pull osmotic systems.

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Chapter IV

Evaluation of the tablet core factors influencing the release kinetics and the loadability of push-pull osmotic systems

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Evaluation of the Tablet Core Factors Influencing the Release Kinetics and the Loadability of Push–Pull Osmotic Systems

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Push–pull osmotic systems have been developed to deliver poorly soluble drugs in a modified-release fashion. The aim of this study was to investigate the influence of the tablet core factors on the drug release kinetics and loadability. The release kinetics was efficiently modulated by varying either the proportion of osmotic agent or the drug layer polymer grade as an alternative to change the membrane characteristics. High osmotic agent proportions and viscous-grade polymers were recommended to formulate high drug loads up to 20% without losing both the release completeness and the zero-order drug release kinetics.

Keywords controlled drug delivery; oral osmotic pumps; osmotic pump; push–pull osmotic systems; poorly soluble drug; extended release

INTRODUCTION

Push–pull osmotic systems (PPOS), also known as push–pull osmotic pumps, have been successfully developed and marketed to extend the release of poorly soluble compounds for various indications, such as hypertension, diabetes, and asthma. In these chronic disease treatments, PPOS were reported as a drug delivery technology reducing the food interaction often observed with poorly soluble drug substances (Abrahamsson et al., 1998; Schug et al., 2002a, b) as well as enabling a once-a-day administration and thereby patient compliance (Prisant & Elliott, 2003). After more than 20 years of use, the low incidence of adverse events of drug products formulated as PPOS gives confidence in the safety of this technology (Bass, Prevo, & Waxman, 2002).

PPOS typically consist of a bilayer tablet core coated with a semipermeable membrane with a laser-drilled orifice as shown in Figure 1. The bilayer tablet core is designed in a way that the first layer is mainly composed of the drug substance, a viscous polymer, and an osmotic agent, whereas the second layer mainly contains a swellable polymer and an osmotic agent. Both polymers in the drug and the push layers are preferably polyethylene oxides (PEOs) because of their singular swelling kinetic as well as their good flowability and compressibility properties (Wu, Wang, Tan, Moochhala, & Yang, 2005; Yang, Venkatesh, & Fassihi, 1996). In addition to the polymers, osmotic agents such as xylitol, sodium, or potassium chloride are added to the tablet core formulation to increase the osmotic pressure (Liu et al., 2000; Thombre et al., 2004; Wong, Donn, Zhao, & Pollock-Dove, 2006). The tablet core is surrounded by a semipermeable membrane that is composed of an insoluble polymer and a plasticizer/pore former. In contact with physiologic fluids, the leachable plasticizer of the semipermeable membrane is dissolved to create a porous permeable structure into the insoluble polymer. As shown in Figure 2, the water diffuses through the membrane and hydrates the polymers of both the drug and the push layers (A) leading to the formation of a drug dispersion in the drug layer and swelling of the push layer. The hydrodynamic pressure generated by the swelling of the push layer (B) forces the drug dispersion through the orifice (C) until drug release completion (D). The drug release mechanism allows the drug to be delivered independently of the drug characteristics and external physiological conditions.

In this study, the PPOS core formulation was evaluated and optimized to deliver a poorly soluble compound, isradipine—a

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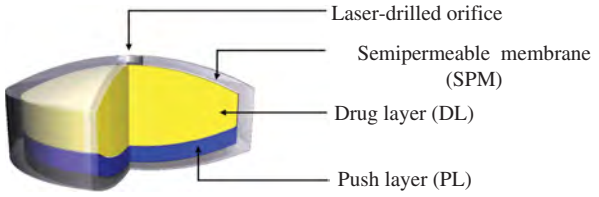

FIGURE 1. Design of a bilayer push–pull osmotic system.

calcium channel blocker from the group of dihydropyridine derivatives (Fitton & Benfield, 1990). The core formulation factors, such as the drug loading, molecular weights (Mws) and proportions of polymers in both layers, the osmotic agent location and proportion, and the drug layer/push layer ratio, were combined following an experimental design to study their influence on the drug release profile. Subsequently, the robustness of the drug release profile was tested for different orifice sizes as well as under various pH and hydrodynamic conditions.

MATERIAL AND METHODS

Materials

Isradipine is a practically insoluble drug substance with a water solubility below 4 mg/L. This neutral compound is light sensitive requiring adequate handling procedures (Bartlett et al., 1998). In addition to the drug substance, the drug layer contains PEO with a Mw of 200, 300, 400, or 600 kDa (Polyox WSR N-80, WSR N-3000, and WSR 205, respectively; Dow Chemical, Midland, MI, USA) or hydroxypropylmethyl cellulose (HPMC Methocel E3 LV or K15M; Dow Chemical) as polymers controlling the drug layer viscosity. The push layer was composed of PEO with a Mw of either 4,000 or 7,000 kDa (Polyox WSR 301 and WSR 303; Dow Chemical) as swellable polymers and indigotin blue (FD&C No. 2, Univar Ltd., Bradford, UK) as dye. Sodium chloride (NaCl, VSR AG, Pratteln, Switzerland) and magnesium stearate (FACI SRL, Carasco, Italy) were added to both layers as osmotic agent and lubricant, respectively. The components of the semipermeable membrane were cellulose acetate with 39.8 wt% of acetyl content (Mw 30 kDa, Eastman Chemical Production, Kingsport, TN, USA) and polyethylene glycol (PEG, Macrogol 3350, Clariant GmbH, Sultzbach, Germany) as plasticizer. The commercialized tablets, Dynacirc CR® (10 mg isradipine, Reliant Pharmaceuticals, Liberty Corner, NJ, USA) were purchased from the US market.

Tabletting

Tablets were manufactured with a single biconcave round shape design composed of a 250-mg tablet core and a 25-mg membrane. The basic amounts and varying ranges of the different components are listed in Table 1. Each tablet was prepared according to the following procedure: The ingredients were sieved through a 500-µm mesh size screen and blended. A pre-compression force of 0.5 ± 0.2 kN was applied to the drug layer blend using a single punch press (EK0, Korsch, Berlin, Germany). Subsequently, the push layer blend was added and a final compression force of 6.0 ± 1.0 kN was applied. The tablet cores were coated using a pan coater (BFC5, Bohle GmbH, Reichshof, Germany). An orifice with a diameter of 1 mm or alternatively a size ranging from 0.5 to 1.5 mm was drilled manually into the drug layer membrane face using a handle drilling machine and micro-drill bits (Dremel AG and Guhring HSS, Basel, Switzerland).

Dissolution Tests

The in vitro isradipine dissolution test was carried out according to USP standards and isradipine USP monograph (US Pharmacopoeia XXX, 2006). Tablets were dissolved in a medium containing lauryldodecylamine-*N,N*-oxide at levels ranging from 0.1 to 2% (wt/vol). The in vitro drug release performance was tested at two levels of pH (1.1 and 6.8) under two hydrodynamic conditions (basket 100 rpm and paddle 150 rpm). Samples were collected at selected time points and analyzed by high-pressure liquid chromatography with a dual UV absorbance detection at 230 and 328 nm wavelengths (Waters GmbH, Eschborn, Germany). The amount of drug released at the defined time points were quantified using a reference solution. The drug release profiles were characterized by three time points ($t_{10\%}$, $t_{50\%}$, and $t_{90\%}$) and the final drug release proportion (CumRel).

The $t_{10\%}$, also called lag time, was defined as the time needed to release 10% of the labeled drug content. Similarly, the $t_{50\%}$ and $t_{90\%}$ were calculated as the times needed to deliver, respectively, 50% and 90% of the labeled drug content.

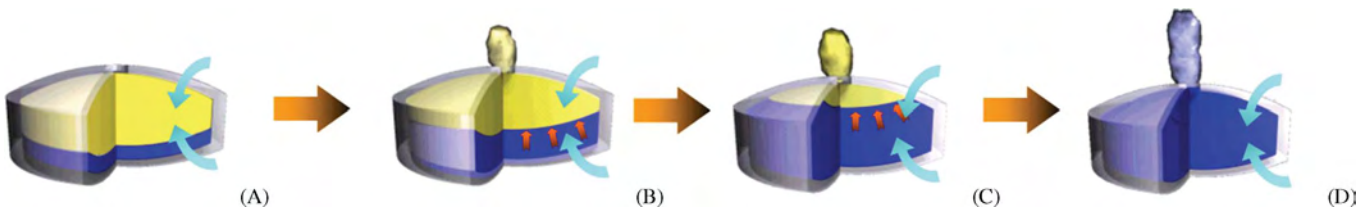

FIGURE 2. Drug release mechanism of push–pull osmotic systems.

TABLE 1
Amount and Range of Tablet Components

Component	Basic Formulation—mg (%tcw)	Range—mg (%tcw)
Drug layer	*187 (66)*	*125–187 (50–66)*
Isradipine	5 (2)	5–75 (2–30)
PEO (Mw: 200 kDa)	155 (62)	0–170 (0–68)
PEO (Mw: 300, 400, or 600 kDa)		0–170 (0–68)
HPMC E3 LV or K15M		0–25 (0–10)
NaCl	25 (10)	0–25 (0–10)
Magnesium stearate	2 (1)	2 (1)
Push layer	*63 (34)*	*63–125 (34–50)*
PEO (Mw: 4,000 kDa)		0–100 (0–40)
PEO (Mw: 7,000 kDa)	35 (14)	0–85 (0–35)
NaCl	25 (10)	0–25 (0–10)
Indigo blue	2.5 (1)	2.5 (1)
Magnesium stearate	0.5 (0.2)	0.5 (0.2)
Membrane	*25 (10)*	*25 (10)*
Cellulose acetate	18.8 (7.5)	18.8 (7.5)
PEG (Mw: 3,350 Da)	6.2 (2.5)	6.2 (2.5)

%tcw, percentage of component related to the tablet core weight.

The drug release rate (RR) was calculated for dissolution profiles with linear correlation coefficient $r^2 > .95$ using both times $t_{10\%}$ and $t_{90\%}$ as follows:

$$\mathrm{RR} = \frac{90\% - 10\%}{t_{90\%} - t_{10\%}} \tag{1}$$

The cumulated 24-h drug release was also estimated as the percentage of the drug released at 24 h relative to the labeled content. The response or dependent variables were analyzed using the analysis of variance (MANOVA F-test, $\alpha < 0.05$) and linear regression analysis with the JMP (SAS, 2002) and Matlab (Mathwork, 2005) software. The dissolution profiles were also individually compared using the "similarity factor, f_2" (Pillay & Fassihi, 1998; Shah, Tsong, Sathe, & Liu, 1998), which could be defined as follows:

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} 100\right\} \tag{2}$$

where n is the sample number, w_t an optional weight factor, R_t the reference assay, and T_t the test assay at time point t.

Finally, an extrapolation of the $t_{90\%}$ was performed by linear regression of the data from 10 to 50% drug release and compared with the experimental value to evaluate the deviation from the zero-order drug release kinetic.

RESULTS AND DISCUSSION

Evaluation of the Tablet Formulation Variables

In order to investigate the influence of the core composition variables on drug release, eight tablet core formulations were prepared as summarized in Table 2. These core compositions were formulated varying the drug load, the PEO amount and type, the sodium chloride (NaCl) amount and location, and the drug layer/swellable layer mass ratio. Dissolution results show that $t_{10\%}$ was mainly influenced by the Mw of the drug layer PEO (F-test, $\alpha < 0.05$, Table 2). The 24-h release was significantly influenced by the drug loading, the osmotic agent proportion, and the location (F-test, $\alpha < 0.05$). All other parameters, such as the drug layer/push layer ratio and the Mw of the push layer PEO, did not significantly influence the drug release. In the following analysis, the influence of each core parameter is displayed in detail.

Modulation of the Drug Release Profile

The drug release profiles of PPOS are usually modulated by modifying the characteristics of the semipermeable membrane (Liu & Xu, 2008; Thombre et al., 2004). An alternative formulation approach was proposed by modifying the tablet core composition. Figure 3 shows the $t_{10\%}$ and the $t_{90\%}$ values obtained for various drug layer PEO types and osmotic agent proportions. The previous outcomes of the statistical design experiments were confirmed showing that the osmotic agent proportion mainly influences the drug RR, whereas the PEO Mw modifies both $t_{10\%}$ and $t_{90\%}$ to the same extent. Hence, the

TABLE 2
Core Formulation Factors and Dependent Variables

	Independent Variables[a]						Dependent Variables		
Core Form.	Drug Load (%tcw)	DL PEO Mw (kDa)	NaCl Proportion (%)	NaCl Location	PL PEO Mw (kDa)	DLPLR	CumRel[b] (%)	$t_{10\%}$ (h)	$t_{50\%}$ (h)
1	2	200	5	DL	7,000	3	99.3	1.7	5.5
2	2	200	10	DL	4,000	1.5	98.6	1.6	4.3
3	2	600	5	PL	7,000	1.5	93.7	3.9	8.9
4	2	600	10	PL	4,000	3	83.5	3.3	8.2
5	20	600	10	DL	7,000	3	92.9	3.0	6.5
6	20	600	5	DL	4,000	1.5	87.4	3.6	8.0
7	20	200	10	PL	7,000	1.5	54.6	2.9	21.2
8	20	200	5	PL	4,000	3	51.0	2.7	22.0
9	20	200	0	DL	7,000	3	55.0		
10	20	200	5	DL	7,000	3	67.1		
11	20	200	10	DL	7,000	3	93.6		
12	20	300	0	DL	7,000	3	62.4		
13	20	300	5	DL	7,000	3	80.3		
13b	20	300	5	DL	7,000	3	79.9		
14	20	300	10	DL	7,000	3	91.5		
15	20	300/600	0	DL	7,000	3	76.1		
16	20	300/600	5	DL	7,000	3	86.8		
17	20	300/600	10	DL	7,000	3	92.7		
18	20	600	0	DL	7,000	3	82.4		
19	20	600	5	DL	7,000	3	87.2		
20	20	600	10	DL	7,000	3	93.1		

[a]%tcw, percentage of component related to the tablet core weight; DL and PL PEO, polyethylene oxide in the drug layer and the push layer, respectively; NaCl, sodium chloride; DLPLR, drug layer/push layer ratio (wt/wt).
[b]CumRel, cumulated drug release at 24 h.

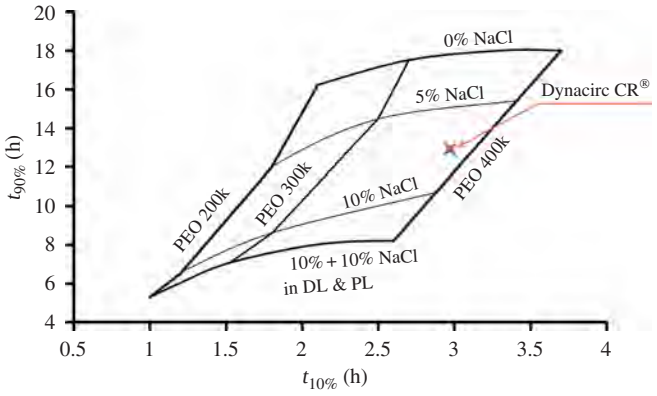

FIGURE 3. Dissolution performance of 2% isradipine formulations containing various osmotic agent proportions and drug layer PEO Mw: The dissolution profile was defined by the $t_{10\%}$ and $t_{90\%}$, which are the times needed to deliver 10 and 90% of the drug-labeled content, respectively; the acronyms DL and PL designate the drug and the push layers, respectively.

drug delivery was delayed by approximately 1.5 h without impacting the drug RR by modifying the PEO Mw from 200 to 400 kDa in the drug layer. Nevertheless, no further release modifications were observed when switching from PEO 400 to 600 kDa, possibly explained by their similar viscosity behavior (Yu, Amidon, Weiner, & Goldberg, 1994). Alternatively, small proportions of HPMC could also be added to PEO to delay the drug release, for example, similar release profiles obtained for formulations containing PEO 300 kDa were achieved by adding either 2% HPMC K15M or 4% HPMC E3 LV in the drug layer composition (data not shown). Increasing either HPMC amount or Mw was also reported as potential approach for modifying the release profile of swellable elementary osmotic pumps (Nokhodchi, Momin, Shokri, Shahsavari, & Rashidi, 2008; Shokri et al., 2008).

The drug RR was subsequently varied by changing the osmotic agent proportion. The variation from 0 to 10% of osmotic agent led to an increase of the drug RR from 5 to 15%/h. A further acceleration of the RR toward 20%/h, was obtained by adding osmotic agent to the push layer in addition to the 10% in the drug layer. It should be noted that the

modification of the osmotic agent also impacts the shape of the drug release curve and thereby the release kinetic linearity. Figure 4 shows the predicted $t_{90\%}$ values estimated by linear regression versus the observed values. An interesting zero-order drug release kinetic was achieved for all formulations containing above 10% osmotic agent in the drug layer. The deviation of the values for lower osmotic agent proportions illustrates a change of drug delivery kinetics from zero order to first order.

Influence of Both the External Conditions and the Orifice Size

In line with the general in vivo observation that drugs are delivered from PPOS independently of the gastrointestinal mobility and fed state (Jamzad & Fassihi, 2006; Wonnemann et al., 2006), the drug delivery from PPOS is generally not influenced by the pH and hydrodynamic conditions in in vitro dissolution experiments (Liu et al., 2000; Thombre et al., 2004). To confirm that none of the formulation modifications described in the present publication made the drug release susceptible to in vitro hydrodynamic changes, the systems were tested at two pHs and agitation speeds. The results show that the isradipine release of formulation containing either PEO 200 or 600 kDa was not significantly influenced by the dissolution conditions ($f_2 > 75$, f_2-test, Figure 5A). Furthermore, various orifice sizes ranging from 0.5 to 1.5 mm were drilled into the membranes of the formulations to evaluate if the increase of drug layer viscosity impacts on the drug release. No impact of the orifice diameter was observed in either case ($f_2 > 75$, f_2-test, Figure 5B).

Drug-Loading Capacity

The loadability of a dosage form is an important criterion for the choice of technology delivering poorly soluble drugs.

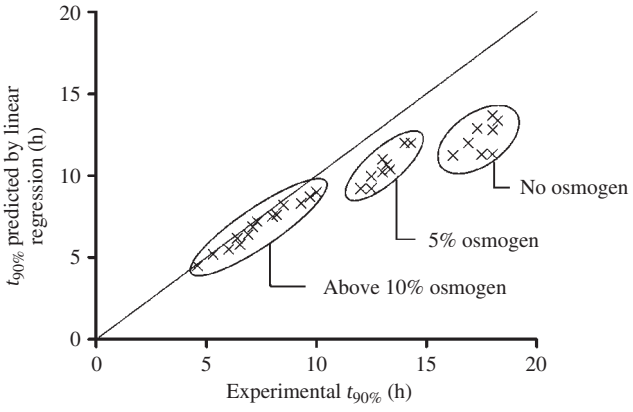

FIGURE 4. Deviation of the experimental $t_{90\%}$ to the extrapolated value by linear regression for formulations containing various osmotic agent proportions in the drug layer.

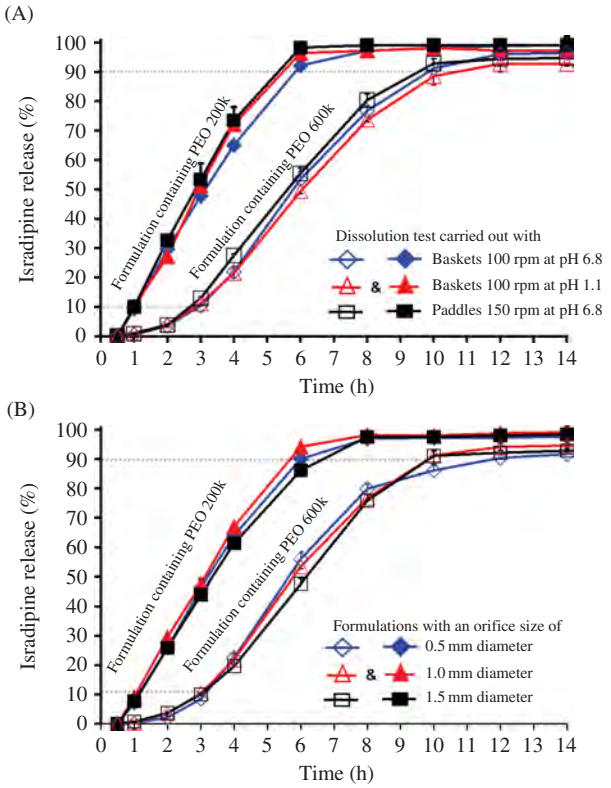

FIGURE 5. Influence of the orifice size, pH, and agitation speed on the drug release of two formulations containing PEO 200 and 600 kDa.

In the past, the achievable drug loads in PPOS (especially in case of poorly soluble drugs) have somewhat limited the applicability of this technology. This study has shown that specific variations of the tablet core formulation have an impact on the completeness of the drug release and should be effective measures to achieve completeness of drug release also for higher drug loads. The influence of the drug load on the drug release profile, including the final drug release proportion, was therefore studied. Figure 6 shows that the isradipine release of over 95% was achievable for formulations loaded up to 20% isradipine (50-mg dose) avoiding the need of a drug overage typically used for these dosage forms (Ayer & Ridzon, 1993; Verma, Viswanathan, Raghuvanshi, & Pampal, 2006). The osmotic agent proportion and the drug layer polymer need to be adjusted to maximize the drug release completeness. It can be hypothesized that an insufficient hydration and drug dispersion had been the root cause for the incomplete drug delivery observed for highly loaded formulations in the past. The experiments of this study show that even with high osmotic agent proportions and by using different PEO viscosities in the drug layer, PPOS with isradipine loads beyond 20% remain somewhat challenging if one does not want to use a drug overage (see Figure 7). Although the drug release profiles were similar up to $t_{50\%}$ irrespective of the PEO polymer, the completeness

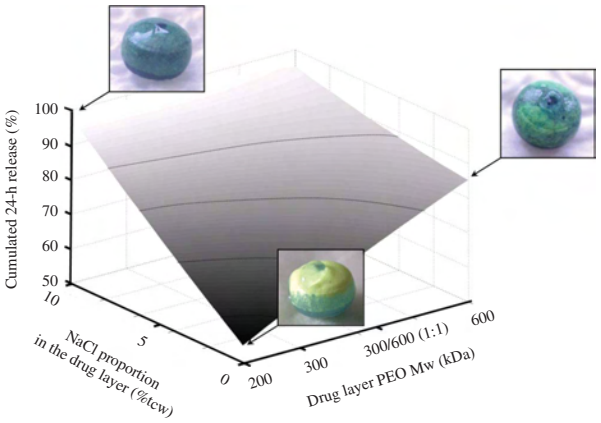

FIGURE 6. Influence of the NaCl proportion and the drug layer PEO Mw on the cumulated 24-h isradipine release for formulations containing 20% drug load (50 mg dose) (r^2 = .944). Pictures illustrate the yellow-colored drug remaining within the shell after the dissolution test (a colorful version is available online).

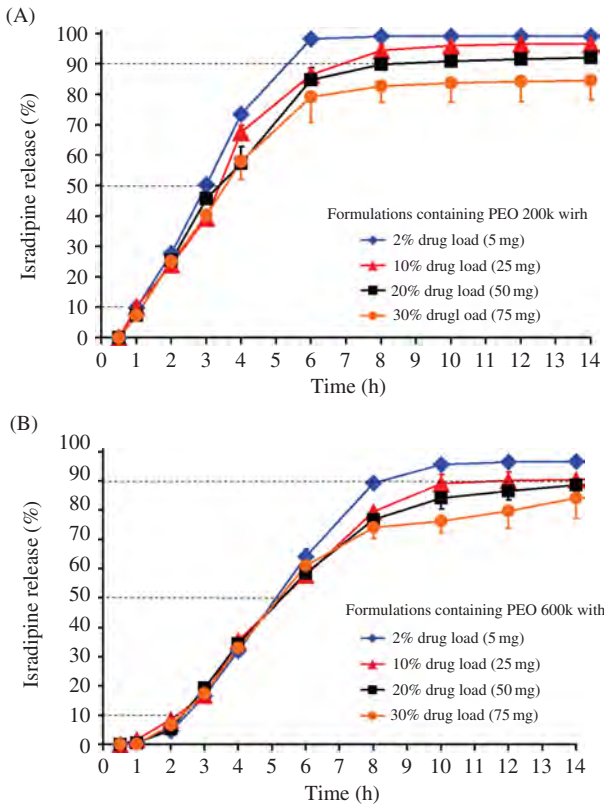

FIGURE 7. Influence of the drug loads (doses) on drug release for formulations containing PEO 200 and 600 kDa.

of drug release was not achievable with formulations having 30% drug load. However, the similarity of the dissolution profiles up to 20% isradipine shows that various drug loads can be formulated without modifying the tablet design spotlighting the flexibility of this dosage form.

CONCLUSION

In conclusion, PPOS are a robust modified-release technology. This technology allows to deliver poorly soluble drugs in a well-controlled release fashion over a wide range of dosage strengths. The core tablet formulations were varied to efficiently modulate the drug release profile without impacting the drug release completeness. The drug RR can be adjusted by varying the osmotic agent proportion in the drug layer. The choice of PEO in the drug delivery system is also a valuable option to modify the dissolution profile as well as to better disperse the drug layer at high drug loadings without losing both the zero-order drug release kinetics and the independent delivery from the pH and hydrodynamic conditions. The use of the identified tablet core factors, which ensure the completeness of drug release, has led to drug loads up to 20%. This equates to a five-fold drug load increase compared with the commercialized product (Dynacirc CR®).

ACKNOWLEDGMENTS

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Chapter V

Approach to design push-pull osmotic systems

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Approach to design push–pull osmotic pumps

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ABSTRACT

Despite more than 30 years of clinical use, only few studies have been published reporting on the release mechanism underlying the drug delivery from push–pull osmotic pumps (PPOP). The aim of this study is to understand which factors have an effect on the drug delivery for modelling the drug release and to develop a mathematical model predictive of the drug release kinetics. The influence of the drug property was tested on two model drugs, isradipine (ISR) and chlorpheniramine (CPA) which are respectively practically insoluble and freely soluble. Results show that, regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by four factors, (i) the PEG proportion in the membrane, (ii) the tablet surface area, (iii) the osmotic agent proportion and (iv) the drug layer polymer grade. The influence of each key formulation factors on the release mechanism was investigated defining their applicability range. A mathematical approach was developed to predict the drug delivery kinetics varying the PPOP controlling factors and helps to more efficiently design PPOP.

1. Introduction

Oral osmotic pumps (OROS™) were introduced in the 1970s by Theeuwes and co-workers as an alternative to polymeric erodible systems (Theeuwes, 1975, 1983b, 1984). Distinguished by their ability to release drug substances independently of the medium composition and hydrodynamics, these systems offer potential clinical benefits, such as being potentially able to mitigate the food-effect (Abrahamsson et al., 1998; Wonnemann et al., 2006), increase patient compliance (Grundy and Foster, 1996) and treatment tolerance (Rahima-Maoz et al., 1997).

Specifically designed to deliver poorly soluble drugs (Theeuwes, 1983b, 1984; Thombre et al., 2004; Verma et al., 2000), push–pull osmotic pumps (PPOP) consist of a bilayer core surrounded by a semipermeable membrane with a laser-drilled orifice as shown in Fig. 1. In contrast to the previous single-core design, the polymeric nature of the drug layer of the tablet core allows the drug to be dissolved or dispersed and released in a zero-order kinetics fashion under the pressure generated by the swelling of the push layer at a constant rate (Liu et al., 1999, 2000; Thombre et al., 2004).

Drug release kinetics of PPOP has been hypothesized to be controlled by the hydration kinetics of both membrane and tablet core. Thus, several mathematical models were proposed to predict the drug delivery rate from osmotic pumps based on fluid diffusion equation (Eq. (1)) through a semipermeable membrane (Theeuwes, 1975; Theeuwes and Yum, 1976; Thombre et al., 1989) based on a product of the membrane thickness (h) and surface (A), the water permeability (L_p), difference of hydraulic pressure (ΔP) and the osmotic gradient ($\sigma \cdot \Delta\pi$).

$$\left(\frac{dV}{dt}\right)_{\text{inlet}} = \frac{A \cdot L_p}{h}(\sigma \cdot \Delta\pi + \Delta P) \quad (1)$$

Further adaptation of the model was also proposed taking in account the surface area of each layer and introducing the degree of hydration (Anderson and Malone, 1974). The water permeability through a semipermeable membrane was correlated with the leachable agent proportion in the membrane composition largely independently of the pore former properties (Bindschaedler et al., 1987; Guo, 1993). The osmotic pressure can be estimated using Van't Hoff law as a function of the proportion of ionic agent in the tablet core (Theeuwes and Yum, 1976; Theeuwes, 1983a). The flow rate through the orifice was estimated using Ostwald-de Waele power fluid law (Eq. (2)) assuming non-Newtonian, laminar and incompressible flow as a product of the dynamic viscosity (η), the orifice radius (R), the depth of the tablet core (h) and a flow index value (n). If the flow behavior index is closed to 1.0, this equation corresponds to Hagen–Poiseuille's law used for Newtonian fluid. Nevertheless, the Newtonian behavior is only applicable for low concentration of polymer i.e. up to 10% (Bansal et al., 2009) as described for elementary osmotic pump containing polyethylene oxide (Lu et al., 2003). The fluid behavior index decreases for highly concentrate polymer solution or dispersion below 0.7 but, in the case of PPOP, the rheologic behavior of a saturated polymer/drug

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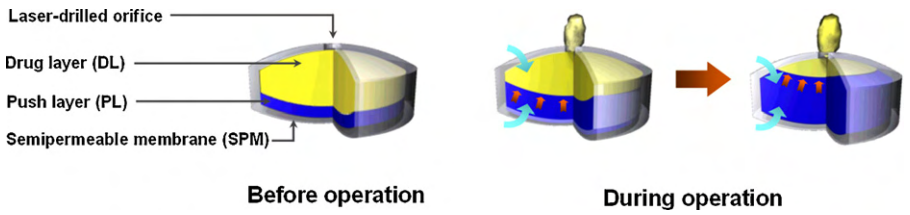


Fig. 1. Schematic diagram of push–pull osmotic pumps (PPOP).

dispersion is difficult to estimate.

$$\left(\frac{dV}{dt}\right)_{\text{outlet}} = \frac{\pi \cdot R^3 \cdot \rho}{1/n+3}\left(\frac{R \cdot \Delta P}{2 \cdot \eta \cdot h}\right)^{1/n} \quad (2)$$

The applicability of this model appears therefore limited due to the complexity of the PPOP design/composition and the insufficient data providing from a systematic investigation of the formulation factors. For example, it has been shown that the orifice diameter did not significantly influence the drug release profile (Liu et al., 2000; Thombre et al., 2004) whereas the model predicts a major influence on the release. Recent publications (Malaterre et al., 2008, 2009a) also describe the hydration kinetics of the PPOP tablet core using NMR imaging. Authors presented that hydration kinetics between both the drug and the push layers needs to be balanced in order to achieve a complete delivery of the drug. The aim of the present study was to identify the controlling factors influencing the drug delivery and their quantitative effect on the drug release kinetics. Due to the complex PPOP geometry and composition, the influence of formulation factors was first investigated to determine their respective applicability range and influence on the release kinetics. A statistical approach was then developed varying the PPOP controlling factors to predict the drug release kinetics.

2. Materials and methods

2.1. Material and tablet preparation

Isradipine (ISR) and chlorpheniramine maleate (CPA) were both purchased from Selectchemie AG, Zürich, Switzerland and formulated as PPOP. The properties of both drugs are summarized in Table 1. The drugs were blended with the other ingredients of the drug layer after a primary sieving through 150 mesh. As indicated in Table 2, polyethylene oxides (PEO) with a molecular weight (Mw) of 200, 300, 400 or 600 kDa (Polyox WSR N-80, WSR N-750, WSR N-3000 or WSR 205, Dow Chemical, Midland, United States) as dispersive polymer, NaCl (VSR AG, Pratteln, Switzerland) as osmotic agent and magnesium stearate (FACI SRL, Carasco, Italy) as lubricant were added to the drug layer composition. Separately PEO 7000 kDa (Polyox WSR 303 respectively, Dow Chemical, Midland, United States) and indigotin blue (FD&C n°2, Univar Ltd., Bradford, UK) as dyes and magnesium stearate was blended as the push layer.

Table 1
Model drug properties.

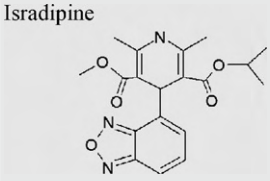
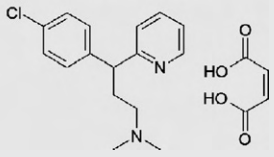
Model drug	Properties	Pharmacological class	Ref.
Isradipine 	Neutral, sparely insoluble drug, substance (S ~5 mg/L)	Calcium channel blocker from the group of dihydropyridine derivates	Fitton and Benfield (1990)
Chlorpheniramine maleate 	Weak base, freely soluble drug, substance (S >5 g/L)	H1 histamine receptor antagonist	Rumore (1984), Smith and Feldman (1993), Assanasen and Naclerio (2002)

Table 2
Formulations and levels of formulations used in the various investigations.

Study reference	Tablet core					Membrane parameters			Tablet design
	ISR[a] (%ctw[c])	CPA[a]	PEO type (kDa)	NaCl in DL[b] (%ctw[c])	NaCl in PL[b]	PEG type (Da)	PEG% (%ctw[c])	Membrane thickness (μm)	Surface/weight (cm^2/g)
A	2%		200	10%	10%	400–3350	3–33%	100–200	8.44
B	2%		200	10%	10%	3350	25%	100	*Round*: 6.8–11.4; *Oblong*: 9.5–12.2
C	2–10%	2–10%	200–600	0–20%	0–10%	3350	5–25%	100–200	8.44
D	2%	2%	100–600	10%	10%	3350	25%	100	8.44
E	2–20%	2–40%	200	10%	10%	3350	25%	100	8.44

[a] PPOP formulated with either isradipine (ISR) or chlorpheniramine maleate (CPA).
[b] NaCl located respectively either in drug layer (DL) and/or in the push layer (PL).
[c] Proportion is relative to the tablet core weight.

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The drug layer composition was pre-compressed under 0.5 ± 0.2 kN with single punch press (Korsch EK0, Germany) and a final compression under a pressure of 6.0 ± 1.0 kN was performed to obtain the tablet with the different shapes from 6 mm-round to 19 mm-oblong varying the tablet surface area.

The tablet core was subsequently coated in a pan coater (Bohle BFC5, Germany) equipped with a diphasic spray nozzle (Schlick, Germany). The 7.5% (w/w) coating solution was prepared by dissolving cellulose acetate with 39.8 wt% acetyl content (Mw 30 kDa, Eastman Chem. Prod., Kingsport, United States) and polyethylene glycols (PEG 400, 1500 or 3350 Da, Clariant GmbH, Sultzbach, Germany) in acetone/water 19:1 (w/w). A 1 mm-diameter orifice was drilled manually on the drug layer membrane face using a handle drilling machine and micro-drillbits (Dremel AG and Guhring HSS, Switzerland).

2.2. Membrane thickness and surface morphology

The membrane thickness was determined following tablet cross-section using optical microscopy (Sterni V11 Zeiss, Jena, Germany) and AnalySIS v5.1 software (Soft Imaging System GmbH, Muenster, Germany). The surface morphology before and after dissolution was evaluated by Scanning Electronic microscopy (SEM, JSM 6400, Joel Ltd., Tokyo, Japan). Samples were previously scattered with gold during 160 s under a vacuum of 0.05 mA and a field of 16 mA using a sputter coater (SCD-004 Oerlikon Balzers AG, Balzers, Liechtenstein). Pictures were taken under 15 kV. Special attention was given to limit the exposition time of the sample under the electron stream to avoid artefacts due to sample degradation.

2.3. Kinetics of the polyethylene glycol depletion

The release kinetic of polyethylene glycol (PEG) from the membrane was monitored over time using High Performance Liquid Chromatography (HPLC, Waters Corp., Milford, USA) equipped with an PL-Aquagel-OH 30 column, 8 μm (Agilent, Santa Clara, USA) and a refraction index detector (Waters 410, Waters Corp., Milford, USA). This method was discriminative between the different PEG grades used in this evaluation and the PEO from the tablet core composition. The limit of detection was estimated at 3 mg/L therefore the none-drilled PPOP tablets were placed in 100 mL Milli-Q water with different osmolarities. The PEG proportion in the membrane over time was fitted using an exponential model (Eq. (3)) to determine the constant k_{PEG}:

$$\left.\frac{M_t}{M_0}\right|_{PEG} = e^{-k_{PEG}\cdot t} \tag{3}$$

The PEG depletion kinetics was compared varying the membrane thickness, PEG proportions and grades.

2.4. Drug release study

Dissolution tests were conducted in accordance with the USP monographs of isradipine and chlorpheniramine tablets using USP apparatus I (basket, 100 rpm) in 500 mL monobasic phosphate pH 6.8 buffer with or without 0.2% (w/v) LDAO (US Pharmacopeia XXXI, 2006). Samples were collected every hour over 16 h and analysed by High Performance Liquid Chromatography with UV-detection at specific wavelengths (Waters, Milford, US). The similarity of dissolution profiles was analysed using both the "difference factor, f_1" (Moore and Flanner, 2008) and the "similarity factor, f_2" (Shah et al., 1998; Pillay and Fassihi, 1998) defined in Eqs. (4) and (5).

$$f_1 = \left(\frac{\sum_{t=1}^{n}\left|R_t - T_t\right|}{\sum_{t=1}^{n} R_t}\right)\cdot 100 \tag{4}$$

$$f_2 = 50\cdot\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n} w_t\cdot(R_t-T_t)^2\right]^{-0.5}\cdot 100\right\} \tag{5}$$

where n is the sample number, w_t is an optional weight factor, R_t the reference assay and T_t the test assay at time point t.

The $t_{10\%}$ (so-called lag time) and $t_{90\%}$ were defined as the time needed to release 10% and 90% of the labelled drug content. Both the lag time and drug release rate were separately modelled using both 2^n reduced and 3^n full fractional design approaches. Variance (MANOVA F-test, α <0.05) and linear regression analyses were performed with Matlab software (Mathwork 2005, Natick, US). The predicted dissolution profiles were compared with the observed data using mean dissolution time (MDT) defined in Eq. (6) (Rinaki et al., 2003):

$$\mathrm{MDT} = \frac{\int_0^\infty t\cdot W_d(t)\cdot dt}{\int_0^\infty W_d(t)\cdot dt} \tag{6}$$

3. Results and discussion

3.1. Parameters affecting the membrane porosity

The PEG role in the membrane has been described in literature with a dual functionality of plasticizer (Guo, 1993) and pore former (Rani and Mishra, 2004). Prior to drug release investigation, the role of PEG in the membrane was studied. The membrane surface morphology appeared smooth for all formulations as illustrated in Fig. 2A and C. Pores were observed on the surfaces of membranes containing PEG at levels above the ratio of 1:3 PEG/CA after dissolution as shown in Fig. 2D. Pores had a diameter which could be estimated in a range of 20–50 nm and were uniformly distributed on the surface. Below a ratio of 1:6 PEG/CA, the pores were not observable probably due to their low size. Results confirmed the PEG role as pore former/leachable agent.

To further investigate the effect of the PEG on the activation of PPOP, the PEG release over time was monitored varying the membrane compositions and thickness at two ionic strengths of the dissolution medium. The kinetic profile of PEG release from the membrane was fitted with a first-order equation as summarized in Table 3. Rows #1–6 show that the PEG depletion kinetics increased with the PEG/CA ratio and decreased with the membrane thickness. The comparison of either rows #2 with #10–11 or #6 with #12–13, shows that the depletion kinetics slows down with increasing molecular weight of PEG.

3.2. Parameters having an effect on the activation of the drug delivery

3.2.1. Influence of the membrane and core factors on lag time

The drug release from PPOP as from any other coated modified-release system is characterized by a lag phase. The influence of the PEG depletion kinetics on the lag time was first investigated (Fig. 3A) showing an exponential relationship regardless of the membrane thickness or the PEG type. It can be hypothesized that the activation of the drug release from PPOP starts with the depletion of the leachable agent from the membrane followed by the hydration of the tablet core. This is consistent with the finding discussed above that the lag time increased with increasing of PEG molecular weight. Above a PEG/CA ratio of 1:3, the membrane is not anymore semipermeable allowing the drug diffusion and release through the membrane despite that the tablet was not drilled. This was nevertheless only observable for soluble drug such as CPA. Results also show that the lag time was influenced by the tablet surface (Fig. 3B), the osmotic agent proportion (Fig. 3C), and the drug layer polymer Mw (Fig. 3D). Thus, the increase of the proportion of the osmotic

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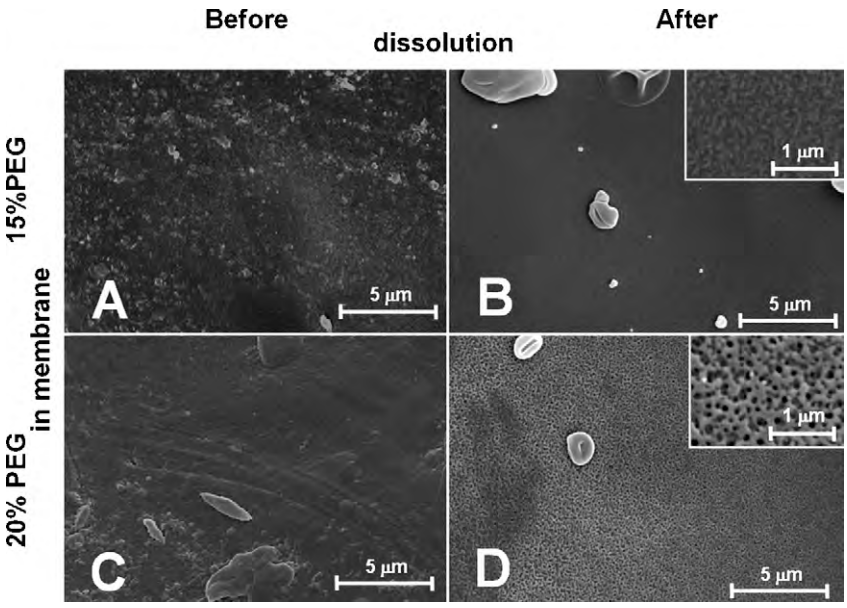

Fig. 2. SEM surface images of membranes containing 1:6 and 1:2 PEG/CA ratios, before and after dissolution.

agent in the tablet core composition increased the rate of water hydration of the core decreasing the lag time up to 15%. Interestingly, the addition of osmotic agent into the push layer did not significantly change the lag time. This result can be explained by the fact that the swelling of the drug layer is responsible for the initial drug fraction delivered through the orifice as recently hypothesized in the literature (Malaterre et al., 2009a). The lag time was further modified by varying the viscosity of the drug layer via the molecular weight of PEO (Fig. 3D). It is interesting to notice that the drug property did not influence the lag time despite the difference of water solubility.

3.2.2. Lag time mechanism and mathematical model

The investigation of the lag time proves that the lag time is the result of sequential processes driven mainly by the time needed to (i) leach PEG out of the membrane creating pores increasing the membrane permeability, (ii) hydrate the tablet core depending on the osmotic proportion and the table surface area, and (iii) dissolve the drug from the composition pushed out in the medium. The effect of the four parameters controlling the lag time, was studied using a 3^n full-factorial design. The model well fits the observed lag times with a correlation coefficient of $r^2 = 0.946$. No quadratic interactions were significant (F-test, $\alpha = 0.05$). Coefficients of −1.2151, 0.2479 g/cm^2, −7.0609 and 0.0065 mol/g, respectively, were found for the correlation of lag time with $\ln(k_{PEG})$, the tablet surface area, the osmotic agent proportion (%NaCl) and PEO Mw in the drug layer with a residue of −9.9673 h. The variance analysis showed that the main influencing parameters are ranged in the order of $\ln(k_{PEG})$ > %NaCl > PEO Mw > tablet surface (F-test, $\alpha = 0.05$) showing that the membrane permeability and the osmotic pressure of the core composition are mainly controlling the tablet hydration kinetics.

3.3. Influence of the formulation parameters on release rate

3.3.1. Effect of the membrane composition, thickness and surface on release rate

PPOP are designed to deliver the drug in a zero-order kinetic fashion for a prolonged duration (Liu et al., 1999, 2000; Thombre et al., 2004). The membrane composition is the key parameter to control the drug release rate as confirmed in Fig. 4A. The PEG proportion significantly controlled the release rate only up to 20% i.e. a 1:4 PEG/CA ratio. Above 1:4 PEG/CA ratio, the release rate was not significantly influenced as previously reported (Thombre et al., 2004). It is also interesting to notice that the release rate varied as an exponential function of the PEG proportion in the membrane as reported for other osmotic pumps for which the water permeability also monitored as an exponential of the pore former proportion

Table 3
PEG release kinetics from the membrane.

#	Formulation factors			Responses		
	PEG Mw (Da)	PEG/CA ratio	Membrane thickness (µm)	PEG half-life (min)	First order model	
					k (10^{-5} h^{-1})	r^2
1	400	1:2	96 ± 4	15.5	70.1	1.000
2	400	1:3	94 ± 6	16.7	69.0	1.000
3	400	1:4	96 ± 3	18.1	63.7	0.999
4	400	1:6	96 ± 3	22.6	51.1	0.998
5	400	1:9	89 ± 7	37.7	30.6	1.000
6	400	1:19	91 ± 7	70.2	16.4	1.000
7	400	1:32	98 ± 4	131.0	8.8	0.999
8	400	1:3	178 ± 9	44.0	26.2	0.993
9	400	1:19	173 ± 13	226.3	4.8	0.991
10	1500	1:3	92 ± 7	21.9	52.6	0.999
11	3350	1:3	96 ± 4	26.3	44.0	0.999
12	1500	1:19	95 ± 7	105.2	11.0	0.996
13	3350	1:19	91 ± 7	134.1	8.6	0.997

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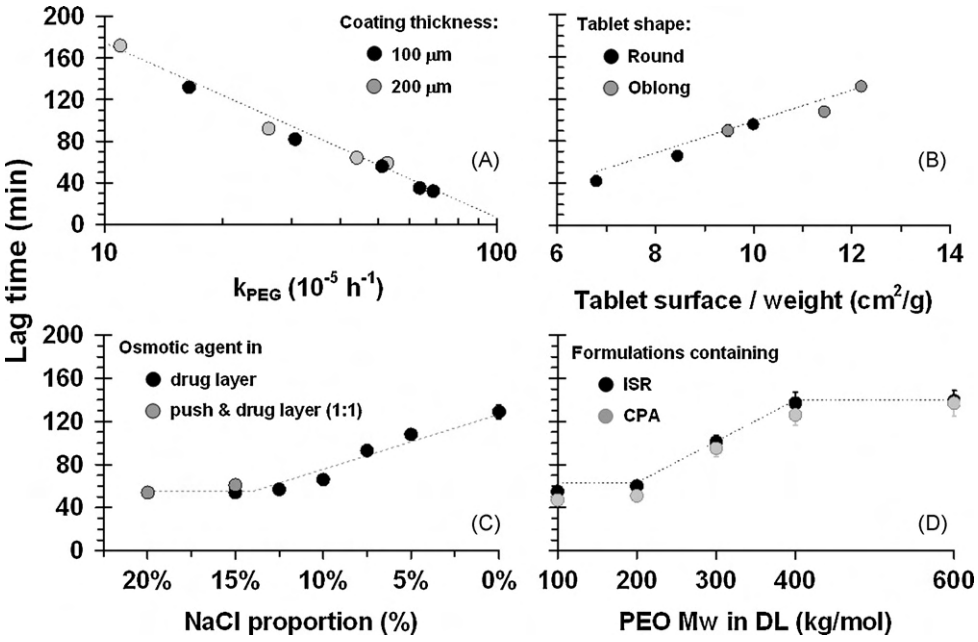

Fig. 3. Lag time of PPOP formulations varying: (A) the PEG depletion kinetics, (B) tablet surface/weight, (C) the osmotic agent proportion and (D) the drug layer PEO molecular weight (see Table 2); ISR and CPA, respectively isradipine and chlorpheniramine maleate; the dotted line figures out the results of the drug release model.

independently of the nature of the pore former (Bindschaedler et al., 1987; Guo, 1993). The tablet surface was not significantly impacting the release rate (Fig. 4B, *t*-test, $\alpha = 0.05$) but release rate from oblong tablets was slightly lower than from round tablets.

3.3.2. Modulation of the release rate by varying the tablet core formulation

A linear relationship was found between the osmotic agent proportion and release rate (Fig. 4C). Interestingly, PPOP performed without osmotic agent showing that the polymer has an intrinsic osmotic pressure and the release rate increased linearly up to 12% in the drug layer. Above 15% NaCl, the osmotic agent needs to be balanced between both layers. This result confirmed the importance to maintain a "hydration balance" as already suggested in previous hydration studies (Malaterre et al., 2008, 2009a). Results also showed that the drug release rate was not significantly affected by either the drug layer polymer or the drug properties (Fig. 4D, *t*-test, $\alpha = 0.05$).

3.3.3. Modelling of drug release rate

A statistical design approach was used to investigate the joint influence of the studied formulation factors. A 2^n reduced

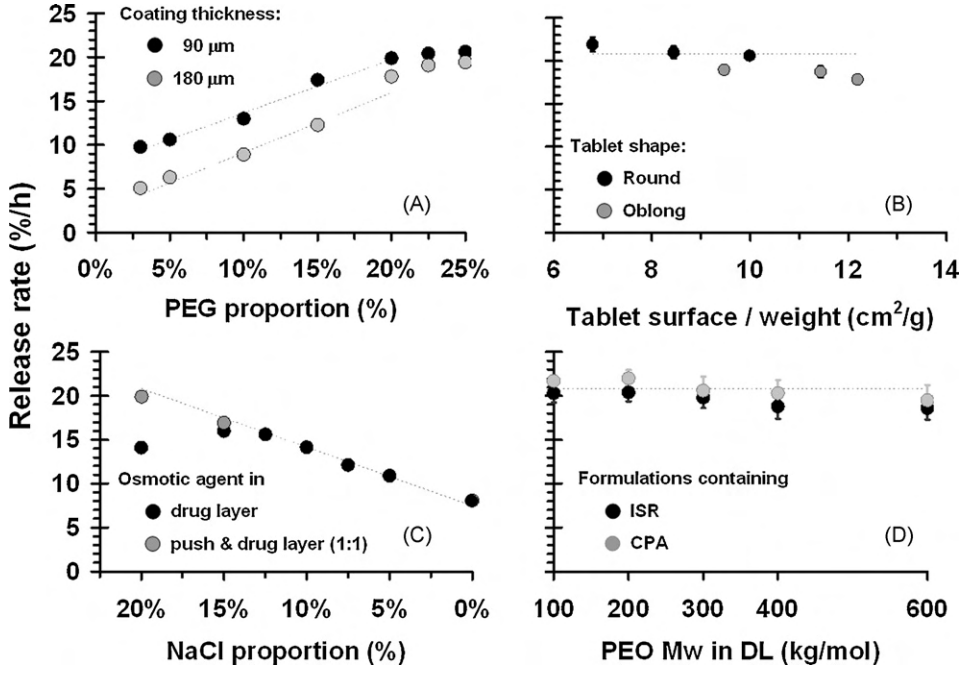

Fig. 4. Drug release rate of PPOP formulation varying: (A) the PEG depletion kinetics, (B) tablet surface/weight, (C) the osmotic agent proportion and (D) the drug layer PEO molecular weight (see Table 2); the acronyms ISR and CPA represent respectively the two model drugs, isradipine and chlorpheniramine maleate; the dotted line figures out the results of the drug release model.

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experimental design was used to determine the influencing parameters i.e. X_1, the osmotic agent proportion (% tablet weight); X_2, the PEG proportion (% coating weight); X_3, the membrane thickness (mm); X_4, the drug loading, X_5, the drug type (ISR or CPA) and X_6, the PEO Mw on the drug release rate (RR). As predicted by the osmotic pressure model (Eq. (1)), only the osmotic agent proportion (X_1) and the membrane properties (X_2 and X_3) significantly controlled the drug release rate (F-test, $\alpha = 0.05$). A full 3^n factorial design was applied to quantify the joint influence of three main parameters on the release kinetics. No quadratic interactions were significant giving the following drug release model (Eq. (7)) with a regression coefficient, $r^2 = 0.941$:

$$RR_{est} = 2.338 + 57.963 \cdot X_1 + 60.7636 \cdot X_2 - 70.561 \cdot X_3 \quad (7)$$

where RR, release rate (%/h); X_1, the osmotic agent proportion (% tablet weight); X_2, the exponential of the PEG proportion (% coating weight); X_3, the membrane thickness (mm). The variance analysis showed that the main influencing parameters are both the PEG and NaCl proportions (F-test, $\alpha = 0.05$).

3.4. Influence of the drug solubility and loading

The drug loading is an important parameter in the development and the choice of a controlled-release system for a particular drug substance (Thombre, 1999). Often used with relatively low drug loading, the robustness of PPOP for formulations containing up to 30% drug load (Thombre et al., 2004; Malaterre et al., 2009b). In this study, the drug load of CPA and ISR was increased up to a level of 20% as recommended for PPOP containing ISR (Malaterre et al., 2009b) and 40% for CPA. No significant difference of release kinetics was observed by increasing the drug load (within the investigated range) or changing the drug substance (Fig. 5). As hypothesized, the drug delivery from a PPOP could be considered as independent of the drug property and loading up to about 20–30% because of the delivery of the drug as a relatively highly viscous hydrogel either as a solution or a dispersion.

3.5. Approach to design PPOP

The complex design is often perceived as a drawback for the development and manufacture PPOP. Nevertheless, the special design of PPOP ensures probably the robustness of the drug delivery and its flexibility. Thus, designing PPOP needs a clear formulation strategy which depends on the dosage strength and the targeted release profile. Furthermore, drugs with loading <10%, could be formulated independently of the drug properties. For less potent drugs (loads >10%), formulation recommendations were given in previous publications (Malaterre et al., 2009a,b) i.e. optimization of the osmotic agent proportion in the drug layer to the loading. However, a minimal proportion of 5% osmotic agent in drug layer could be advised to release drug in a zero-order kinetics. The drug

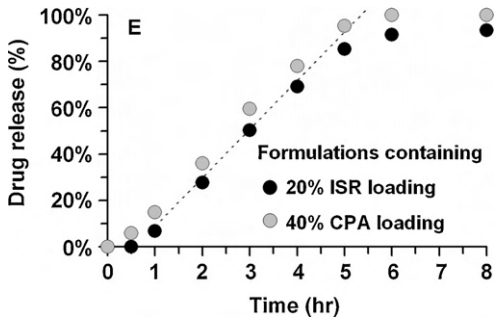

Fig. 5. Drug release profiles of formulations containing respectively 20% CPA and 40% ISR loading (dotted lines = model predictions for 2% loading drug).

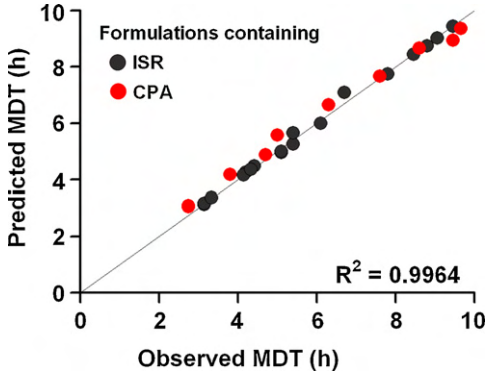

Fig. 6. Predicted mean dissolution times (MDT) vs experimental.

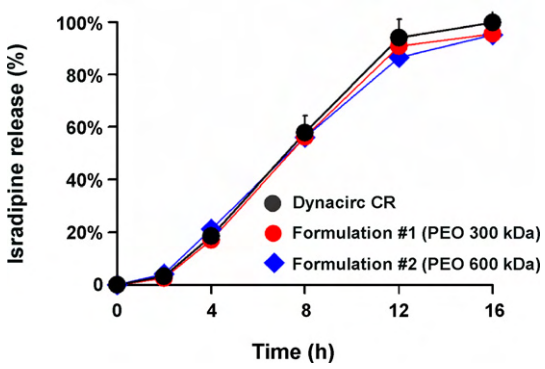

Fig. 7. Dissolution profiles of IRS marketed PPOP vs formulations with calculated parameters; formulations #1 and #2 containing respectively PEO with a Mw of 300 and 600 kDa and a PEG proportion in the coating of 8% and 14%.

load has a direct impact on the tablet size and thereby, the tablet surface. The expected dissolution profile should therefore be modulated by varying both the PEG proportion in the membrane (*%PEG*) and the PEO grade in the drug layer (*PEO Mw*) on top of the osmotic agent proportion (*%NaCl*). For example, the release profile given by Dynacirc CR 5 mg could be simulated using Eq. (8) fixing the NaCl proportion at 10% level in the drug layer and the tablet surface at 8.44 cm^2/g (equivalent to 8 mm round shape):

$$\left.\frac{M}{M_\infty}\right|_{0\to 90\%}(\%) = RR_{est} \cdot (t - t_{10\%,est}) + 10\% \quad (8)$$

with RR_{est}, the estimated release rate (Eq. (7)) and $t_{10\%,est}$, the estimated lag time.

The mean dissolution times showed that the proposed model well-estimates the experimental data ($r^2 = 0.912$) as shown in Fig. 6 disregards of the formulated drug. The release profiles of two formulations were predicted based on the developed model. Formulations were prepared with PEO Mw 300 and 600 kDa, #1 and #2 respectively. PEG proportions in the membrane were calculated at levels of 10% and 17.5%. Both formulations were prepared and compared with Dynacirc CR. Fig. 7 shows that dissolution profiles were not significantly different to the Dynacirc CR's profile ($f_1 < 5, f_2 > 90$). Thus, the presented formulation strategy shows its strengths in the selection and development of future PPOP.

4. Conclusion

The role and the quantitative effects of the key factors on the drug release from PPOP have been investigated in the present study. Drug loads ranging between 2% and 10% were prepared with lag times from 0.5 to 4 h and zero-order controlled drug release within 5 to >24 h. Influencing formulation factors were individually

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investigated defining the applicability ranges of the key parameters and providing a deeper understanding of the drug release mechanism. The interest to develop streamlined mathematical approach has been demonstrated to facilitate the selection of the most appropriate PPOP design. Based on these results, PPOP formulations can be developed in a fast and efficient manner focusing on mainly three key formulation parameters, the NaCl proportion, the polymer grade of the drug layer and the PEG proportion in the membrane. This study confirms that PPOP is an interesting controlled-release platform to deliver drugs independently of their properties in a predictable controlled-release manner.

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Chapter VI

Terahertz pulsed imaging, a novel process analytical tool to investigate the coating characteristics of push-pull osmotic systems

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Research paper

Terahertz pulsed imaging, a novel process analytical tool to investigate the coating characteristics of push–pull osmotic systems

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ABSTRACT

The aim of this study was to investigate coating characteristics of push–pull osmotic systems (PPOS) using three-dimensional terahertz pulsed imaging (3D-TPI) and to detect physical alterations potentially impacting the drug release. The terahertz time-domain reflection signal was used to obtain information on both the spatial distribution of the coating thickness and the coating internal physical mapping. The results showed that (i) the thickness distribution of PPOS coating can be non-destructively analysed using 3D-TPI and (ii) internal physical alterations impacting the drug release kinetics were detectable by using the terahertz time-domain signal. Based on the results, the potential benefits of implementing 3D-TPI as quality control analytical tool were discussed.

1. Introduction

Cellulose-acetate-based coatings have been commonly used as insoluble membranes in the formulation of modified-release medicines. Part of the oral modified-release technologies using cellulose-acetate-based films are the osmotically driven systems developed in the 1970s by Theeuwes and associates to deliver poorly soluble drugs independently of the GI mobility [1]. Push–pull osmotic system (PPOS) is one of the osmotically driven systems specially designed to deliver poorly soluble drugs. This technology typically consists of a bilayer tablet core surrounded by a laser-drilled semipermeable membrane [2]. As illustrated in Fig. 1, the semipermeable membrane controls the water ingress and thereby the swelling kinetics of the push layer which pushes the drug layer through the orifice. Therefore, small variations in the semipermeable membrane properties can affect the drug release performance of these systems.

Recently, a number of imaging and spectroscopic techniques have been suggested for the quality control of pharmaceutical products, including X-ray microcomputed tomography [3], Raman imaging [4,5], near-infrared imaging [6,7] and terahertz imaging [8,9]. Many of these techniques have yet to be applied to osmotically driven systems. Nevertheless, some limitations could be anticipated using either near-infrared imaging, X-ray tomography or Raman spectroscopy for studying PPOS. Indeed, the laser-excitation used in Raman imaging technique can destroy the polymeric membrane of the drug product; this coupled with the long data acquisition times are the major limitations of this technique. X-ray tomography has high running costs, issues with beam hardening towards the edge of products as well as the long data analysis times that will limit its application. The low penetration depth of near-infrared imaging generates the requirement for cross-sectioning of samples. It was, therefore, the aim of this study to evaluate the potential of the three-dimensional terahertz pulsed imaging (3D-TPI) to characterize, in a non-destructive manner, the spatial and statistical coating thickness distribution of PPOS. The terahertz time-domain waveform was also used to detect internal physical alterations due to interruptions during the coating process. This investigation was conducted based on the methodology successfully applied to the investigation of various coating systems such as controlled-porosity coatings [10–12] and cosmetic and enteric coatings [13]. The implementation of 3D-TPI as a in-process control (IPC) tool was finally discussed.

2. Experimental

2.1. Materials

The ingredients of the bilayer tablet core were isradipine, polyethylene oxides (PEO, Polyox WSR N-80 and WSR 303, Dow Chem-

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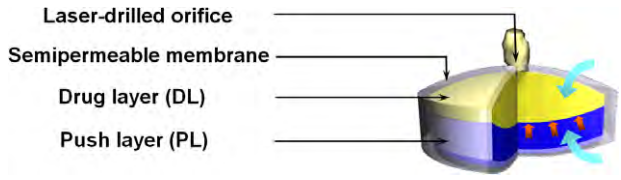

Fig. 1. Drug release mechanism from push–pull osmotic systems.

ical, Midland, US), sodium chloride (VSR AG, Pratteln, Schwitzerland), indigo blue (FD&C No. 2, Univar Ltd., Bradford UK), and magnesium stearate (FACI SRL, Carasco, Italy). Cellulose acetate (Mw 30 kDa, Eastman Chem. Prod., Kingsport, US) and polyethylene glycol (PEG 400, Clariant GmbH, Sultzbach, Germany) were the ingredients of the coating formulation. All the components were sieved through a 500-μm mesh sieve prior to use.

2.2. Tablet compression

Two tablet core formulations were prepared as summarized in Table 1. All ingredients of both the drug and the push layers were blended separately using a Turbula T2F shake-mixer (WAB AG, Basel, Switzerland) except the magnesium stearate which was added finally as external phase. The bilayer tablet cores were compressed on a single press (Korsch EK0, Berlin, Germany). The drug layer was compressed first with a pre-compression pressure of 0.5 kN. After the addition of the push-layer blend, a 6-kN compression force was applied. Round 8-mm biconvex tablet cores were finally obtained.

2.3. Tablet coating

The tablets were coated in a pan coater (Bohle BFC5, Ennigerloh, Germany) equipped with a two-fluid nozzle (Schlick, Coburg, Germany). The coating conditions are listed in Table 2. A coating formulation consisting of cellulose-acetate plasticized with 5% PEG and diluted to a concentration of 7.5% solids in acetone/water (95:5 v/v), was prepared and applied to the tablet cores. Process endpoints were fixed to targets of 10% and 20% of coating weight gain. Subsequently, a coating defect was simulated by interrupting the coating process. Thus, the coating process was stopped 30 min after spraying two-third of the coating solution. A final coating gain weight of 20% was finally reached. A 1 mm size orifice was manually drilled on the drug layer face of each tablet.

Table 1
Composition of the tablet cores.

Ingredients	Quantity (mg)	
	Formulation #1	Formulation #2
Drug layer		
Isradipine	5	50
PEO (Mw: 200 kDa)	155	110
NaCl	25	25
Magnesium stearate	2	2
Push layer		
PEO (Mw: 7000 kDa)	60	60
Indigo blue	1.5	1.5
Magnesium stearate	1	1

Table 2
Coating conditions.

Tablet batch quantity (kg)	1.2
Inlet air temperature (°C)	30
Fluid bed/nozzle distance (cm)	7
Chamber air flow ($Nm^3\ h^{-1}$)	100
Spray rate ($ml\ min^{-1}$)	16
Spray air pressure (bar)	0.7
Atomization air pressure (bar)	0.7
Rotation rate (rpm)	14

2.4. Terahertz pulsed imaging

Terahertz 3D data of tablets under investigation were recorded using TPI Imaga 2000 (TeraView, Cambridge UK). The operation of this instrument had been previously reported [13]. Briefly, an ultrashort terahertz pulse is generated by the instrument; when it encounters a tablet surface or tablet coating, this pulse is reflected back to a time-gated terahertz detector. The resulting terahertz waveform thus consists of multiple pulses arriving at the detector at delayed time points depending on the index of refraction and the thickness of the penetrated layer, see Fig. 2. The pulses generated by this technique have an extremely low average power (<100 nW), and therefore do not destroy the polymer membrane within the product. As most pharmaceutical ingredients are semi-transparent to terahertz radiation, pulses can penetrate several millimetres into final dosage forms and thereby eliminate the need to tablet cross-section [13].

Terahertz 3D data set maps (x-direction, y-direction and z-direction) comprising different number of point measurements with 200 μm point spacing were recorded. About 1400 pixels on the tablet-face and -end surfaces were scanned, and the measurement took in the region 15-min per surface. Terahertz waveform consisting of 512 data points was recorded at each point of the image.

2.5. Coating thickness determination

The tablets were cut in the centre to determine the membrane thickness using optical microscopy (Sterni V11 Zeiss, Jena, Germany). The average coating thickness for each batch was calculated based on six tablets with a 66× focus with AnalySIS v5.1 (Soft Imaging System GmbH, Muenster, Germany). The coating thickness average was defined as the mean value of 20 measurements uniformly distributed around the tablet.

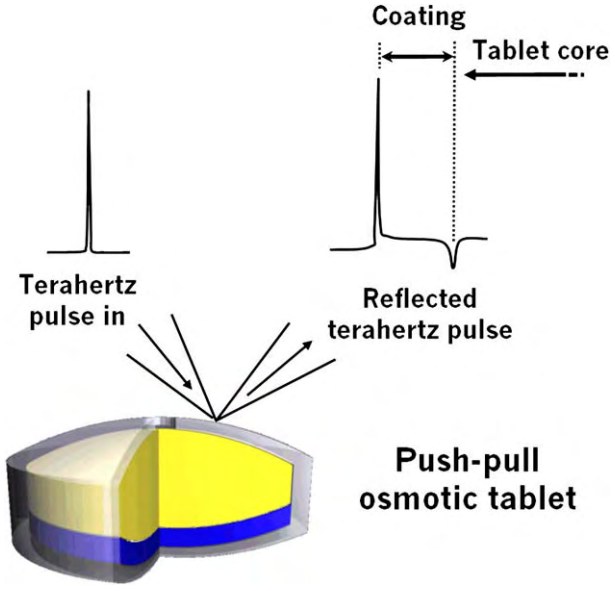

Fig. 2. Schematic diagram of the experimental arrangement to examine coating of push–pull osmotic systems.

Table 3
Thickness measurements by 3D-TPI vs optical microscopy.

Tablet core	Coating weight gain (%)	Thickness averages[b] measured by		Two-tailed, paired *t*-test		
		3D-TPI ($n = 4$)	Microscopy ($n = 6$)	*t*	*p*	Result[a]
Formulation #1	9 ± 0.5	112 ± 6	112 ± 3	0.112	0.91	*N*
Formulation #2	10 ± 0.3	119 ± 7	114 ± 5	1.245	0.24	*N*
Formulation #2	18 ± 1.3	268 ± 5	259 ± 7	2.150	0.06	*N*

[a] *N* means not significantly different at 0.05 level.
[b] Data described as average ± standard deviation. List of figures.

2.6. Dissolution test

The *in vitro* isradipine dissolution test was carried out on six tablets per batch using USP dissolution apparatus I (Varian, Edison, US) with a basket rotation speed of 100 rpm. The dissolution medium was buffered at pH 6.8 and 0.2% of lauryldodecylamine-*N*,*N*-oxide was added to reach sink condition. Samples were collected every hours over 16 h and were analysed according to isradipine USP 30 monograph by High Performance Liquid Chromatography with UV-detection at 328 nm wavelength (Waters, Milford, US). The dissolution profiles were also individually compared using both the "difference factor, f_1" [14] and the "similarity factor, f_2" [15,16] defined as Eqs. (1) and (2)

$$f_1 = \left(\frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right) \times 100 \quad (1)$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t \cdot (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where n is the sample number, w_t is an optional weight factor, R_t is the reference assay and T_t is the test assay at time point t.

3. Results and discussion

3.1. Coating thickness measurement

The coating thickness average determined by terahertz pulsed imaging (TPI) was primarily validated *versus* the optical microscopy destructive measurements. A comparison of the average thicknesses from three batches is shown in Table 3. Thickness measurements performed by terahertz and microscopy were not significantly different (*t*-test, $\alpha = 0.05$). TPI measurements were also repeated on tablets with different tablet cores coated at the same time. It appears that the tablet core composition did not influence the coating thickness distribution as shown in Fig. 3. Nevertheless, it was observed that the thickness distribution was not truly uniform around the tablets. More specifically, the coating thickness of the tablet central band was 30% thinner than the tablet face in case of the batch with 10% of film coat. Similar observation was reported by Ho and co-workers for bi-concave tablets coated with a 150-μm poly(vinyl-acetate)-based film with a 33% thinner central band [10,12]. Authors hypothesized that the difference was possibly due to either the TPI-signal distortion or the measurement coating layer thickness discrepancy. Interestingly, no significant difference was further observed for 20% coating gain, despite an extremely low variation of tablet shape. Therefore, the present results seem to exclude that the difference is due to thickness determination method. As already hypothesized in the previous publication [12], the coating thickness difference is probably due to the tablet shape which leads to a statistically longer spray exposure time of tablet face during the tablet rolling in the coater pan.

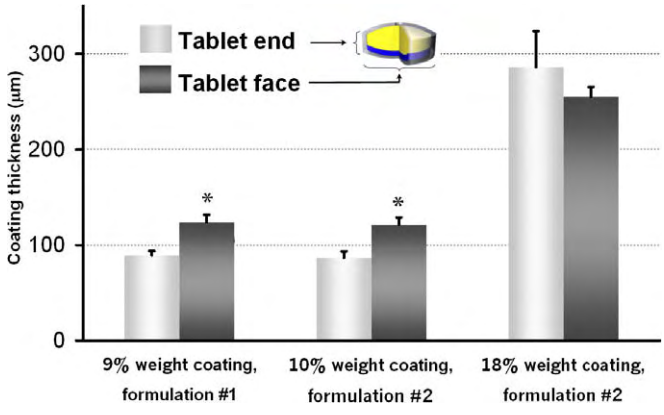

Fig. 3. Coating thickness of the tablet faces and ends varying in either the tablet core or the coating gain weight.

3.2. Prediction and detection of coating quality deviations affecting the drug release performance

The drug release profile of formulation #1 was determined and correlated with the TPI measurements. The drug release rates were 8%/h and 5%/h for the tablets with 10% and 20% film coat weight, respectively. By linearly correlating the thickness and the drug release data, it can be estimated that a variation of 10 μm thickness average (1% weight gain) leads to a deviation of 0.3%/h drug release rate. It is therefore important to keep under control the coating thickness which directly impacts on the drug release profile.

Furthermore, the coating process can also influence the drug release performance as demonstrated by simulating a 1-h interruption. Fig. 4 shows that the drug release profiles of both formulations #1 and #2 were significantly decreased for those tablets that had been discontinuously coated ($f_1 > 15$ despite $f_2 > 50$). Interestingly, an internal coating interface was detected on the terahertz domain waveform and was confirmed by optical micros-

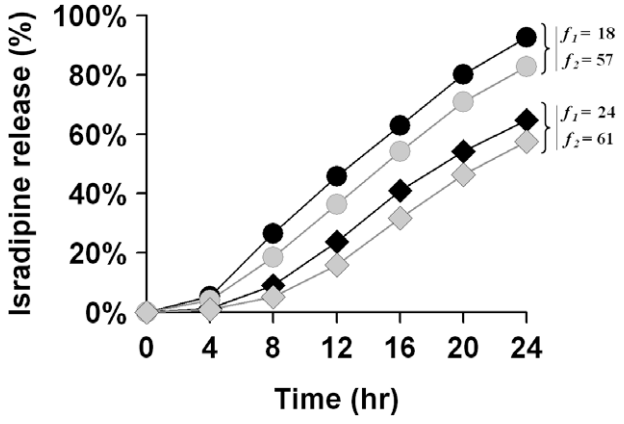

Fig. 4. Dissolution profiles either with (● and ♦) or without (● and ♦) coating process interruption of formulations #1 & #2, respectively ($n = 6$, error smaller than symbols).

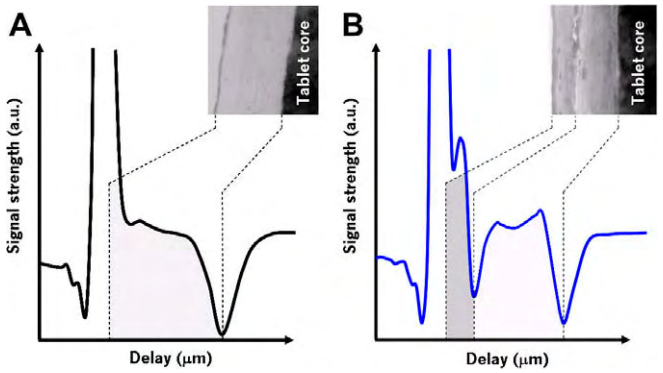

Fig. 5. Time-domain waveform allowing the detection of internal alteration due to coating process interruption: spectra without and with internal physical alteration in (A) and (B), respectively.

copy as shown in Fig. 5. Furthermore, the coating interface was located at a depth of about 120 μm below the surface, which corresponded to the one-third proportion sprayed after the interruption. An additional curing step in the coating process attenuated the interface creation, but only partially reduced the effect of the coating step interruption on the drug release performance.

3.3. Potential applications of 3D-TPI strengthening the PPOS development

Already presented by US Food & Drug Administration analytical experts as an "attractive replacement of wet dissolution testing" for delayed-release tablets [12], the present study opens new perspectives to ensure the quality along the development of PPOS. Controlled by the coating properties, the presented study highlights the importance of evaluating the coating properties to predict the drug release performance of PPOS. The interest in developing imaging techniques has grown in the recent few years with the raising complexity of new PPOS, e.g. methylphenidate PPOS (Concerta™) [17] consisting of a tri-layer tablet core and tri-layer coating. The root-cause analysis of drug delivery deviations becomes quite difficult by only using dissolution tests. Already tested on multilayer systems [9,13], 3D-TPI could potentially be used during pharmaceutical development to detect non-destructively and concurrently (i) variations of the coating and/or drug over-coating thickness and properties and (ii) delamination issues during the tablet core compression [9,18]. In the same setting, information on the drilling quality may also be collected as illustrated in Fig. 6. Therefore, the non-destructive nature of the TPI measurements could potentially benefit to strengthen the quality control during the development and manufacturing of PPOS. However, further work is required to address the correlation of information provided by TPI images to each of these physical product performances.

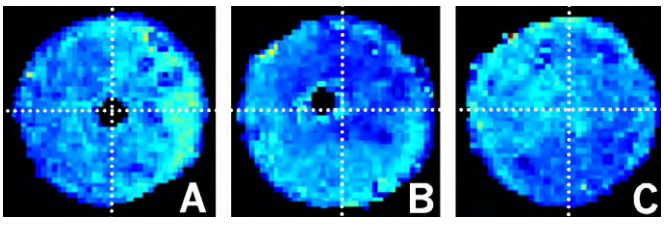

Fig. 6. Terahertz 2D mapping of the drug layer allowing to determine the drilling quality: (A) tablets drilled with a centred orifice; (B) the non-centered and smaller orifice; and (C) not drilled tablet.

4. Conclusions

In this study, the membrane characteristics of push–pull osmotic systems were investigated using the novel 3D-terahertz pulsed imaging technique. Intra- and inter-PPOS membrane variations were non-destructively detected. Thickness distribution variations were correlated with the drug release kinetics to better predict the effect of thickness variations on the release performance. In addition to spatial information, a mapping was also performed to get a profound understanding of the membrane physical properties. Internal physical changes leading to lower release kinetics were detected and further explored. The implementation of terahertz pulsed imaging as quality control analytical tool in the development and the manufacturing may represent a major step forward to improve the design, the scalability and potentially the quality control during the routine manufacture of push–pull osmotic systems.

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Chapter VII

Conclusions and Outlooks

Conclusions

Push-pull osmotic pumps are advantageous technology to deliver drugs whatever the drug are soluble or dispersed within the released hydrogel. This property is particularly under interest for delivering pH-dependent and poorly soluble drugs in a controlled-release manner over a prolong period, independently of the environmental conditions.
In this present program, the mechanisms underlying the drug delivery of push-pull osmotic systems, were investigated to get a better picture on the importance of the hydration kinetics on the drug delivery. Formulation strategy and analytical tools were proposed to support development of future push-pull osmotic systems.
Three main points could however be spotlighted the importance to

- use a systematic approach based on adapted analytical tools to better characterize complex drug delivery systems
- develop formulations based on statistical approach more efficiently discriminating the relative influence of the formulation factors.

In-vitro and *in-vivo* investigations were initiated at Novartis Pharma AG (Basel) mainly on two active compounds, a poorly soluble and a pH-dependent soluble drugs. Fast early development was successfully applied to both projects based on both the technical expertise and the predictive drug-release statistical model.

In conclusion, the present work show that push-pull osmotic systems are an interesting platform modified-release technology to deliver poorly and pH-dependent soluble drugs either as viscous solution or dispersion. This confers to the technology an independent drug release from the drug property allowing to set up a global formulation strategy. Thus, the tablet-core needs to be adequately formulate allowing a fast and sufficient drug composition hydration leading to an homogeneous dispersion. Driven by the osmotic gradient through the system's membrane, the drug release profile could subsequently be tailored by modifying the membrane characteristics delivering drug over 4 to 24 hours.

Chapter VIII

Summary (in French)

Résumé en français

CHAPITRE II: Tour d'horizon des différentes technologies de comprimés osmotiques et de leur utilisation clinique au cours des 30 dernières années

Relativement peu répandu en Europe et au Japon, les comprimés osmotiques prennent une place de plus en plus importante au sein des technologies permettant la libération prolongée de principe actif. Ainsi, représentant déjà plusieurs milliards de dollards aux Etats-Unis pour plus de 35 produits mis sur le marché au cours des 10 derniéres années, cette technologie semble susciter de plus en plus l'intérêt des compagnies pharmaceutiques comme des génériqueurs. Il est donc intéressant de voir en détail les différences qui distinguent les produits et ainsi d'appréhender les facteurs qui orientent le choix de tel ou tel approche.

Les trois premiers chapitres de ce travail passent en revue la place des comprimés osmotiques dans la littérature scientifique et leur marché. Une analyse des différents technologies sur le marché et en développement est proposée. Ainsi, l'intérét particulier des comprimés osmotiques dits 'push-pull' pour délivrer des actifs peu solubles est illustré à travers plusieurs exemples. La quatriéme et dernière partie se propose de sensibilier le lecteur aux principaux risques, mais aussi bénéfices liés à l'utilisation clinique des formes osmotiques. En effet, les comprimés osmotiques sont par conception, non-dégradables et donc sujets à être soit source de gène lors de leur déglutition, mais aussi ralentissent leur transit à travers le tube digestif. Cet effet doit être pris en compte lors de l'installation d'un traitement excluant les patients ayant subis certaines chirurgies digestives ou présentant des troubles de la déglutition. Malgré ces restrictions, les résultats cliniques montrent que les comprimés osmotiques permettent une absorption indépendante de la prise de nourriture contrairement les autres formes à libération modifiée. Néanmoins, les études par scintigraphie montrent que les comprimés osmotique par le fait qu'ils sont non dégradables, présentent des temps de séjours dans l'estomac augmentés de plusieurs heures lors de prise alimentaires ce qui pourrait amener affecter l'absorption de façon très prononcée. Cependant, ceci ne ressort pas de l'analyse détaillée de leur résultat *in-vitro in-vivo* au travers des divers classes de molécules. Les comprimés osmotiques représentent donc une approche intéressante pour délivrer les actifs faiblement solubles.

Malgré certaines polémiques autour des comprimés osmotiques comme dans le cas de l'Osmosin®, les comprimés osmotiques peuvent avec le recul de 30 ans présenté une option intéressante pour des molécules difficile à formuler comme formes à libération modifiée dont les actifs faiblement solubles.

<u>Chapitre III:</u> Evaluation de comprimés osmotiques dits ‘push-pull’ par imaginerie magnétique

La libération d’actif des comprimés osmotiques push-pull a souvent été décrite comme dépendant de la cinétique d’hydratation des polymères qui composent sa bi-couche centrale.
Cette étude en collaboration avec l’Universté de Halle-Wittenberg (Allemagne) se propose de vérifier cette hypothése en étudiant la vitesse d’hydration utilisant l’imagerie à résonance magnétique du proton H^1.
Les résultats montrent que la cinétique de libération est contrôlée par l’hydratation du comprimé. Cette étude montre l’importance de balancer l’hydration des deux couches composant le comprimé afin d’obtenir la libération de la dose de façon constant et controllée. Cette étude illustre aussi l’importance de développer des méthodes d’imagerie spécifique pour faciliter le développement de formes à libération modifiée.

<u>Chapitre IV :</u> Evaluation des facteurs influençant la libération et le dosage des comprimés osmotiques ‘push-pull’

Cette étude est une transposition des concepts dégagés de l’étude précédente en formulation. Ainsi, la concentration d’agent osmotique ainsi que la viscosité du polymère composant le coeur du comprimé push-pull ont été modifiés afin d’accroître la concentration d’actif ainsi que la linéarité de la libération. L’importance d’augmenter la concentration d’agent osmotique ainsi que la viscosité du polymère entourant l’actif avec le dosage a été montré. En paralléle, certains paramètres, comme la taille de l’orifice n’influencent pas la libération. Les performances des différentes formulations ont été testées à différent pH et conditions hydrodynamiques afin de prouver que celles-ci sont indépendantes de ces paramètres.

<u>Chapitre V :</u> Stratégie de formulation des comprimés osmotiques 'push-pull'

Aprés avoir étudier l'influence des paramètres lié au dosage dans le chapitre IV, cette étude se propose d'analyser et de corréler des paramètres influençant la cinétique de libération des comprimés push-pull. L'influence relative de chacun de ces paramètres a été testée sur 2 actifs, dont l'un est trés faiblement soluble (l'irsadipine) et l'autre, fortement soluble dans l'eau (la chlorpheniramine). Les résultats montrent que les propriétés de l'actif formulé n'influence pas la libération jusqu'à une proportion d'actif de 10%. Un modéle mathématique basé sur les plan d'experience est aussi proposé afin d'aider le développement de futurs systèmes. Cette investigation reprend les principaux éléments qui peuvent donc permettre à un formulateur de mieux appréhender la complexité liée à la formulation des comprimés osmotiques push-pull.

<u>Chapitre V :</u> Evaluation des propriétés du pelliculage des comprimés osmotiques à l'aide d'ondes terahertz pulsées

Dans ce dernier chapitre, l'application d'une méthode d'imagerie récente est décrite dans le but de caractériser l'épaisseur du film pelliculant les comprimés osmotiques. En effet, les propriétés du film et, en particulier son épaisseur, jouent un rôle déterminant dans le controle de la libération des comprimés osmotiques. Il est donc important de développer des méthodes permettant de mesurer finement la qualité du film. La méthode décrite utilise la réflection d'une onde térahertz réfléchie pour définir l'épaisseur du film, déterminée par le spectre de réflection. La mesure du l'indice de réflection est ici décrite pour détecter des défauts internes du film pouvant, comme dans l'exemple décrit, amener à des différences significatives de profil de dissolution.

LIST OF PUBLICATIONS

Papers

- Vincent Malaterre, Hendrix Metz, Joerg Ogorka, Robert Gurny, Nicoletta Loggia, Karsten Mäder
  Benchtop-magnetic resonance imaging (BT-MRI) characterization of push-pull osmotic systems
  (J.Control.Release, doi:10.1016/j.jconrel.2008.09.007)

- Vincent Malaterre, Joerg Ogorka, Nicoletta Loggia, Robert Gurny
  Evaluation of the tablet core factors influencing the release kinetics and the loadability of push-pull osmotic systems
  (Drug Dev.Ind.Pharm., doi: 10.1080/03639040802425230)

- Vincent Malaterre, Joerg Ogorka, Nicoletta Loggia, Robert Gurny
  Terahertz pulsed imaging, a novel process analytical tool to investigate the coating characteristics of push-pull osmotic systems
  (Eur.J.Pharm.Biopharm., doi:10.1016/j.eppb.2008.10.011)

- Vincent Malaterre, Joerg Ogorka, Nicoletta Loggia, Robert Gurny,
  Approach to design push-pull osmotic systems
  (Int. J. Pharm, doi: 10.1016/j.ijpharm.2009.04.015)

- Vincent Malaterre, Joerg Ogorka, Nicoletta Loggia, Robert Gurny,
  Oral osmotically-driven systems: 30-years of development and clinical use
  (To be submitted to Eur. J. Pharm. Biopharm.)

- Vincent Malaterre, Joerg Ogorka, Nicoletta Loggia, Robert Gurny and Kurt Paulus
  Digital optical and fluorescence microscopy imaging of drug delivery from push-pull osmotic systems
  (To be submitted to Eur. J. Pharm. Biopharm.)

Podium

- Vincent Malaterre, Hendrix Metz, Joerg Ogorka, Karsten Mäder, Robert Gurny, Nicoletta Loggia
  Advances in the Formulation Development and Investigation of Push-Pull Osmotic Systems
  (6th APV/APGI world meeting, Barcelona, April 2008)

Poster

- Vincent Malaterre, Hendrix Metz, Joerg Ogorka, Karsten Mäder, Robert Gurny, Nicoletta Loggia
  Influence of the hydration kinetics and the viscosity balance on the drug release performance of push-pull osmotic systems
  ('2008 CRS oral drug delivery award', 35th CRS world meeting, New York, July 2008)