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Review article

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 10 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 OODS development in the last 30 years, 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.

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 primarily evolved from being device concepts 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 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), the 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

Abbreviations: ADHD, attention deficit hyperactivity disorder; BCS, biopharmaceutical classification system; 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.

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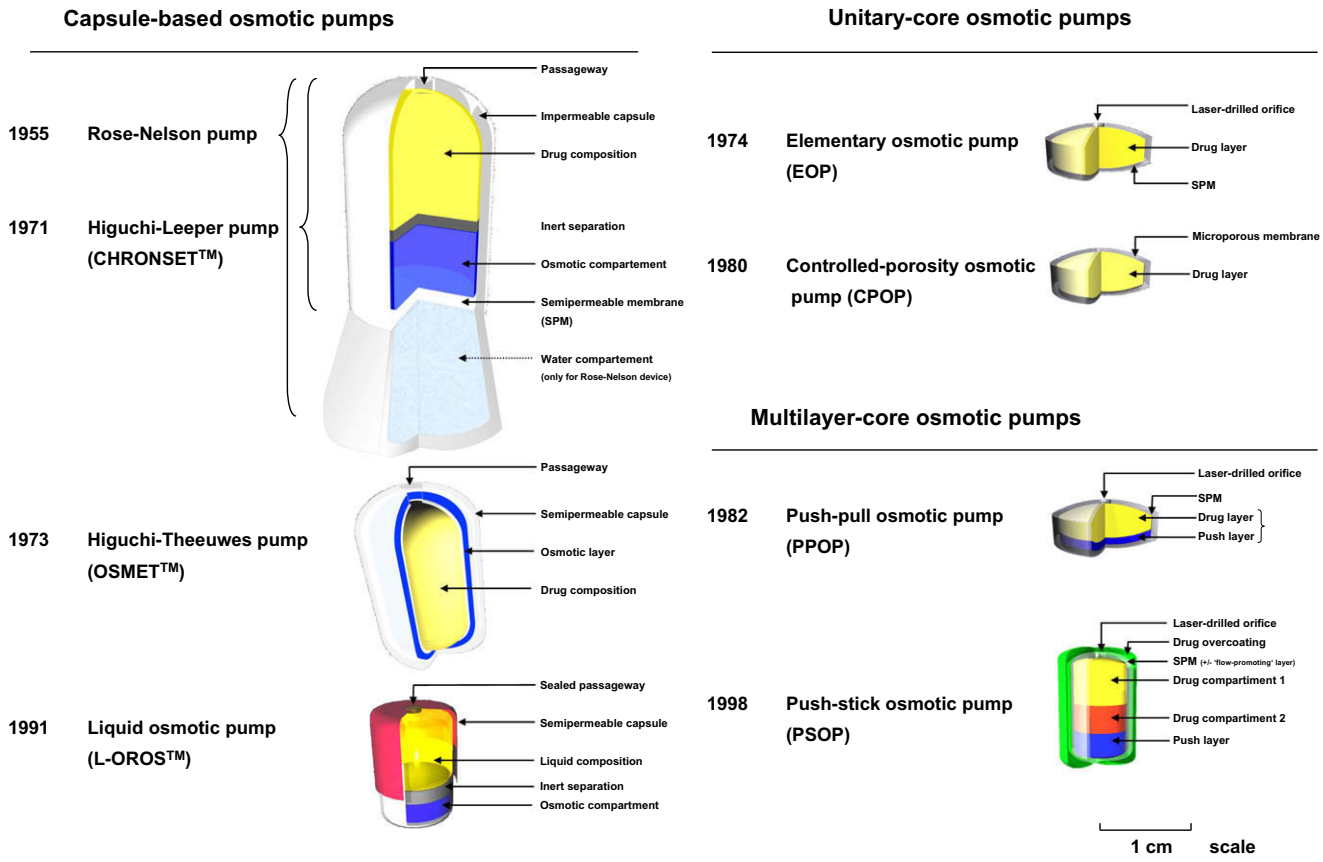

Fig. 1. Design evolution of the oral osmotically-driven systems.

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.

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

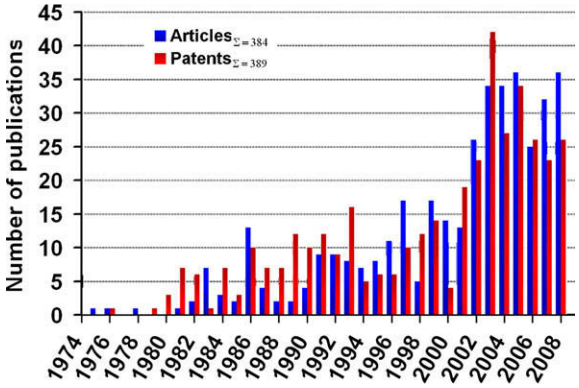

Fig. 2. Publications related to oral osmotically-driven systems (source: ISIweb of Sciences, Pubmed and EMBASE; micropatent, espacenet; end date, December 2008).

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 10 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].

2.2. Marketed products

Thirty-one products have been developed and marketed based on OODS technology. These products cover primarily the following four therapeutic areas[34]: 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, of which three compounds are for pain management [1]. The increasing number of marketed products has translated into a twofold increase in the OODS revenues in the past 5 years, reaching about 3 billion dollars worldwide annual sales. Thus, the OODS worldwide sales increased from about 3.0% of the modified-release forms in 2002 to 6.2% in 2007 (Top 300 worldwide sales, http://www.pharmacircle.com).

To further deeply understand the increased interest around the OODS, it is interesting to pay attention to the pharmacokinetic properties of the drugs. Controlled-release systems are generally used to deliver drugs with short half-life. It appears that about 30% of the formulated drugs have a half-life longer than 12 h and 50% longer than 6 h as summarized in Table 2. 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].

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 pharmacokinetic 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 and 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 OODSs 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

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]

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

Product	Active	Form	Strength (mg)	F (%)[a]	Rel. F (%)[b]CR/IR	$t_{1/2}$ (h)	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 and Seasonal disorders								
Teosona Sol	Theophylline	DOEOP	400	100%	n.p.	5–8	Osmotica/Phoenix	1997 (South Am)
Allegra D 24 h	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 h 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 of controlled-release *vs* immediate-release calculated as ratio between two dose exposures after the same dose administration with an immediate- or controlled-release pattern (n.p., not published).

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

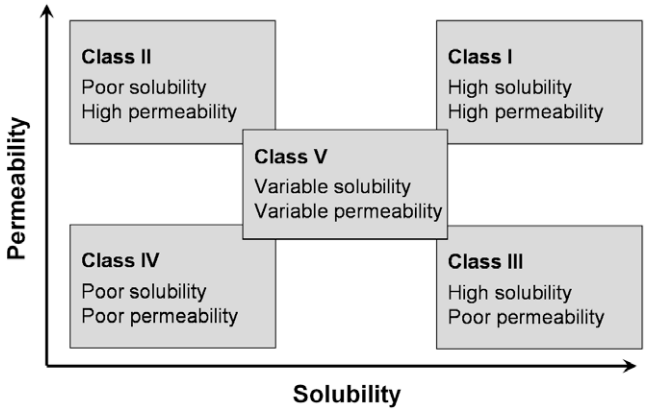

Fig. 4. BCS classification; BCS class I to IV described for immediate- or extended-release dosage forms such as in the FDA guidelines; BCS class V was introduced by Corrigan and Amidon (40–42) for extended-release dosage forms because of the high proportion of basic or acid compounds formulated as controlled-release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

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.

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 30 years, giving several opportunities to adapt technology to drug properties. OODS technologies could be classified as unitary-core, multilayer 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 (Figs. 5 and 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. Multilayer 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.

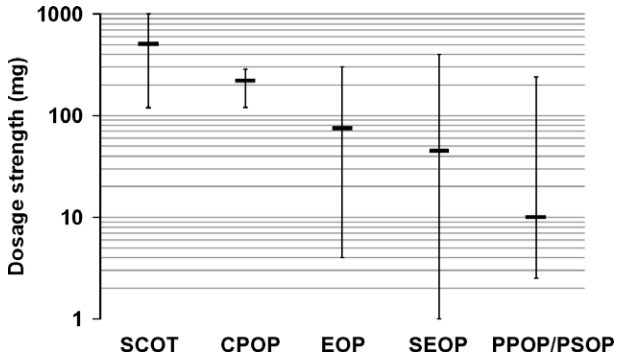

Fig. 6. Dosage strength of the marketed products using OODS (median and range).

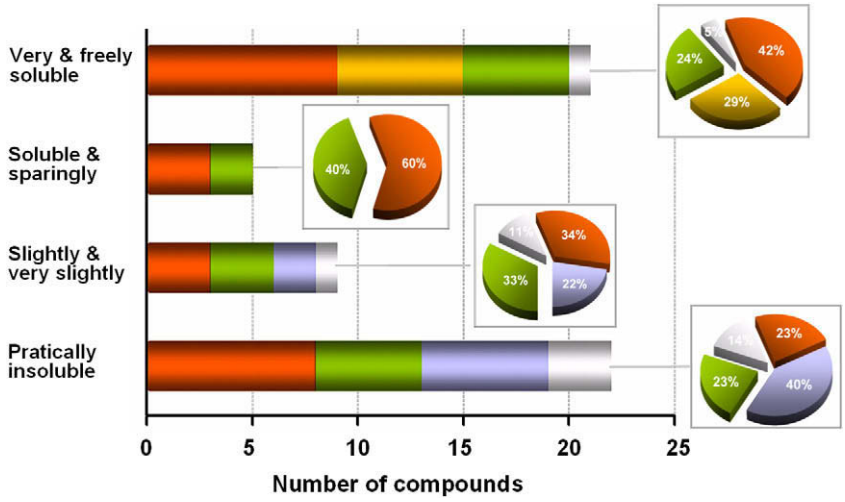

Fig. 5. Number of compounds sorted by USP solubility criteria based on a selection of 57 drugs reported in the literature and formulated as EOP/SCOT (), CPOP (), PPOP (), SEOP/SCPOP () or capsule devices ().

Table 3
Principal oral osmotically 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) salts 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	EOP with incorporated agent for modifying the drug thermodynamic properties(e.g. solubility), such as	
	Ranbaxy, India		
	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	Tablet-core surrounded by a membrane that allows the diffusion of the drug	[53,56,104,105]
	Merck & Co, USA		
Self-emulsified CPOP	Merck & Co, USA	CPOP containing agents to modify the drug thermodynamics i.e.	
		(i) complexing agent e.g. cyclodextrins	[62,80,106]
		(ii) pH-modifying agents	[95,107,108]
(II) Multilayer 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	[109–117]
Push-stick osmotic pump (PSOP)	Alza Corp., USA	PPOP improved to deliver high dose with both a sub-coating of the semipermeable membrane to avoid drug adhesion and an immediate-release drug overcoating	[118–121]
Over-coated PPOP	Alza Corp., USA	PPOP coated with enteric coating, delivering the drug without (OROS-CT™) or with a special onset (COER-24™)	[54,122–126]
Muco-adhesive osmotic system (MOTS)	Alza Corp., USA	PPOP specially designed for buccal administration of drugs	[125–127]
(III) Capsule-based osmotic pumps			
CHRONSET™	Alza Corp., USA	System specially designed to deliver a bolus (>80% drug within 15 min) for intestinal or colonic absorption of protein or muco-adhesive particles	[128,129]
OSMET™	Alza Corp., USA	Device design to study the colonic absorption of drugs delivering the drug as bolus or over a prolonged period up to 8 h	[130–133]
Asymmetric-membrane osmotic pump	Pfizer, USA	Systems coated subsequently with a semipermeable membrane and a highly porous membrane allowing higher water inflow	[134–137]
Liquid osmotic system (L-OROS™)	Alza Corp., USA	Osmotic system delivering either liquids, lipid–lipid emulsion or solid dispersion	[138,139]

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 h. 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 is 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, three to fourfold 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 cellulose-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 Poiseuille's law [10] depending on the tablet-core composition and the coating property. In the calculated range, the drug delivery remained independent of the passageway size [78–80], except in the case of highly viscous compositions [70,81,82]. Various drilling techniques were developed depending on the scale using either manual-drilling [12,83], laser-drilling [84], or indentation techniques consisting of a double-cylinder punch making a central hole in the table face [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 h. Immediate-release drug layers around the semipermeable membrane were sprayed, for example, around EOP, the 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 a controlled manner [88]. Enteric-coated EOP, the so-called OROS-CT™, has also been proposed to target colonic absorption [89].

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 [140]. 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 [109,113–115] over a prolonged period, i.e., from 4 to 24 h, by varying the membrane characteristics [112,114–116]. Because of the drug dispersion delivery, a larger passageway size should be preferably drilled using laser [112], manual [113] 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 designed to deliver verapamil, Covera HS™ [141]. Delivering the drug constantly after a delay of 2 h, 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 semipermeable membrane, avoiding internal drug adhesion [120]. Surrounded by an immediate-release drug layer, the tri-layer tablet core (Fig. 1) gives

additional flexibility to adapt the drug delivery to an optimal plasma profile [119]. 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 [121,142].

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 [129,143,144]. For example, Chronset™ osmotic pumps were designed as a pulse-delivery system, releasing mucoadhesive particles containing peptides or proteins [128,129]. The Osmet™ design was developed as a miniature osmotic pump to deliver a drug as bolus or over 8 h in the colon [130,143]. 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 h [36]. Site-specific deliveries of oxprenolol [132], nitrendipine enantiomers [133] or lidocaine [145] 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 [146,147]. Results show that the retention time in the stomach was drastically increased (5.3 h *vs.* > 12 h) 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 [148]. 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 [149].

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 the case of the delivery of irritating drug substances, the concern is over 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 [19,21,23,150] 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 [146,151]. 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 $\gg$ 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 [152] and carbamazepine SEOP [153]. 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 OODSs 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 [154]. However, an extensive investigation on overall transit time showed that the excretion of incompletely depleted systems occurred only in a minority of patients [151]. 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 matrices 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 [146,147]. 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 [155], large non-disintegrable systems, like Osmet® capsules [147,148] or 9-mm round tablets [156], remained 0 h in the stomach for more than 10 h. Contradictory results for larger round tablets with diameters up to 10 mm, carbamazepine SEOP [153] and indomethacin EOP, were reported, [157] with lower gastric retention times of about 3 to 5 h depending on 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, thereby the absorption of the drug delivered from oral drug delivery systems. 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 the 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 [158]. 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 as shown in Table 4. 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) was significantly influenced by concomitant food intake [159,160]. On the other hand, erodible matrix tablets [159], coated minitablets [159] or pellets [161], 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

Table 4
Food effect on pharmacokinetics.

Drug	Drug delivery systems	n^*	Dose (mg)	Variations fed vs. fasted		
				$AUC_{(0-inf)}$	Cmax	Ref.
Practically insoluble						
Nifedipine	Push–pull osmotic pump	28	30	6%	29%	[159]
		22	60	17%	11%	[160]
		24	60	9%	23%	[160]
		24	60	6%	18%	[163]
	Erodible matrix					
	Sandoz Retards™	28	30	29%	209%	[159]
	Hydrophilic matrix	18	90	76%	303%	[164]
	Coral™	22	60	44%	217%	[162]
	Enteric-coated erodible matrix (Slofedipine™)**	24	60	−12%	6%	[160]
	Encapsulated minitablets (Nifedicron ™)	24	60	23%	151%	[160]
	Multiparticulate systems filled in capsule	9	60	120%	180%	[161]
Oxybutinin	Push–pull osmotic pump	50	15	−11%	−9%	[165]
		35	20	−27%	−31%	[166]
	Enteric-coated erodible matrix	35	20	−21%	−17%	[167]
	Hydrophilic matrix (Cystrin™)	23	10	6%	121%	[168]
		29	10	−10%	72%	[166]
Slightly soluble						
Doxazosin	Push–pull osmotic pump	24	4	18%	31%	[169]
Freely soluble						
Methylphenidate	Push-stick osmotic pump	24	18	20%	33%	[171]
		31	36	17%	11%	[171]
		35	36	22%	18%	[172]
	Multiparticulate pump (Ritalin LA™)	18	40	5%	−5%	[173]
		24	40	31%	17%	[170]
	Immediate-release formulation (Ritalin™)	24	40	15%	23%	[170]
		15	10	1%	−14%	[174]
Pseudoephedrine	Elementary osmotic pump	12	240	−9%	−10%	[175]
	Drug-overcoated EOP	24	240	1%	5%	[176]
Hydromorphone	Push–pull osmotic pump	27	16	−7%	22%	[177]
	Melt-extruded multiparticulate system	22	24	−3%	17%	[178]
Oxprenolol	Elementary osmotic pump	6	160	−9%	−23%	[179]
	Immediate-release formulation	6	160	17%	8%	[179]
Metoprolol	Elementary osmotic pump	8	190	−2%	−5%	[180]
		12	190	13%	11%	[181]
	Immediate-release formulation	12	50	14%	15%	[182]

* n: number of patients studied.

bioavailability was reported as threefold lower than the OODS, Adalat™ [160]. No significant food effects were reported on freely soluble drugs for both immediate- or modified-release systems.

4.4. In vivo–In vitro correlations (IVIVCs)

The IVIVCs 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 [183]. This correlation was defined by Food Drug Administration (FDA) as "a predictive mathematical model describing the relationship between an *in vitro* property of an oral dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response (e.g., plasma drug concentration or amount of drug absorbed)" [184]. Often targeted in the modified-release formulations, high degree of linear correlation, the so-called "level-A" correlation, may be expected when the absorption tends to become the rate-limited step overcoming the drug permeation [183,185]. Table 5 summarizes the 'level A' IVIVC reporting for OODS reported in dogs or healthy volunteers. That is to say, *in vitro* drug release

Table 5
Literature showing *in vitro–in vivo* correlations.

Drug substance	BCS class	Formulated as	Dose (mg)	Model	References
Melatonin	II	PPOP	0.11	Fasting human	[47]
Nifedipine	I	PPOP	30, 60	Fasting human	[186]
Oxybutinin	II	PPOP	10, 20	Fasting/fed human	[188]
Salbutamol	III	EOP	8	Fasting human	[189]
Metoprolol	I	EOP	190 and 285	Fasting human	[190,191]
Indomethacin	II	EOP	85	Fasting mongrel	[12]
Prednisolone	I	SEOP	20	Fasting/fed beagle	[44]
Tenidap	IV	PPOP	50	Fasting beagle	[114]
Pseudoephedrine/brompheniramine	I/II	DOEOP	240/16	Fasting beagle	[175]
Metformin/glipizide	III/V	EOP	500/5	Fasting beagle	[187]
WAG994	V	EOP	5	Fasting beagle	[192]
Carvedilol	II	SEOP	12.5	Fasting beagle	[193]

and *in vivo* deconvoluted drug 'input' were directly superimposable for drugs classified as BCS class-I (metoprolol or nifedipine), class-II (indomethacin or oxybutinin), class-III (salbutamol or metformin), and class-V (tenidap or WAG994). Absorption profiles of two drugs concomitantly delivered by OODS [186] or separately i.e. one in an immediate-release fashion and the other in a controlled-release pattern [175] were, in both cases, linearly correlated with *in-vitro* dissolution rate. No IVIVC was found on hydrophilic matrix tablets concomitantly delivering the same drugs at the same rate [187], potentially showing the superiority of OODS. Similar results were reported in a study on a class-V weak-base compound formulated as push–pull osmotic pumps, pellets and hydrophilic matrix tablets [192]. Despite similar zero-order *in vitro* release kinetics, PPOP was the only modified-release form out of the three formulations to show a linear IVIVC.

Of interest, two studies were conducted to establish IVIVC for drugs subject to food effects. Thus, IVIVC was demonstrated to be independent of food intake for two OODSs delivering poorly soluble drugs i.e. SEOP delivering prednisolone [44] and PPOP delivering oxybutinin [188].

5. Conclusion

Development efforts of oral osmotically driven systems (OODSs) 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 (OODSs) have several applications (i) in early clinical phases (including early-stage exploration of pharmacokinetics), (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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