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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^{TM}) 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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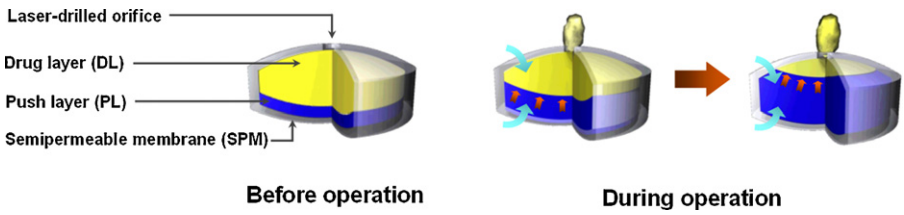


Fig. 1. Schematic diagram of push–pull osmotic pumps (PPOP).

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.

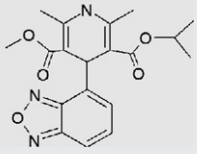
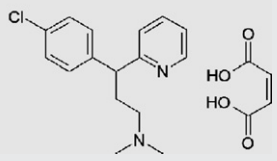
Model drug	Properties	Pharmacological class	Ref.
Isradipine 	Neutral, sparely insoluble drug, substance (S ~5 mg/L)	Calcium channel blocker from the group of dihydropyridine derivates	Fitton and Benfield (1990)
Chlorpheniramine maleate 	Weak base, freely soluble drug, substance (S >5 g/L)	H1 histamine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

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

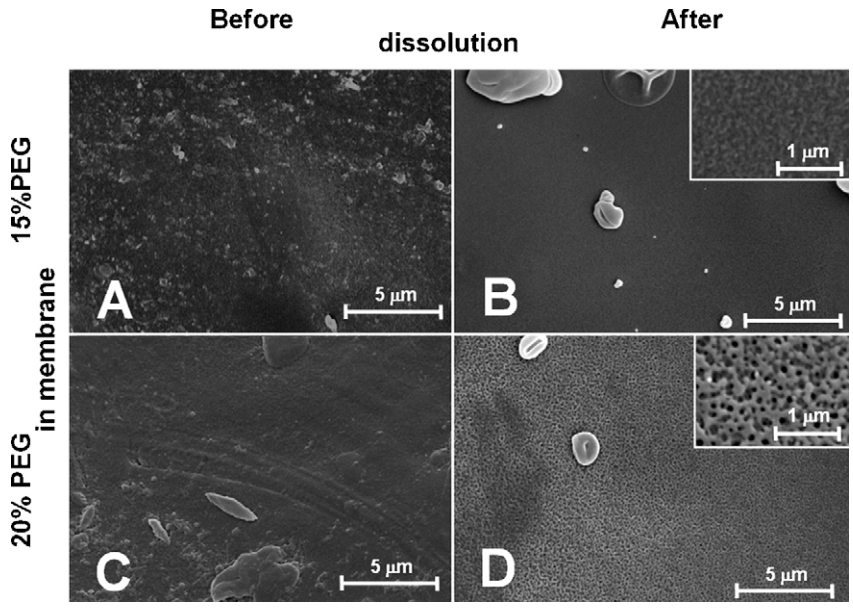


Fig. 2. SEM surface images of membranes containing 1:6 and 1:2 PEG/CA ratios, before and after dissolution.

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

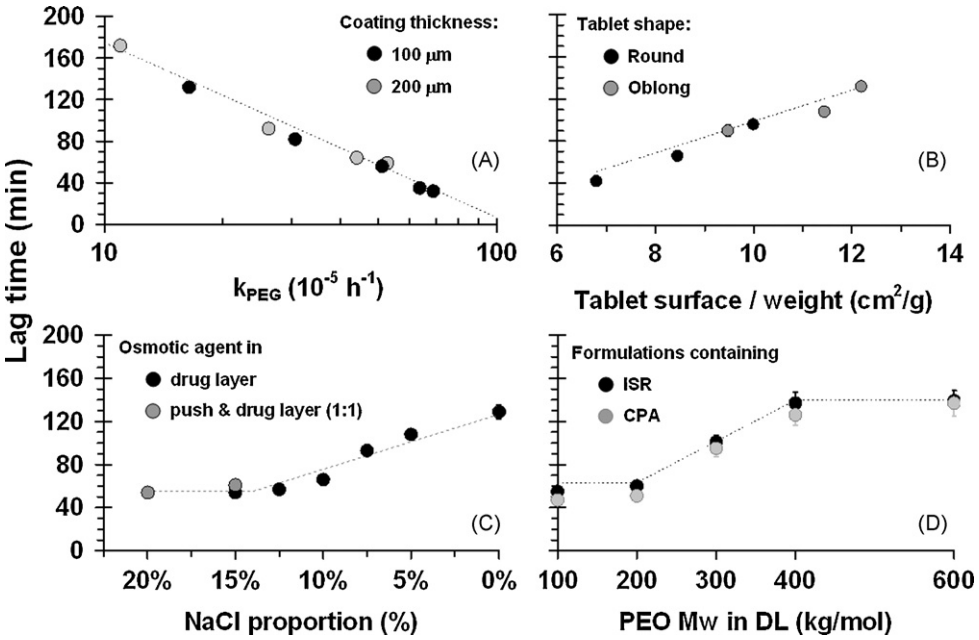


Fig. 3. Lag time of PPOP formulations varying: (A) the PEG depletion kinetics, (B) tablet surface/weight, (C) the osmotic agent proportion and (D) the drug layer PEO molecular weight (see Table 2); ISR and CPA, respectively isradipine and chlorpheniramine maleate; the dotted line figures out the results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

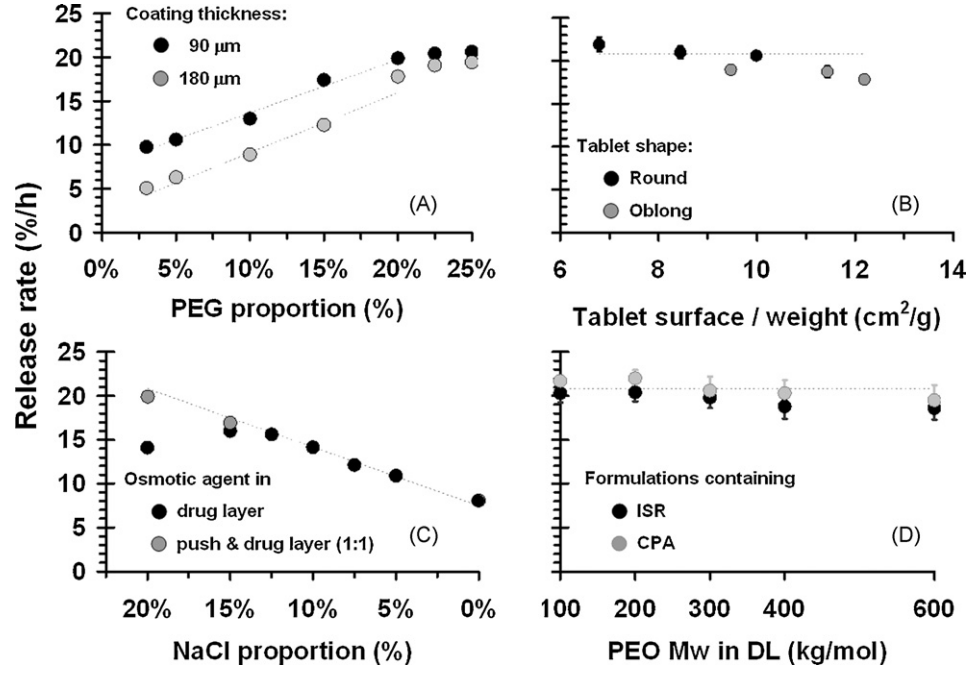


Fig. 4. Drug release rate of PPOP formulation varying: (A) the PEG depletion kinetics, (B) tablet surface/weight, (C) the osmotic agent proportion and (D) the drug layer PEO molecular weight (see Table 2); the acronyms ISR and CPA represent respectively the two model drugs, isradipine and chlorpheniramine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

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

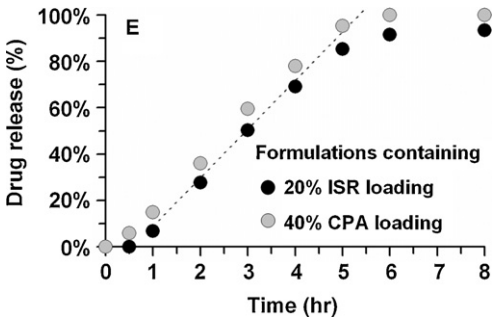


Fig. 5. Drug release profiles of formulations containing respectively 20% CPA and 40% ISR loading (dotted lines = model predictions for 2% loading drug).

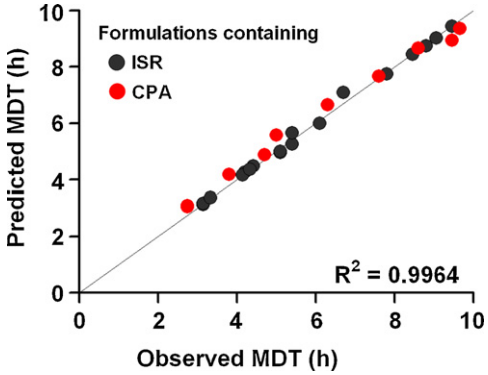


Fig. 6. Predicted mean dissolution times (MDT) vs experimental.

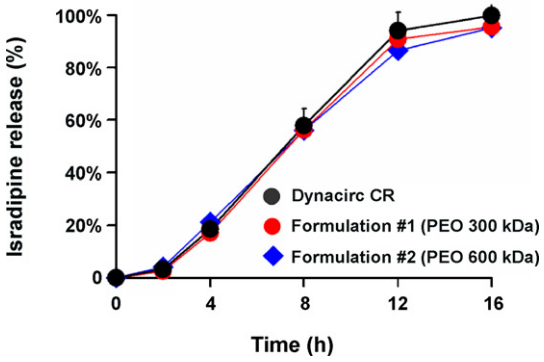


Fig. 7. Dissolution profiles of IRS marketed PPOP vs formulations with calculated parameters; formulations #1 and #2 containing respectively PEO with a Mw of 300 and 600 kDa and a PEG proportion in the coating of 8% and 14%.

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

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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