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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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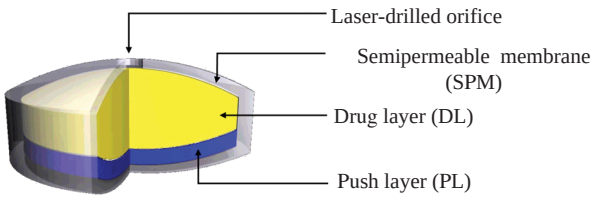

FIGURE 1. Design of a bilayer push–pull osmotic system.

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.

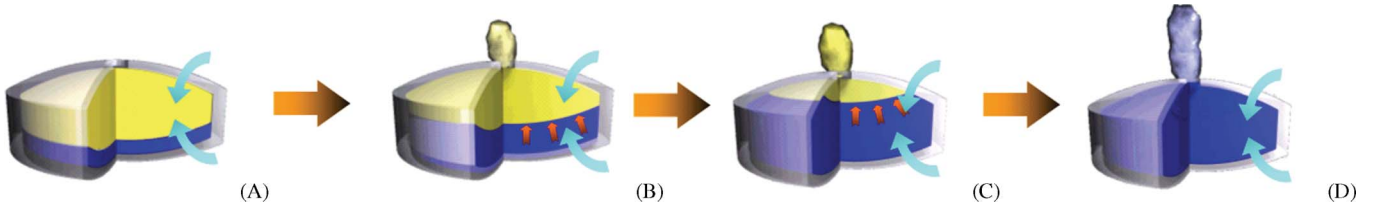

FIGURE 2. Drug release mechanism of push–pull osmotic systems.

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 kDa)	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:

$$RR = \frac{90\% - 10\%}{t_{90\%} - t_{10\%}} \quad (1)$$

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:

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

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.

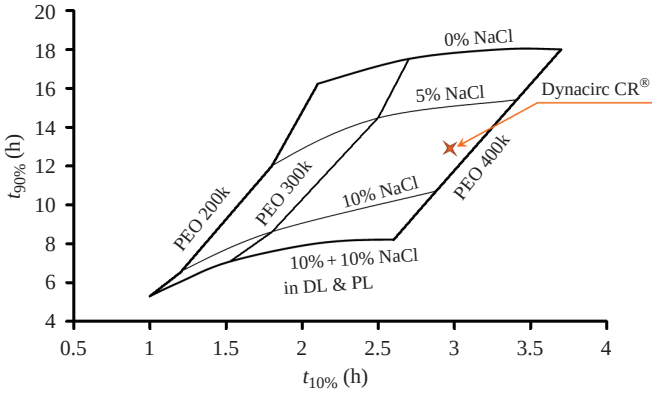

FIGURE 3. Dissolution performance of 2% isradipine formulations containing various osmotic agent proportions and drug layer PEO Mw: The dissolution profile was defined by the $t_{10\%}$ and $t_{90\%}$, which are the times needed to deliver 10 and 90% of the drug-labeled content, respectively; the acronyms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

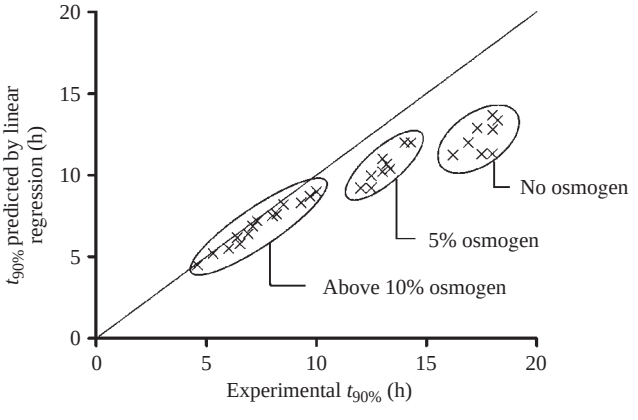

FIGURE 4. Deviation of the experimental $t_{90\%}$ to the extrapolated value by linear regression for formulations containing various osmotic agent proportions in the drug layer.

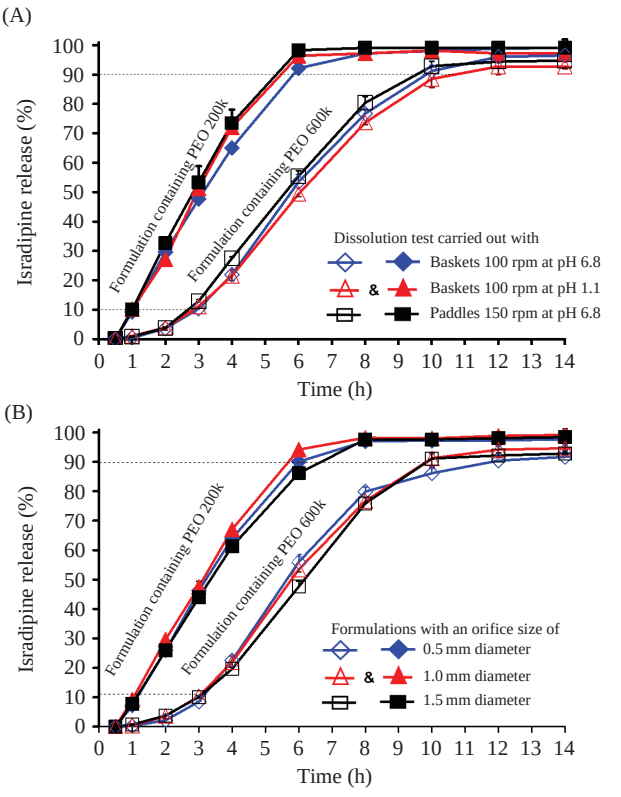

FIGURE 5. Influence of the orifice size, pH, and agitation speed on the drug release of two formulations containing PEO 200 and 600 kDa.

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

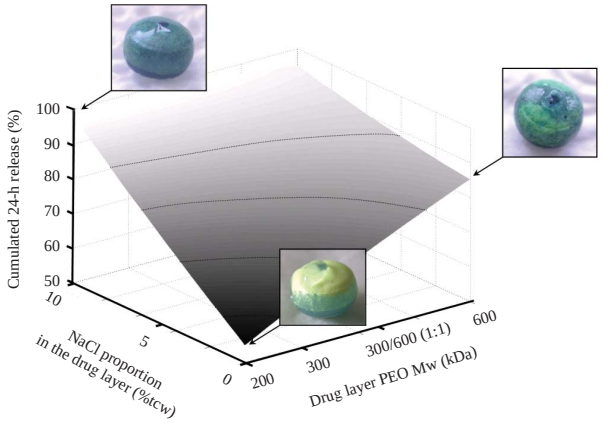

FIGURE 6. Influence of the NaCl proportion and the drug layer PEO Mw on the cumulated 24-h isradipine release for formulations containing 20% drug load (50 mg dose) (r^2 = .944). Pictures illustrate the yellow-colored drug remaining within the shell after the dissolution test (a colorful version is available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

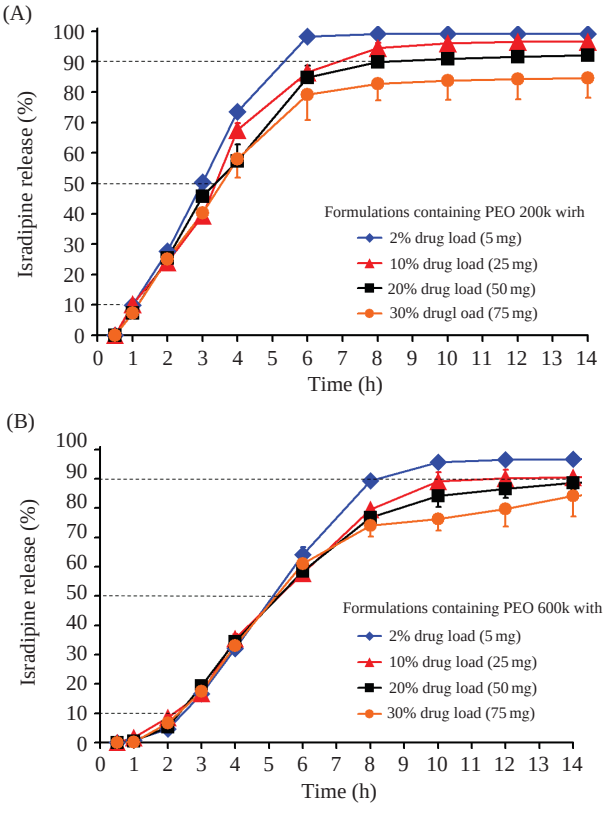

FIGURE 7. Influence of the drug loads (doses) on drug release for formulations containing PEO 200 and 600 kDa.

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®).

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