Vol. 14(4), pp. 87-98, May, 2020
DOI: 10.5897/AJPP2020.5133
Article Number: C71101F63707
ISSN: 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Designing polyethylene oxide and hydroxypropyl methylcellulose matrix tablets with comparable dissolution properties

Petra Draksler[1,2*] and Biljana Janković[1,2]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia.
[2]Sandoz Development Center, Lek d.d., Verovškova 57, 1526 Ljubljana, Slovenia.

Received 8 March, 2020; Accepted 7 May, 2020

Polyox™ coagulant (molecular weight 5 × 10^6 Da) and hydroxypropyl methylcellulose (HPMC) K4M (USP substitution type 2208) were used to identify the composition variables that ensure the production of polyethylene oxide (PEO) matrix tablets with the same dissolution characteristics as those containing HPMC. Based on the dissolution results obtained using Apparatus 3, a 53% concentration of PEO polymer in the matrix tablet generates comparable drug release as matrix tablets containing 37% HPMC. During the dissolution test, several conditions simulating mechanical stresses in the gastrointestinal tract were investigated, in order to assess the robustness of the gel layer formed in selected PEO and HPMC matrix tablets. Increased mechanical stresses enhanced gel erosion from both matrix tablets evaluated and increased the drug release rate by approximately 10% regardless of the polymer type used. The HPMC gel layer formed was more resilient to mechanical stress and resulted in significantly slower drug release when compared to PEO matrix tablets with the same polymer concentration (37%). The research showed that gel robustness and the PEO polymer percolation threshold are dependent on the mechanical stresses applied. The percolation threshold changed from 30 to 37% when different mechanical stress was applied on Apparatus 2 and 3, respectively. The study revealed that the selection of in vitro dissolution method as well as polymer concentration is important for the evaluation of gel mechanical robustness.

Key words: Polyethylene oxide (PEO), hydroxypropyl methylcellulose (HPMC), drug release, percolation threshold, matrix tablets.

INTRODUCTION

Matrix systems are generally designed with a drug, standard tableting excipients, and the most important ingredient: water-swellable polymers. The most commonly used hydrophilic polymer is hydroxypropyl methylcellulose (HPMC) (Kojima et al., 2008) that could be replaced by semi crystalline polymers such as polyethylene oxide (PEO) or polyvinyl alcohol (PVA), which have similar water solubility, drug compatibility,

*Corresponding author. E-mail: petra.draksler@sandoz.com.

and gelation ability (Kim, 1995, 1998; Kojima et al., 2008; Ganji and Vasheghani-Farahani, 2009). For semicrystalline polymers, the solid phase transition depends on the degree of crystallinity, which is connected to solvent transport into the solid phase and crystallite unfolding (Trotzig et al., 2007). Although it is hydrophilic, HPMC is an ion-sensitive polymer, whereas PEO is unsusceptible to ionic strength and pH. PEO generally provides faster drug release and greater water uptake, and it forms a weaker gel that is more sensitive to erosion compared to HPMC (that is, it hydrates slowly and forms a thick and strong gel layer). With a combination of both polymers, it is possible to obtain matrix systems with optimal dissolution properties (Katakam et al., 2013; Hu et al., 2017). With increasing PEO content in the matrix tablet, it is possible to improve its gel strength and therefore simulate HPMC gel behavior. With increased polymer concentration and its viscosity, the drug release mechanism can be changed from mainly erosion-dependent to diffusion-dependent (Maggi et al., 2002; Tajiri et al., 2010; Katakam et al., 2013; Hu et al., 2017, Wen et al., 2018).

Generally, the mechanism of drug dissolution is the same for all hydrophilic polymers: they hydrate in gastric media and form a viscous gel layer, functioning as a diffusional barrier, controlling further water penetration into the tablet, drug release rate, and therefore bioavailability. Simultaneously, an erosion barrier is formed on the matrix surface; this is the part of the matrix system that is removed quickly, and therefore drug release from this part is faster (Harland et al., 1988; Timmins et al., 2014). In this manner, the drug release mechanism from matrix systems is governed by drug and gel layer characteristics (Kim, 1998). The potential critical material attributes that regulated drug dissolution from matrix systems are: polymer content and viscosity, ratio of selected polymers in the blend, particle size of polymer and drug substance, tablet size, and surface area (Kim, 1995; Li et al., 2008; Moodley et al., 2012; Siepmann and Peppas, 2012; Wang et al., 2017; Wen et al., 2018).

To form robust matrix systems, suppliers of matrix agents recommend the use of at least 20% polymer in the matrix formation to maintain a homogenous gel layer (Colocon, 2009; *POLYOX ™ water soluble resins combining flexibility with consistency*, 2013). For better understanding of drug release from matrix systems, the effect of tablet composition based on percolation theory is generally applied (Caraballo, 2010). The percolation threshold is the critical polymer concentration at the gel-solvent boundary, which overcomes the polymer entanglement forces under hydrodynamic stresses, making the polymers free to diffuse into the solution (Kaunisto et al., 2010). Moreover, it is a critical concentration point of the polymer at which one of the components undergoes sudden change and alteration in the release rate noticed (Bonny and Leuenberger, 1991, 1993; Leu and Leuenberger, 1993; Miranda et al., 2006; Caraballo, 2010). Therefore, it is important to determine the percolation threshold for a formulation containing hydrophilic polymer because it ensures the formation of a robust gel layer barrier around the tablet core and prevents a burst effect (Bonny and Leuenberger, 1991, 1993; Aharony and Stauffer, 2003; Caraballo, 2010). The application of percolation theory has been studied on binary systems (Bonny and Leuenberger, 1991; Leu and Leuenberger, 1993) and some multicomponent systems (Choi et al., 2003; Gonçalves-Araújo et al., 2008; Colorocon, 2009).

To obtain the bioequivalent generic drug, the *in vitro* dissolution should have adequate *in vivo* predictability. Mechanical stresses along the gastrointestinal tract should be considered to ensure constant drug release from matrix systems, avoiding a burst effect (Siepmann and Peppas, 2000). One proposed dissolution test used to assess matrix systems' resistance under mechanical stresses is Apparatus 3 (a reciprocating cylinder, BIO-DIS III) (Rohrs et al., 1995; Mu et al., 2003; Klein et al., 2008) according to United States Pharmacopoeia (USP) (United States Pharmacopeia and National Formulary (USP 41-NF 36) Rockville, MD: United States Pharmacopeial Convention, 2016), and its modification using plastic beads offers a good *in vitro–in vivo* correlation (Klančar et al., 2013).

The objective of the study was to investigate the formulation factors of PEO matrix tablets that ensure the same mechanical and drug release characteristics as HPMC. The dissolution testing of selected HPMC and PEO formulations was performed in different dissolution media with the following instruments: Apparatus 2 (paddle method), Apparatus 3 (BIO-DIS III) according to USP, and modified USP Apparatus 3 (BIO-DIS III) with plastic beads. Based on the dissolution method results, the gel layer robustness of selected PEO and HPMC formulations was estimated and the PEO matrix system with a gel strength and drug release comparable to the HPMC system was determined.

MATERIALS AND METHODS

The excipients used in the formulation of the proposed matrix tablets were the following: PEO Polyox™ coagulant (Dow-Colorcon, Dartford, UK) with M_w of 5×10^6 Da, HPMC USP Type 2208, grade K4M (Dow Chemical Company, Midland, MI, USA), lactose monohydrate 200 mesh (Friesland Campina, the Netherlands), and microcrystalline cellulose (MCC) Avicel PH 200 (FMC BioPolymer, Norway). Selected excipients were blended with levofloxacin as a highly soluble and permeable drug with water solubility of 25 mg/ml at room temperature (Koeppe et al., 2011). All other chemicals and solvents were of analytical grade and were used without further purification. The levofloxacin working standard used was a gift sample from Lek Pharmaceuticals d.d. with a standard purity of 100%.

Preparation of standard stock solution

An accurately weighed quantity (around 22 mg) of levofloxacin working standard was dissolved in a 200 ml volumetric flask using a

Table 1. Composition of PEO and HPMC matrix tablets.

Composition (%)	Test formulations										
	A	B	1	2	3	6	7	8	9	10	11
HPMC	80									37	37
PEO		80	40	33	33	30	30	37	37		
Levofloxacin	20	20	33	33	33	33	33	33	33	33	33
MCC			27	33	33	37	37	30	30	30	30
Tablet mass (mg)	500	500	250	250	300	250	300	250	300	250	300
Tablet diameter (mm)	12						10				

Table 2. Compositions of PEO matrix tablets prepared to obtained drug release comparable to HPMC TF 11.

Composition (%)	Test formulations									
	M1	M2	M3	M4	M5	M6	M7	M10	M11	M12
PEO	38	40	42	37	33	30	43	53	57	60
Levofloxacin	33	33	33	33	33	33	33	33	33	33
MCC	29	27	25	33	33	37	24	14	10	7
Tablet mass (mg)	250									
Tablet diameter (mm)	10									

water-ethanol mixture in a 1:1 ratio. The aliquot portion of standard stock solution was then diluted with selected dissolution media to obtain a 100% concentration of levofloxacin in prepared samples within selected dissolution test. The solutions were scanned in a range of 400-200 nm against blank to find the absorbance maximum. The levofloxacin absorbance maximum in water dissolution media and potassium phosphate buffer with a pH of 6.8 was found at 287 nm, and in pH 1.2 the absorbance maximum was detected at 294 nm.

Preparation of matrix tablets

Two 500 mg test formulations (TFs) were prepared, containing only matrix system polymers-HPMC (TF A) and PEO (TF B)-with the addition of 20% levofloxacin as a model drug. The selected polymer and model drug were mixed and manually sieved through 1.0 mm mesh. The dry blend was then compressed into round flat 500 mg tablets 12 mm in diameter and with an average hardness around 90 N.

TFs were also prepared using direct compression of prepared blends containing PEO polymer (Polyox^{TM} coagulant) with the model drug and MCC as the filler in various ratios (Table 1: TFs 1–7) to determine the percolation threshold. The prepared samples were then blended and sieved manually through 1.0 mm mesh and compressed into 250 mg and 300 mg round tablets 10 mm in diameter and with an average hardness around 90 N. The percolation threshold was defined as the critical polymer concentration at which the drug release kinetics significantly changed. After determining the percolation threshold, the gel strength at percolation thresholds was evaluated. Therefore, 250 mg and 300 mg round tablets 10 mm in diameter were prepared containing 37% PEO (TF 8 and TF 9) and 37% HPMC polymer (TF 10 and TF 11).

Finally, 250 mg round tablets 10 mm in diameter were prepared with PEO using various polymer filler ratios (Table 2; TF M1–M12). The main aim of the proposed compositions was to determine PEO formulations with the same gel strength as the selected HPMC TF 11, set as the target for matrix tablet gel strength evaluation, for which after 2 h not more than 30%, after 4 h not less than 50 %, and after 8 h more than 85% of levofloxacin is dissolved (250 ml of water, USP Apparatus 3, 20 DPM).

Dissolution media for *in vitro* testing

For evaluating drug release, the following dissolution media were utilized: deionized water, a 0.05 M phosphate buffer with a pH of 6.8 (USP) (United States Pharmacopeia and National Formulary (USP 41-NF 36) Rockville, MD: United States Pharmacopeial Convention, 2016), and simulated gastric fluid (SGF) with a pH of 1.2. The SGF medium was prepared by adding NaCl and 1M HCl to the water, adjusting the pH value to 1.2, and degassing (Table 3).

Apparatus used for *in vitro* testing

Drug release from matrix tablets was evaluated using Apparatus 2 (paddle method) in accordance with USP (United States Pharmacopeia and National Formulary (USP 41-NF 36) Rockville, MD: United States Pharmacopeial Convention, 2016). The dissolution tests were performed using a dissolution tester (VanKel Dissolution Apparatus, model VK 7000, USA). Standard vessels with paddles were utilized at a stirring rate of 50 revolutions per minute (rpm) with 900 ml of selected dissolution media at a temperature of 37 ± 0.5°C and at least three repetitions (n = 3). The tablets were put into a string sinker to prevent floating of the swollen matrix tablets several hours after commencing the test and to prevent tablet adhesion to the beaker wall. The dissolution medium was not replaced because sink conditions were ensured after sampling. The robustness of the gel layer was evaluated using Apparatus 3, a reciprocating cylinder (Varian Vankel BIO-DIS III, USA). In addition, gel robustness was tested using the dissolution-

Table 3. Compositions of used dissolution media per liter.

Media	Water	SGF	Phosphate buffer pH 6.8
Composition	Deionized water	0.034 mol NaCl 0.08 mol HCl	0.05 mol KH_2PO_4 0.022 mol NaOH
pH	7.0	1.2	6.8

testing method principle adopted by Klančar et al. (2013), in which a standard testing station with 10 dips per minute (DPM) and 20 DPM was used together with 10 mm round plastic beads (density 1.1 g/cm^3). For the pH change simulation test, USP Apparatus 3 was used, whereby the tablets were first dipped in the SGF medium for 2 h, and then in the phosphate buffer medium with a pH of 6.8. For each time point, 5 ml of sample was automatically collected, filtered through 1.0 µm Full Flow filters (P/N FIL001-EW; Erweka, Germany), and diluted accordingly (1/5 or 1/10).

The UV spectrophotometric method

A Varian Cary 50 UV-vis spectrophotometer with a 1.5 nm spectral bandwidth and 10 mm matched quartz cells was used to develop the analytical assay method over a range of 190 to 1,100 nm. The UV-vis wavelengths for levofloxacin were dependent on the media used. The levofloxacin absorbance maximum in water dissolution medium and a potassium phosphate buffer with a pH of 6.8 was at 287 nm, and with a pH of 1.2 at 294 nm.

Similarity factor calculation

The drug release profiles of selected formulations were compared using a similarity factor (f_2) in Eq. 1, where n is the number of dissolution sample times and R_t represents the percent of drug dissolved at each sample point t of the reference and T_t in the test product, respectively. The drug release profiles of the two dissolution profiles are similar if $f_2 \geq 50$.

$$f2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} \times 100\right\} \quad (1)$$

Statistical data analysis

The values reported are means and standard deviations (*SD*) of experiments carried out at least three times. Data were analyzed a one-way ANOVA analysis of variance (a *t*-test), and $p < 0.05$ was considered significant using Minitab® software.

RESULTS AND DISCUSSION

Impact of polymer type on drug release

A comparison between TFs A and B was made in order to evaluate how the polymer type (HPMC vs. PEO) influences drug release. Dissolution in water, using Apparatus 2 at 50 rpm, showed no difference in average drug release ($f_2 > 50$). Based on the results ($f_2 = 78$), the gel layer strengths at 80% of the polymers used are comparable.

The difference between selected TFs A and B (Table 4) had significantly higher relative standard deviations (RSDs) of PEO (TF B) when compared to HPMC (TF A) matrix tablets. Higher variability of the results (RSD > 10%) at the beginning of the dissolution profile can indicate lower robustness of the PEO gel layer due to a faster and greater swelling rate and consequently higher erosion of the PEO gel layer (Kim, 1995b; Maggi et al., 2000, 2002) related to uncontrolled disentanglement of polymer chains (unpublished data). After 12 h, a constant and robust gel layer is formed, which controls drug release from matrix tablets and leads to lower RSD values. Based on the dissolution results obtained (Table 4), it was confirmed from previously published data that HPMC gel layers are more resistant than PEO, leading to constant drug release (Colombo et al., 2000; Maggi et al., 2000; Hewlett et al., 2012; Hu et al., 2017).

Effect of PEO polymer concentration on drug release

For evaluation of the selected PEO M_w percolation threshold, the concentration range of PEO between 30 and 40% was tested (TFs 1, 2, and 8; Figure 1), using 900 ml SGF, USP Apparatus 2, and using a paddle speed of 100 rpm. No effect on drug release was noticed; confirming that 30% PEO with a M_w of 5×10^6 Da (Polyox™ coagulant) for selected formulation is already above its percolation threshold, which results in the constant drug dissolution profile. Above the determined percolation threshold, a gel layer with comparable robustness and consequently similar drug release of the model drug is attained using USP Apparatus 2.

Matrix tablet gel strength evaluation

USP Apparatus 3 (SGF)

The impact of different mechanical stresses applied with USP Apparatus 3 was evaluated for the HPMC TF 11 and PEO TF M10 in SGF medium with 10 DPM and 20 DPM. Due to higher discriminatory power (Figure 2), 20 DPMs were chosen as the dipping speed for the robustness test at USP Apparatus 3.

The results showed (Figure 2) that both polymers are

Table 4. Dissolution profile comparison between HPMC (TF A) and PEO (TF B) matrix tablets using apparatus 2, 50 rpm, 900 ml of water, and its similarity factor (f2).

Time (hthes)	TF A		TF B	
	Average % of dissolved levofloxacin (n = 3)	RSD	Average % of dissolved levofloxacin (n = 6)	RSD
8	28.0	4.8	23.9	16.2
12	40.1	1.9	38.5	5.5
16	47.2	1.6	48.3	3.0
20	56.0	1.2	58.4	1.2
24	64.5	1.1	67.2	1.4
f2			78	

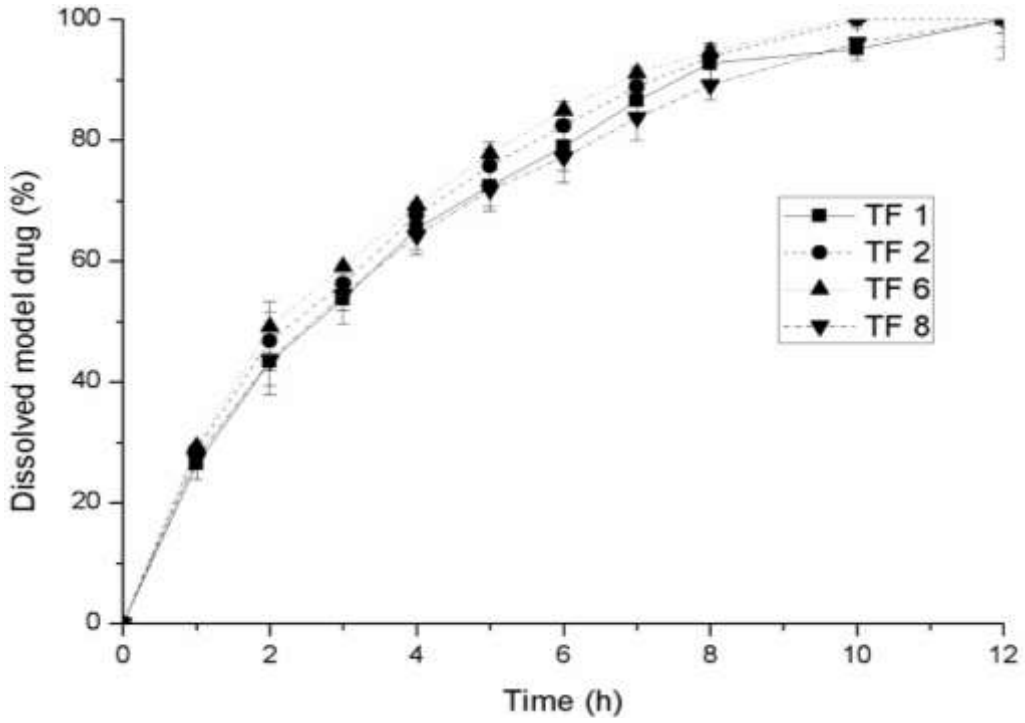

Figure 1. Dissolution profile comparison between 250 mg PEO TFs (TF 1 (40% PEO), TF 2 (33% PEO), TF 6 (30% PEO), TF 8 (37 % PEO)) using USP Apparatus 2, 100 rpms, 900 ml of SGF (n=3).

sensitive to mechanical stresses, resulting in enhanced drug release after increased mechanical stress (DPM). The drug release rate is faster in the case of a higher dipping speed (20 DPM) due to destruction of gel layers. It is interesting, that drug release rate is fastened for the same rate regardless polymer type, showing that mechanical stress affect the gel layer to the same extend in case of PEO matrix tablet than in case of HPMC matrix tablet. Drug release rate is faster in case of PEO matrix tablets, showing the formation of more sensitive gel layer.

USP Apparatus 3 (water)

To improve the mechanical robustness of the gel layer in 250 mg PEO matrix tablets, TFs with increased polymer concentration were produced (M1–M12, Table 2). Based on f_2 calculations ($f_2 > 50$; Table 5), all selected PEO TFs have dissolution profiles comparable to HPMC TF 11 (Figure 3), regardless of the polymer concentrations.

Moreover, the comparable mechanical robustness of PEO and HPMC TFs were determined from dissolution profile. In the case of PEO TFs with less than 37% polymer (TFs M5 and M6, Table 2), the dissolution is significantly faster after 2 h compared to HPMC TF 11 (Figure 3), still within dissolution profile similarity (f_2 close to 65; Table 5), but with lower mechanical robustness of the gel layer according to faster dissolution results. Based on f_2 close to 75 (Table 5), it can be concluded that a 37% PEO concentration (TF M4) is the percolation

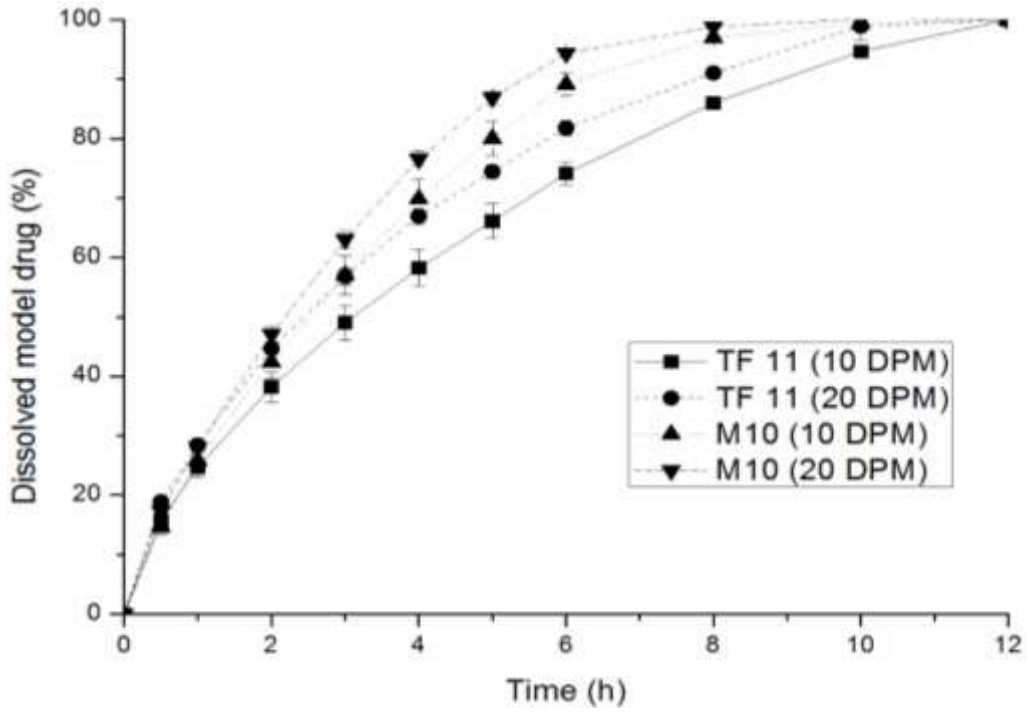

Figure 2. Dissolution profiles from PEO (TF M10) and HPMC (TF 11) TFs were analyzed under different mechanical stresses (10 DPM vs. 20 DPM) in 250 ml of SGF, USP Apparatus 3 (n = 6).

Table 5. Similarity factor (f2) calculation of PEO M1–M12 TFs to HPMC TF 11 in 250 ml of water, USP Apparatus 3, 20 DPM (n = 3).

Composition (%)	Test formulations										
	11	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M10**	**M11**	**M12**
f2	NA	77	74	76	73	66	65	84	78	68	63

threshold for selected PEO formulation, since all higher polymer concentrations (TFs M1, M2, M3, M7, M10, M11 and M12) have similar drug release rate. Based on the results, PEO TF M10 was selected for further mechanical robustness evaluation.

Moreover, the results demonstrated that the PEO percolation threshold depends on the dissolution method used. With increased mechanical stress using USP Apparatus 3, the detected percolation threshold for the selected PEO is higher (37%, Figure 3) when compared to USP Apparatus 2 (30%, Figure 1), again raising the question which method is suitable for predicting the in vivo behavior of PRTs though the gastrointestinal tract (GIT) (McAllister, 2010; Lu et al., 2011; Kostewicz et al., 2014; Schneider et al., 2017; Hribar et al., 2018; Milanowski et al., 2020) when in vivo data are not available.

USP Apparatus 3 (SGF + potassium phosphate buffer with a pH of 6.8)

To simulate the influence of GIT conditions on gel robustness, PEO TF M10 and HPMC TF 11 were dissolved first for 2 h in SGF and then in potassium phosphate buffer with a pH of 6.8 for the next 10 h, using USP Apparatus 3 with 10 DPM. Regarding the dissolution results (Figure 4), similar behavior to TF 11 under simulated gastric conditions was also determined for PEO TF M10, containing 53% PEO polymer (f_2 = 64). According to the results, similar drug release and therefore gel robustness between PEO and HPMC TFs can be obtained with increased PEO concentration.

USP Apparatus 3 with the addition of plastic beads (SGF + potassium phosphate buffer with a pH of 6.8)

The assessment of gel robustness for selected PEO TF M10 and HPMC TF 11 was further tested by using USP Apparatus 3 with different dipping speeds (10 or 20 DPM) and with the addition of plastic beads (Klančar et al., 2013) without changes in the dipping speeds after the transportation of matrix tablets to a medium with a different pH. As can be observed from Figure 5, increased mechanical stress (addition of plastic beads) insignificantly

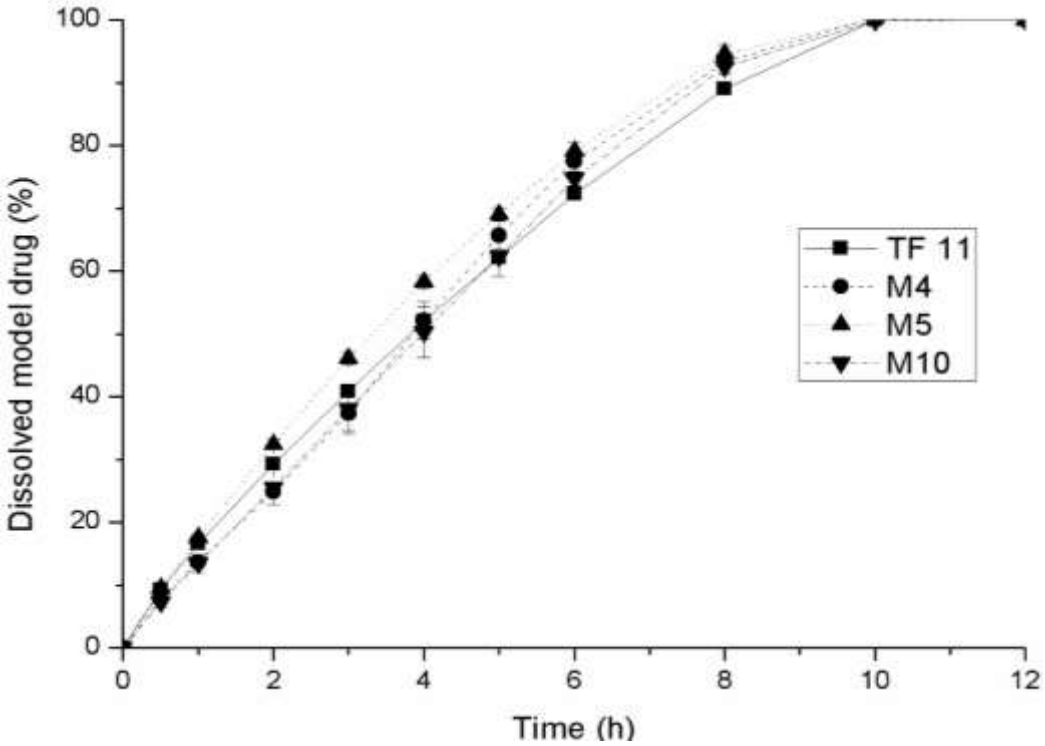

Figure 3. Dissolution profiles of TFs with different PEO polymer concentrations (M4 = 37%, M5 = 33%, M10 = 53%) compared to HPMC TF 11 (37% HPMC) in 250 ml of water, USP Apparatus 3, 20 DPM (*n* = 3).

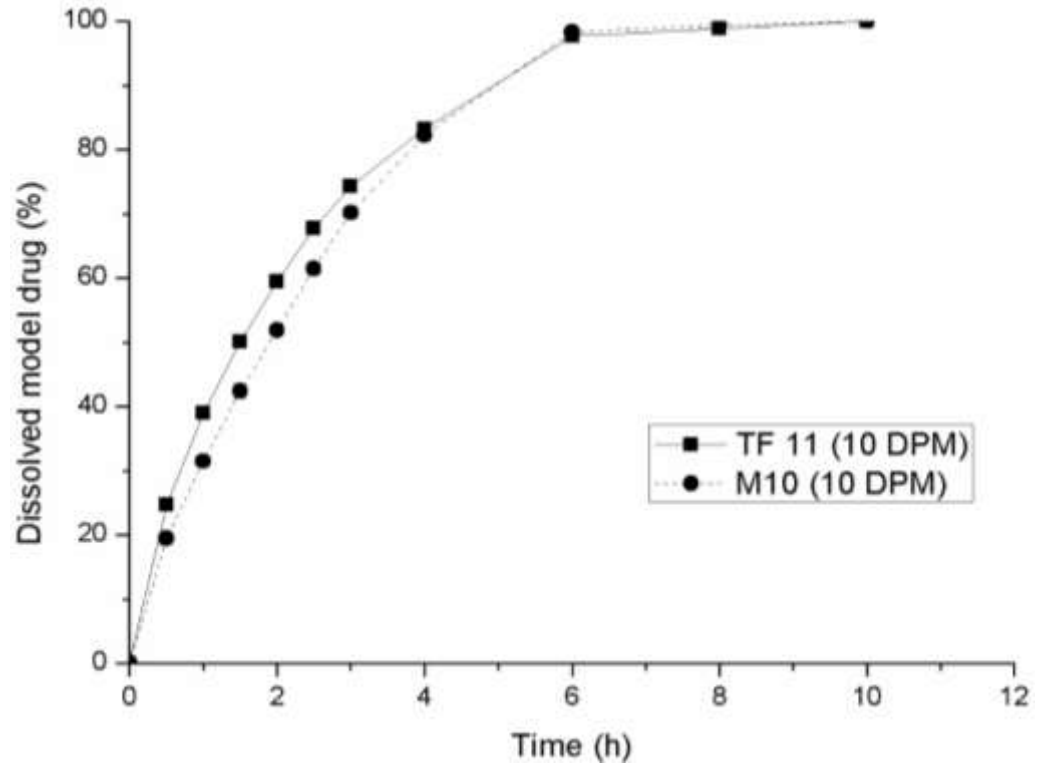

Figure 4. Dissolution profiles of PEO TF M10 (53% PEO) and HPMC TF 11 (37% HPMC) gel layers in 250 ml, simulated gastric media (2 h pH 1.2 + 10 h pH 6.8), USP Apparatus 3, 10 DPM (*n* = 3).

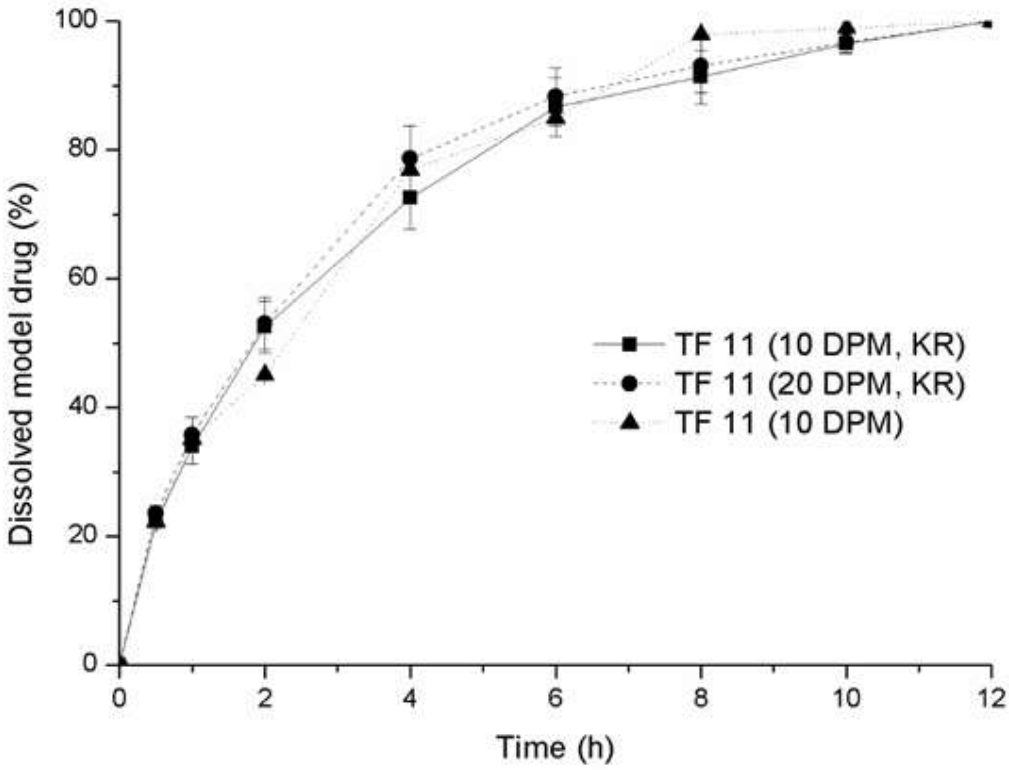

Figure 5. Comparison of HPMC TF 11 gel robustness using different mechanical stresses without (10 or 20 DPM) and with plastic beads (10 DPM KR; 20 DPM KR) in simulated gastric media (2 h pH 1.2 + 10 h pH 6.8), 250 ml, USP Apparatus 3 (n = 3).

accelerates drug release rate and gel erosion of HPMC TF 11. The gel layer is non-susceptible to the addition of beads at 10 DPM, but the increased dipping speed of 20 DPM insignificantly enhanced erosion of the gel layer for HPMC matrix tablets.

In the case of PEO TF M10 (Figure 6), the addition of plastic beads already accelerated the drug release rate at 10 DPM, and erosion of the gel layer is significantly faster when the dipping speed is increased to 20 DPM. The results thus demonstrated that an increase in mechanical stress (20 DPM) decreases gel robustness of PEO matrix tablets (Figure 6), while in case of HPMC matrix tablets the effect is insignificant (Figure 5). This observation is in agreement with the results obtained with USP Apparatus 3 without plastic beads. Moreover, even in a formulation comprised of 53% PEO, significant differences in gel strength exist (Kim, 1995b; Kojima et al., 2008; Li et al., 2008; Park et al., 2010; Tajiri et al., 2010) between HPMC and PEO, confirming the polymer hydration differences (Colombo et al., 2000; Maggi et al., 2000; Hewlett et al., 2012; Hu et al., 2017).

The HPMC gel layer is less susceptible to mechanical stress than PEO regardless of the dissolution method used (Maggi et al., 2000). The differences in gel robustness are the result of polymer type interactions, which in the case of HPMC matrices are dependent on its substitution type and the ratio between hydroxypropyl and methyl groups, defining its hydrophilic/hydrophobic properties and gel hydration abilities (Viriden et al., 2010; Joshi, 2011). On the other hand, PEO polymer chains during hydration disentangle and hydrogen bonds are formed between water molecules and oxygen in the polymer chain, leading to complete polymer disentanglement. Subsequently, hydrophobic intrapolymer interactions are established between other parts of the PEO chain, forming polymer agglomerates (Ho et al, 2002; Hammouda et al, 2004). This defines the robustness of the gel layer under mechanical stress (Maggi et al., 2000), which is dependent on polymer M_w (Maggi et al., 2000; Maggi et al., 2002; Körner et al., 2010; Gupta et al., 2013; Choi et al., 2014) and formulation composition (Reynolds et al., 1998; Jamzad et al., 2005; Tajarobi et al., 2009; Caraballo, 2010; Wang et al., 2017; Wen et al., 2018).

The results confirmed the data described because increased mechanical stresses applied with dissolution methods enhanced water penetration into the PEO matrix system, causing its accelerated swelling rate and consequently lower gel consistency after swelling under mechanical stress. Therefore, polymer chain unfolding is accelerated, resulting in faster matrix erosion and drug release. Moreover, the HPMC matrix system contains

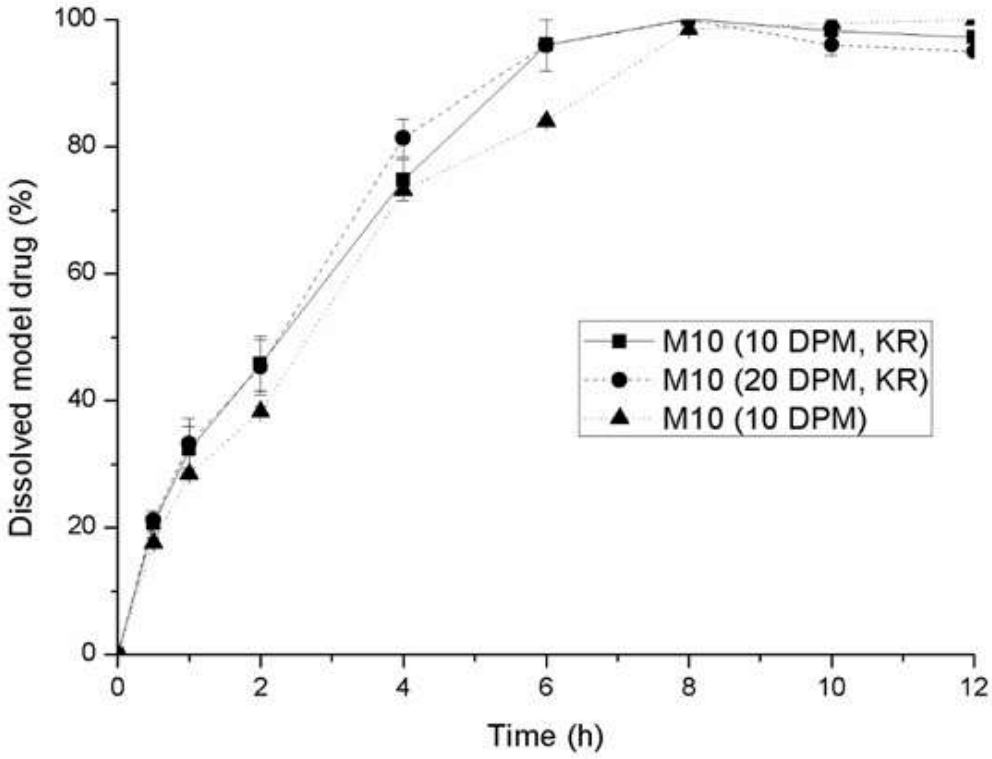

Figure 6. Comparison of dissolution profiles for PEO TF M10 using different mechanical stresses without (10 or 20 DPM) and with plastic beads (10 DPM KR; 20 DPM KR) in simulated gastric media (2 h pH 1.2 + 10 h pH 6.8), 250 ml, USP Apparatus 3 (*n* = 3).

more hydrophobic substituents, reducing water penetration and polymer water connections in the matrix system, leading to a slower hydration rate and higher robustness of the gel layer formed, appearing in slower drug release (Hu et al., 2017).

When the mechanical stress is increased, the interaction between polymer and water is disrupted and a transient viscoelastic gel is formed, leading to polymer disentanglement and release into the medium (Hewlett et al., 2012). The mechanical susceptibility of the gel layer can correlate with intrinsic polymer viscosity and shear stress, under which both polymers undergo a shear thinning effect; this is lower for PEO than for HPMC (Inc., 2009; Mastropietro et al., 2013).

This was also confirmed by the previous research (unpublished data), in which no erosion of the gel layer was noticed under any mechanical stress, and the drug release was dependent only on drug diffusion through gel layers formed regardless of PEO $M_{w.}$ When mechanical stress is applied, erosion is increased, causing inconsistent disintegration of the gel layer; this is most pronounced for PEO with a lower M_w (Maggi et al., 2000; Narasimhan, 2001; Maggi et al., 2002; Dhawan et al, 2005; Körner et al., 2005, 2010; Wu et al., 2005; Wang et al., 2017).

The research demonstrated that in the case of directly compressed PEO matrix tablets increased mechanical stresses within dissolution methods affect the discriminatory power of its gel robustness. For selected PEO and HPMC matrix tablets containing at least 37% polymer, the most discriminatory dissolution method for gel robustness evaluation was modified USP Apparatus 3 with plastic beads using 20 DPM. The dissolution results obtained with the selected method clearly demonstrated the gel strength differences between formed gels in PEO and HPMC matrix tablets. In addition, the percolation threshold for the selected PEO polymer was also detected, and it depended on the dissolution method used. When USP Apparatus 2 was utilized, the percolation threshold was set at 30% PEO polymer, and USP Apparatus 3 was used at 37%. At the same time, it was shown that the same PEO matrix system characteristics as HPMC containing 37% polymer can be obtained when the PEO polymer concentration is increased to 53%, which is well above the set percolation threshold (37%). These results show that the polymer concentration at the percolation threshold does not ensure mechanical robustness of the gel layer. To attain mechanical robustness, the polymer concentration should be substantially increased in the case of PEO. Finally, the study demonstrated how the choice of dissolution method affects the difference in detection between matrix polymer

types, their concentration, and formulation characteristics; confirming the importance of proper dissolution method selection during matrix tablet development.

Conclusion

In this study, the percolation threshold of the selected PEO coagulant ($M_w = 5 \times 10^6$ Da) was set at 30% with the dissolution test using USP Apparatus 2 and at 37% when USP Apparatus 3 is used. the study demonstrated the possibility of formulating PEO matrix tablets having a similar drug release rate and robustness as HPMC matrix tablets containing 37% polymer. This was attained with a PEO concentration increase to 53%. The polymer concentration ensuring mechanical gel robustness is well above the set percolation threshold concentration, showing that the polymer concentration at the percolation threshold does not provide the mechanical robustness of the PEO gel layer formed. To obtain this, the PEO polymer concentration should be higher. It was confirmed that increased mechanical stress enhances gel layer sensitivity and therefore drug release regardless of the polymer type. The results suggest that the choice of dissolution method and related mechanical stresses affect gel robustness, which increases with polymer concentration. The study also draws attention to open issues regarding the choice of dissolution test for matrix tablets' gel robustness evaluation because with different dissolution methods different results can be obtained.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Aharony A, Stauffer D (2003). *Introduction to percolation theory*. Revised ed. London: Taylor & Francis.

Bonny JD, Leuenberger H (1991). Matrix type controlled release systems: I. Effect of percolation on drug dissolution kinetics. Pharmaceutica Acta Helvetiae 66(5-6):160-164.

Bonny JD, Leuenberger H (1993). Matrix type controlled release systems II. Percolation effects in non-swellable matrices. Pharmaceutica Acta Helvetiae 68(1):25–33. https://doi.org/10.1016/0031-6865(93)90005-Q.

Caraballo I (2010). Factors affecting drug release from hydroxypropyl methylcellulose matrix systems in the light of classical and percolation theories. Expert Opinion on Drug Delivery 7(11):1291-1301. https://doi.org/10.1517/17425247.2010.528199.

Choi DH, Lim JY, Shin S, Choi WJ, Jeong SH, Lee S (2014). A novel experimental design method to optimize hydrophilic matrix formulations with drug release profiles and mechanical properties. Journal of Pharmaceutical Sciences 103(10):3083-3094. https://doi.org/10.1002/jps.24080.

Choi SU, Lee J, Choi YW (2003). Development of a directly compressible poly(ethylene oxide) matrix for the sustained-release of dihydrocodeine bitartrate. Drug Development and Industrial Pharmacy 29(10):1045-1052. https://doi.org/10.1081/DDC-120025863.

Colocon (2009) *POLYOX™*. Available at: https://www.colorcon.com/es/products-formulation/all-products/download/788/2849/34?method=view (Accessed: 24 April 2018).

Colombo P, Bettini R, Santi P, Peppas NA (2000). Swellable matrices for controlled drug delivery: gel-layer behavithe, mechanisms and optimal performance. Pharmaceutical Science and Technology *Today* 3(6):198-204. https://doi.org/10.1016/S1461-5347(00)00269-8.

Dhawan S, Varma M, Sinha VR (2005). High molecular weight poly(ethylene oxide)–based drug delivery systems- part I : hydrogels and hydrophilic matrix systems. Pharmaceutical Technology 29:72-74, 76-80.

Ganji F, Vasheghani-Farahani E (2009). Hydrogels in controlled drug delivery systems. Iranian Polymer Journal 18(1):63-88.

Gonçalves-Araújo T, Rajabi-Siahboomi AR, Caraballo I (2008). Application of percolation theory in the study of an extended release verapamil hydrochloride formulation. International Journal of Pharmaceutics 361(1):112-117. https://doi.org/10.1016/j.ijpharm.2008.05.022.

Gupta CR, Kishore GK, Ratna JV (2013). Development and evaluation of aceclofenac matrix tablets using polyethylene oxides as sustained release polymers. Journal of Pharmacy Research 6(2):249-254. https://doi.org/10.1016/j.jopr.2013.02.007.

Hammouda B, Ho DL. Kline S (2004). Insight into clustering in poly(ethylene oxide) solutions. Macromolecules 37(18):6932-6937. https://doi.org/10.1021/ma049623d.

Harland RS, Gazzaniga A, Sangalli ME, Colombo P, Peppas NA (1988). Drug/polymer matrix swelling and dissolution. Pharmaceutical Research 5(8):488-494. https://doi.org/10.1023/A:1015913207052.

Hewlett KO, L'Hote-Gaston J, Radler M, Shull KR (2012). Direct measurement of the time-dependent mechanical response of HPMC and PEO compacts during swelling. International Journal of Pharmaceutics 434(1):494-501. https://doi.org/10.1016/j.ijpharm.2012.05.001.

Ho DL., Hammouda B, Kline SR (2002). Clustering of poly(ethylene oxide) in water revisited. Journal of Polymer Science, Part B: Polymer Physics 41:135-138. https://doi.org/10.1002/polb.10340.

Hribar M, Jakasanovski O, Trontelj J, Grabnar I, Legen I (2018). Determining the pressure-generating capacity of the classical and alternative in vitro dissolution methods using a wireless motility capsule. Journal of Pharmaceutical Innovation 13(3):226-236. https://doi: 10.1007/s12247-018-9317-1.

Hu A, Chen C, Mantle MD, Wolf B, Gladden LF, Rajabi-Siahboomi A, Missaghi S, Mason L, Melia CD (2017). The properties of HPMC:PEO extended release hydrophilic matrices and their response to ionic environments. Pharmaceutical Research 34(5):941-956. https://doi.org/10.1007/s11095-016-2031-0.

Colorocon (2009). Investigation of the effects of hydro-alcoholic media on rheological and textural properties of various grades of hypromellose (HPMC). Available at: https://www.colorcon.com/products-formulation/all-products/download/262/503/34?method=view.

Jamzad S, Tutunji L, Fassihi R (2005). Analysis of macromolecular changes and drug release from hydrophilic matrix systems. International Journal of Pharmaceutics 292(1-2):75-85. https://doi.org/10.1016/j.ijpharm.2004.11.011.

Joshi SC (2011). Sol-gel behavior of hydroxypropyl methylcellulose (HPMC) in ionic media including drug release. Materials 4(10):1861-1905. https://doi.org/10.3390/ma4101861.

Katakam P, Padala NR, Chandu BR, Elfituri A, Adiki SK, Kommu R (2013). Design of lamivudine XR matrix tablets: Influence of HPMC and PEO on in vitro drug release and bioavailability in rabbits. Journal of Pharmacy Research 6(8):845-852. https://doi.org/10.1016/j.jopr.2013.08.010.

Kaunisto E, Abrahmsen-Alami S, Borgquist P, Larsson A, Nilsson B, Axelsson A (2010). A mechanistic modelling approach to polymer dissolution using magnetic resonance microimaging. Journal of Controlled Release 147(2):232-241. https://doi.org/10.1016/j.jconrel.2010.07.102.

Kim C (1995a). Compressed donut-shaped tablets with zero-order release kinetics. Pharmaceutical Research 12(7):1045-1048. https://doi.org/10.1023/a:1016218716951.

Kim CJ (1995b). Drug release from compressed hydrophilic POLYOX-WSR tablets. Journal of Pharmaceutical Sciences 84(3):303-306. https://doi.org/10.1002/jps.2600840308.

Kim CJ (1998). Effects of drug solubility, drug loading, and polymer molecular weight on drug release from Polyox tablets. Drug development and Industrial Pharmacy 24(7):645-651. https://doi.org/10.3109/03639049809082366.

Klančar U, Markun B, Baumgartner S, Legen I (2013). A novel beads-based dissolution method for the in vitro evaluation of extended release HPMC matrix tablets and the correlation with the in vivo data. The AAPS Journal 15(1):267-277. https://doi.org/10.1208/s12248-012-9422-x.

Klein S, Rudolph MW, Skalsky B, Petereit HU, Dressman JB (2008). Use of the BioDis to generate a physiologically relevant IVIVC. Journal of Controlled Release 130(3):216-219. https://doi.org/10.1016/j.jconrel.2008.06.014.

Koeppe MO, Cristofoletti R, Fernandes EF, Storpirtis S, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM (2011). Biowaiver monographs for immediate release solid oral dosage forms: Levofloxacin. Journal of Pharmaceutical Sciences 100(5):1628-1636. https://doi.org/10.1002/jps.22413.

Kojima H, Yoshihara K, Sawada T, Kondo H, Sako K (2008). Extended release of a large amount of highly water-soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets. European Journal of Pharmaceutics and Biopharmaceutics 70(2):556-562. https://doi.org/10.1016/j.ejpb.2008.05.032.

Körner A, Larsson A, Piculell L, Wittgren B (2005). Tuning the polymer release from hydrophilic matrix tablets by mixing short and long matrix polymers. Journal of Pharmaceutical Sciences 94(4):759-769. https://doi.org/10.1002/jps.20288.

Körner A, Larsson A, Andersson A, Piculell L (2010). Swelling and polymer erosion for poly(ethylene oxide) tablets of different molecular weights polydispersities. Journal of Pharmaceutical Sciences 99(3):1225-1238. https://doi.org/10.1002/jps.21892.

Kostewicz ES, Abrahamsson B, Brewster M, Brouwers J, Butler J, Carlert S, Dickinson PA, Dressman J, Holm R, Klein S, Mann J, McAllister M, Minekus M, Muenster U, Müllertz A, Verwei M, Vertzoni M, Weitschies W, Augustijns P (2014*). In vitro* models for the prediction of in vivo performance of oral dosage forms. European Journal of Pharmaceutical Sciences 57:342-366. https://doi.org/10.1016/j.ejps.2013.08.024.

Leu R, Leuenberger H (1993). The application of percolation theory to the compaction of pharmaceutical powders. International Journal of Pharmaceutics 90(3):213-219. https://doi.org/10.1016/0378-5173(93)90193-J.

Li H, Hardy RJ, Gu X (2008). Effect of drug solubility on polymer hydration and drug dissolution from polyethylene oxide (PEO) matrix tablets. AAPS PharmSciTech 9(2):437-443. https://doi.org/10.1208/s12249-008-9060-x.

Lu Y, Kim S, Park K (2011). In vitro–in vivo correlation: Perspectives on model development. International Journal of Pharmaceutics 418(1):142-148. https://doi.org/10.1016/j.ijpharm.2011.01.010.

Maggi L, Segale L, Torre ML, Ochoa Machiste E, Conte U (2002). Dissolution behavithe of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study. Biomaterials 23:1113-1119. https://doi.org/10.1016/S0142-9612(01)00223-X.

Maggi L, Bruni R, Conte U (2000). High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms. International Journal of Pharmaceutics 195(1-2):229-238. https://doi.org/10.1016/S0378-5173(99)00402-0.

Mastropietro David J, Muppalaneni S, Kariman A, Omidian H (2013). Shear-thinning rheology of the abuse-deterrent dosage form extracts. Journal of Developing Drugs 2(3):1-3. https://doi.org/10.4172/2329-6631.1000114.

McAllister M (2010). Dynamic Dissolution: A Step Closer to Predictive Dissolution Testing?. Molecular Pharmaceutics 7(5):1374-1387. https://doi.org/10.1021 /mp1001203.

Milanowski B, Hejduk A, Marek A Bawiec MA, Jakubowska E, Urbańska A, Wiśniewska A, Garbacz G, Lulek J (2020). Biorelevant in vitro release testing and in vivo study of extended-release niacin hydrophilic matrix tablets. AAPS PharmSciTech 21(3):83. https://doi: 10.1208/s12249-019-1600-z.

Miranda A, Millán M, Caraballo I (2006). Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery. International Journal of Pharmaceutics 311(1):75-81. https://doi.org/10.1016/j.ijpharm.2005.12.012.

Moodley K, Pillay V, Choonara YE, du Toit LC, Ndesendo VMK, Kumar P, Cooppan S, Bawa P (2012). Oral drug delivery systems comprising altered geometric configurations for controlled drug delivery. International Journal of Molecular Sciences 13(1):18-43. https://doi.org/10.3390/ijms13010018.

Mu X, Tobyn MJ, Staniforth JN (2003). Development and evaluation of bio-dissolution systems capable of detecting the food effect on a polysaccharide-based matrix system. Journal of Controlled Release 93(3):309-318. https://doi.org/10.1016/j.jconrel.2003.08.013.

Narasimhan B (2001). Mathematical models describing polymer dissolution : consequences for drug delivery. Advanced Drug Delivery Reviews 48(2–3):195–210. https://doi.org/10.1016/S0169-409X(01)00117-X.

Park JS, Shim JY, Nguyen KVT, Park JS, Shin S, Choi YW, Lee J, Yoon JH, Jeong SH (2010). A pharma-robust design method to investigate the effect of PEG and PEO on matrix tablets. International Journal of Pharmaceutics 393(1-2):79-87. https://doi.org/10.1016/j.ijpharm.2010.04.009.

POLYOX ^{TM} water soluble resins combining flexibility with consistency (2013). Available at: http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_08e5/0901b803808e5467.pdf?filepath=dowwolff/pdfs/noreg/326-00108.pdf&fromPage=GetDoc.

Reynolds TD, Gehrke SH, Ajaz SH, Shenouda LS, Hussain AS, Shenouda LS (1998). Polymer erosion and drug release characterization of hydroxypropyl methylcellulose matrices. Journal of Pharmaceutical Sciences 87(9):1115-1123. https://doi.org/10.1021/js980004q.

Rohrs BR, Burch-Clark DL, Witt MJ, Stelzer DJ (1995). USP Dissolution Apparatus 3 (Reciprocating Cylinder): Instrument Parameter Effects on Drug Release from Sustained Release Formulations. Journal of Pharmaceutical Sciences 84(8):922-926. https://doi.org/10.1002/jps.2600840804.

Schneider F, Beeck R, Hoppe M, Koziolek M, Weitschies W (2017). In vitro simulation of realistic gastric pressure profiles. European Journal of Pharmaceutical Sciences 107:71-77. https://doi.org/10.1016/j.ejps.2017.06.037.

Siepmann J, Peppas NA (2012). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews 64:163-174. https://doi.org/10.1016/j.addr.2012.09.028.

Siepmann J, Peppas NA (2000). Hydrophilic matrices for controlled drug delivery: An improved mathematical model to predict the resulting drug release kinetics (the "sequential layer'' model). Pharmaceutical Research 17(10):1290-1298. https://doi.org/10.1023/A:1026455822595.

Tajarobi F, Abrahmsén-Alami S, Hansen M, Larsson A (2009). The impact of dose and solubility of additives on the release from HPMC matrix tablets - identifying critical conditions. Pharmaceutical Research 26(6):1496-1503. https://doi.org/10.1007/s11095-009-9861-y.

Tajiri T, Morita S, Sakamoto R, Suzuki M, Yamanashi S, Ozaki Y, Kitamura S (2010). Release mechanisms of acetaminophen from polyethylene oxide/polyethylene glycol matrix tablets utilizing magnetic resonance imaging. International Journal of Pharmaceutics 395(1-2):147-153. https://doi.org/10.1016/j.ijpharm.2010.05.021.

Timmins P, Pygall SR, Melia CD (2014). Hydrophilic matrix tablets for oral controlled release 16th ed. AAPS Advances in Pharmaceutical Sciences Series. https://doi.org/10.1007/978-1-4939-1519-4.

Trotzig C, Abrahmsén-Alami S, Maurer FHJ (2007). Structure and mobility in water plasticized poly(ethylene oxide). Polymer 48(11):3294-3305. http://doi.org/10.1016/j.polymer.2007.03.047.

United States Pharmacopeia and National Formulary (USP 41-NF 36) Rockville, MD: United States Pharmacopeial Convention (2016). Available at: https://online.uspnf.com/uspnf/document/GUID-DE944D24-C749-481E-A142-C20E4AE64E3C_1_en

US?highlight=rheology (Accessed: 12 December 2018).
Viriden A, Larsson A, Wittgren B (2010). The effect of substitution pattern of HPMC on polymer release from matrix tablets. International Journal of Pharmaceutics 389(1-2):147-156. https://doi.org/10.1016/j.ijpharm.2010.01.029.
Wang L, Chen K, Wen H, Ouyang D, Li X, Gao Y, Pan W, Yang X (2017). Design and evaluation of hydrophilic matrix system containing polyethylene oxides for the zero-order controlled delivery of water-insoluble drugs. AAPS PharmSciTech 18(1):82-92. https://doi.org/10.1208/s12249-016-0498-y.
Wen H, Li X, Li Y, Wang H, Wang Y, Wang T, Pan W, Yang X (2018). In vitro and in vivo evaluation of controlled-release matrix tablets of highly water-soluble drug applying different mw polyethylene oxides (PEO) as retardants. Drug Development and Industrial Pharmacy 44(4):544-552. https://doi: 10.1080/03639045.2017.1405429.
Wu N, Wang LS, Tan DCW, Moochhala SM, Yang YY (2005). Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. Journal of Controlled Release 102(3):569-581. https://doi.org/10.1016/j.jconrel.2004.11.002.