POLYETHYLENE OXIDES AS MATRIX FORMING AGENTS: DIRECT COMPRESSION VS. WET GRANULATION

Djordje Medarević[*1], Marko Krstić[1], Sofija Stanković[1], Branka Grujić[2], Svetlana Ibrić[1]

[1] Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Serbia

[2] R&D Institute, Galenika a.d. Belgrade, Serbia

[*]**Corresponding author: Djordje Medarevic**

Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, Belgrade University, Vojvode Stepe 450, 11221 Belgrade, Serbia

e-mail: djordje.medarevic@gmail.com

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Polyethylene oxides (PEOs) are widely used in formulation of extended release systems, especially matrix tablets. In this study we examined the influence of different types and concentration of polyethylene oxides as well as various manufacturing procedures on drug release rate. Tablets were prepared by (a) direct compression or (b) compression of granules obtained by fluid bed wet granulation. In both cases, tablets contained paracetamol as model substance, polymer and anhydrous lactose as a diluent. Polymers of different molecular weights were used: Polyox® WSR N-12K (approximate molecular weight 1 000 000) and Polyox® WSR Coagulant (approximate molecular weight 5 000 000) in concentration of 20 % and 30 %. Drug release rate was determined in the rotating paddle apparatus (phosphate buffer pH= 5.8; 50 rpm; volume 900 ml). Swelling behavior of tablets (water uptake and tablets diameter changes) was examined during eight hours. Model-dependent methods were used in evaluation of drug release and swelling behaviour of PEO tablets. Lower release rate was achieved using PEO of higher molecular weight (Polyox® WSR Coagulant) and higher polymer content, as was expected. Both direct compression and wet granulation were efficient in prolonging drug release. Slower drug release was obtained when wet granulation was used. The slowest, drug release was achieved with Polyox® WSR Coagulant in concentration of 30 % and wet granulation as manufacturing procedure with about 53 % of released drug after 8 hours. Tablets prepared by direct compression showed better fitting to zero order kinetics model. Polymer content was optimized considering manufacturing process, drug release kinetics as well as extended release during 8 hours of study.

Keywords: fluid bed granulation, prolonged release, polyethylene oxides

1. Introduction

Matrix tablets have been extensively used as one of the most successful oral drug delivery systems. The greatest challenge in formulating these systems is to select appropriate matrix forming polymer to produce matrix tablets that possess satisfactory processing properties and reproducible drug release profiles. In recent years polyethylene oxide polymers are introduced as an alternative to the most commonly used HPMC. Polyethylene oxides (PEOs) are free flowing, thermoplastic homopolymers synthesized by the heterogeneous catalytic polymerization of ethylene oxide monomer [1]. They are commercially available in a wide range of molecular weights (100 000 – 8 000 000) [2]. PEOs have been widely used as pharmaceutical excipients in the last years due to their non-toxicity, high water solubility and swellability, insensitivity to the pH of the biological medium, ease of production. Their anionic nature makes it possible to expect that they do not exhibit any interactions with drug substances or the surrounding media [3]. Fast formation of the gel layer is essential because the gel layer acts as a "protective" layer for the matrix. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices and gives great advantage to PEO polymers. In the presence of water they control the release of the active moiety either by swelling (low molecular weight) or eroding and swelling (high molecular weight), forming a hydrogel. In both cases, the water triggers the process starting the erosion and/or the swelling processes (4). There are numerous factors that influence drug release from swellable matrix tablets including drug solubility and drug loading, polymer molecular weight and ratio, tablet processing procedure, compression force and tablet physical configuration [5]. Water soluble drugs are released by diffusion across the gel layer, while poorly water soluble drugs are released mainly by erosion of the gel layer [6]. As biodegradable polymers they do not generate residue, sediment, or vaporous elements [7]. All this properties in combination with good physical and chemical stability, compressibility and compactibility make these polymers ideal candidates for different manufacturing processes: direct compression, wet extrusion, hot-melt extrusion and wet granulation. Although PEO showed excellent compressibility, the addition of highly compactible excipients is recommended due to its viscoelastic behavior and large axial expansion [8]. In this study we investigated the influence of different grades of PEO (low molecular weight - LMW and high molecular weight - HMW) as different polymer concentration (20 and 30 %) and tablet preparing method (direct compression - DC and wet granulation - WG) on paracetamol release from hydrophilic matrix tablets. As fluid bed

granulation for preparation of PEO matrix tablets is not been fully investigated, we intended to examine suitability of this method for preparing extended released matrix tablets and possible benefits of this method on prolongation of drug release. Swelling testing and analysis of in vitro drug release profiles were performed to estimate mechanisms of drug released from PEO matrix.

2. Materials and methods

2.1. Tablet formulation

Polyox® WSR N-12K and Polyox® WSR Coagulant were obtained from Colorcon Limited (Dartford Kent, United Kingdom). The tableting mixture consisted of Polyox® WSR N-12K (approximate molecular weight 1 000 000) or Polyox® WSR Coagulant (approximate molecular weight 5 000 000) in concentration of 20 % or 30 %, paracetamol (Ph. Eur. 7.0) in concentration of 10 % and the rest of anhydrous lactose (Ph. Eur. 7.0) as a diluent. Tablets were prepared by either direct compression or compression of granules obtained by fluid bed wet granulation. The granulation was performed in fluid bed granulator Mycrolab (Hüttlin, Germany). The process parameters during the granulation process were the following: the temperature during mixing and granulation (55°C); the air flow rate (20 m^3/h until half amount of binder solution was used, than 30 m^3/h to the end of granulation phase, and 20 m^3/h in drying phase), the spray rate (10 g/min) and the atomization pressure (1 bar). 150 g of powder mass containing anhydrous lactose, polyethylene oxide and paracetamol was mixing in fluid bed granulator, while 75 g of distilled water was sprayed onto powder mass during granulation. Both granulate obtained in the fluid bed granulator and the mass prepared for direct compression were compressed in an eccentric tablet machine (Eko Korch, Germany). A set of tablet punches with flat surfaces was used to prepare tablets with a 13-mm diameter. Different tablet formulations are shown in Table 1.

2.2. Dissolution testing

Dissolution testing was performed in the rotating paddle apparatus (Erweka DT70, Germany). Phosphate buffer (pH= 5.8, USP30-NF25) in volume of 900 ml was used as a medium and the rotating paddle speed was 50 rpm. Sampling was carried out at 5, 10, 20, 30, 60, 90, 120, 150,

180, 210, 240, 270, 300, 330, 360, 390, 420, 450 and 480 minutes and the absorbance of paracetamol was measured at 243 nm by the UV / VIS spectrophotometer Evolution 300 (Thermo Fisher Scientific, Cambridge, UK).

Table 1. Tablet formulation prepared by different method with different polymer type and concentration

Formulation	Type of polymer	Polymer concentration (%)	Tablet preparing method
F1	Polyox® WSR Coagulant	30	direct compression
F2	Polyox® WSR Coagulant	20	direct compression
F3	Polyox® WSR Coagulant	30	wet granulation
F4	Polyox® WSR Coagulant	20	wet granulation
F5	Polyox® WSR N-12k	30	direct compression
F6	Polyox® WSR N-12k	20	direct compression
F7	Polyox® WSR N-12k	30	wet granulation
F8	Polyox® WSR N-12k	20	wet granulation

2.3. Comparasion of the dissolution profiles

Dissolution profiles were compared by model independent method using difference factor (f_1) and similarity factor (f_2) [9]. The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \frac{\sum_{t=1}^{n} |Rt - Tt|}{\sum_{t=1}^{n} Rt} \cdot 100 \quad (1)$$

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves:

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

where n is the number of time points, R_t is the dissolution value of the reference at time t, and T_t is the dissolution value of the test sample at time t.

Two dissolution profiles can be consider as similar when f_1 values are up to 15 ($0<f_1<15$) and f_2 values are greater than 50 ($50<f_2<100$) [9].

2.3. Swelling behavior of PEO tablets

Swelling behavior of PEO tablets was monitored during eight hours. Studies of swelling behavior of tablets were conducted by placing the tablets in a Petri dish containing a previously measured amount of distilled water. At specific time points tablets were taken out of the plate (for each time point there was one plate with a tablet) and their wet mass and diameter were measured. They were then dried until a constant weight was reached. The water uptake capacity was calculated according to the formula:

$$\text{Water uptake (\%)} = \frac{Ms - Mo}{Mo} \cdot 100 \quad (3)$$

where: Ms-weight of tablet after swelling, at time t (g)

Mo-initial tablet weight before swelling (g)

The degree of erosion was calculated from the formula:

$$\text{Erosion (\%)} = \frac{Mo - Md}{Md} \cdot 100 \quad (4)$$

where: Mo-initial tablet weight before swelling (g)

Md- weight of dried tablet (g)

The change in tablet diameter after swelling was calculated from the formula:

$$\text{Diameter change (\%)} = \frac{Ds - Do}{Do} \cdot 100 \quad (5)$$

where: Ds-tablet diameter after swelling (mm)

Do-initial tablet diameter before swelling (mm)

2.4. Drug release kinetics

Analysis of drug release profiles using various kinetic models was performed to identify mechanisms that contribute to drug release from matrix. Zero order kinetics (Eq. 6.) describes the system with the constant drug delivery rate (e.g. the same amount of drug is released by unit of time). Zero order kinetics is regarded as an ideal method for drug releasing in order to achieve prolonged drug action. In first order kinetics (Eq. 7.) drug released rate decrease during time in exponential way. The release of drug from systems that follow first order kinetics is proportional to the amount of remaining drug in such way that the amount of drug released by unit of time diminish. Ritger-Peppas model (Eq. 8.) is often used for characterization of release mechanisms for hydrophilic matrix tablets. In this model the fraction of released drug is linearly related to the time raised to an exponent n, whose values can range between 0.43 and 1.00 according to the geometry of system and prevailing release mechanism. For cylindrical matrix systems n=0.45 indicates Fickian diffusion (Case I) mechanism, while $0.45<n<0.89$ show anomalous (non-Fickian) diffusion. Values of exponent n between 0.89 and 1.00 indicate zero order release mechanism (Case II). Constant k and exponent n were calculated by linear regression analysis (PASW Statistics 18.0) of logarithmic form of equation (8).

Zero order: $$Q_t = Q_0 + k_0 \cdot t \quad (6)$$

First order: $$\ln Q_t = \ln Q_0 + k_1 \cdot t \quad (7)$$

Ritger-Peppas: $$Q = k \cdot t^n \quad (8)$$

where: Q_t - the amount of drug dissolved in time t

Q_0 - the initial amount of drug in the solution

Q – fraction of released drug in time t

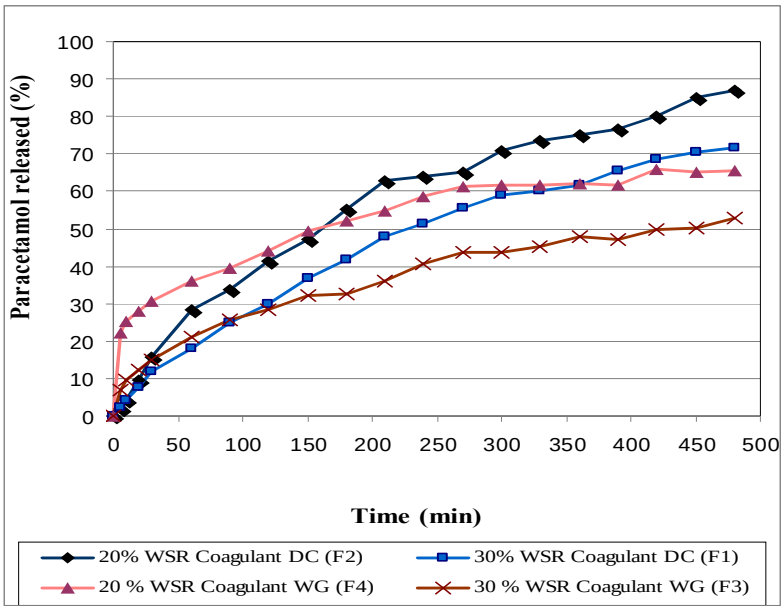
k_0, k_1, k – drug release constants for the coresponding models

n – release exponent, indicating drug release mechanism

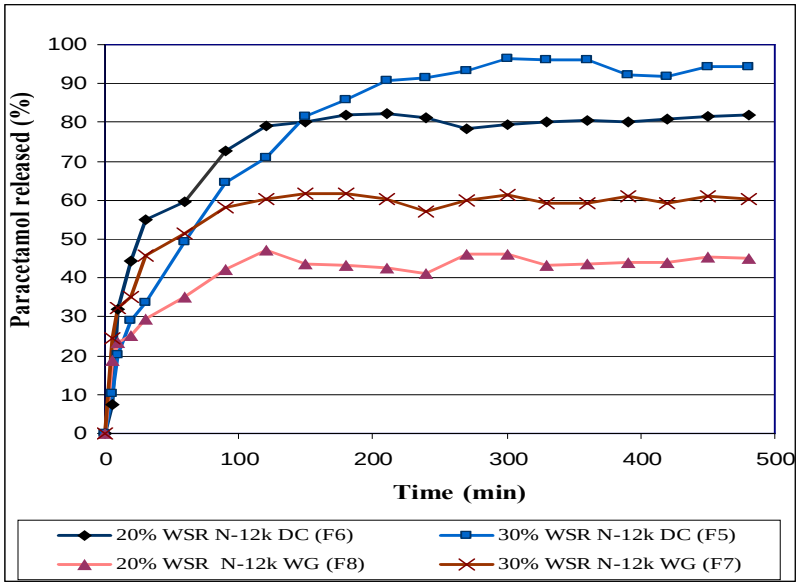
3. Results and Discussion

3.1. In vitro release profiles from tablets

Drug released profiles from formulations prepared by wet granulation or direct compression are shown in Figures 1A and 1B.



(A)



(B)

Figure 1. Dissolution profiles of paracetamol from formulation containing Polyox WSR Coagulant (A) and Polyox WSR N-12K (B) (DC - direct compression, WG - wet granulation)

It is clearly seen that different released patterns are obtained using either different polymer type, polymer concentration or manufacturing procedure. This is confirmed by the calculated values of a difference factor (f_1) and a similarity factor (f_2) (Table 2.). Profiles of any of the compared formulation can not be considered as similar according to the FDA criteria [9].

Table 2. Similarity and difference factors of different tablet formulation

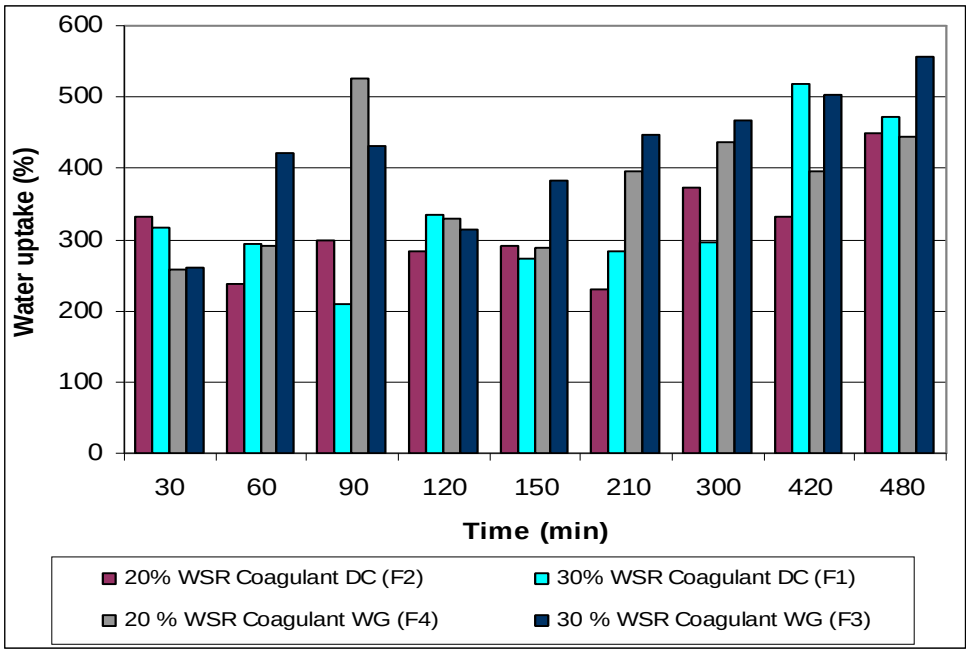
Compared formulations	Difference factor (f_1)	Similarity factor (f_2)
F1 vs. F2	19.34	47.28
F1 vs. F3	24.25	45.59
F1 vs. F5	23.53	42.97
F2 vs. F4	22.28	43.38
F2 vs. F6	27.21	30.98
F3 vs. F4	32.26	38.96
F3 vs. F7	37.78	32.22
F4 vs. F8	27.63	43.16
F5 vs. F6	16.24	44.85
F5 vs. F7	32.21	28.41
F6 vs. F8	44.89	23.86
F7 vs. F8	37.40	40.42

Formulations prepared with Polyox® WSR N-12K (LMW PEO) exhibit higher dissolution rate compared to the formulation with Polyox® WSR Coagulant (HMW PEO). Almost complete release with more than 80 % of released drug was achieved after 2.5 h for tablets made by direct compression with 20 % LMW PEO. On the other hand, in the formulation prepared in the same manner with the same concentration of HMW PEO more than 80 % of drug was released after 7 h. An increased molecular weight leads to increasing of polymer chain length and greater degree of chain entanglement that all contribute to stronger gel layer on the outer surface of the tablet. Stronger gel layer with greater viscosity decreases drug diffusion rate and water diffusion within the matrix which consequently delayed drug release [3,10]. Physical entanglements between neighboring chains can also interference with polymer dissolution [11]. Incomplete drug release was observed in formulations prepared by wet granulation with Polyox® WSR N-12K with slower release with higher polymer concentration. These results revealed that this grade of polyethylene oxide is not suitable for preparing controlled released system by wet granulation. Increased drug dissolution rate with

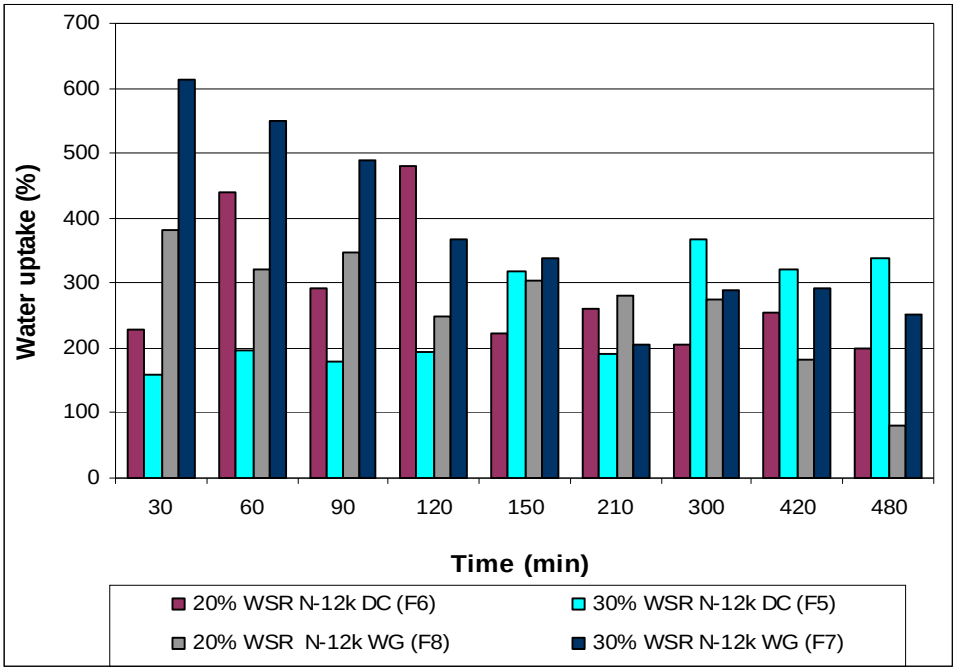
polymer concentration decreasing, observed in formulation F5, F6, F7, F8, may be a consequence of higher solubility of low molecular weight polymer that should promote the dissolution of water soluble drug such as paracetamol. Tablets prepared either by direct compression or wet granulation with HMW PEO exerted extended drug release during at least 8 hours. Although dissolution testing was perform during 8 hours, continuous growth dissolution curve indicates that paracetamol was released over a longer time, 12 hours, or even more especially for tablets prepared by wet granulation method. Initial burst release was observed in formulation F4, which was prepared by wet granulation with 20 % HMW PEO. Formulation F4 exhibited initial burst release with 30 % of released drug after 30 minutes followed by delayed drug release. Increasing polymer concentration decreased drug released rate from formulation containing HMW PEO. We observe opposite effect of polymer concentration on drug delivery rate depending on the polymer molecular weight. While increasing concentration of HMW PEO resulted in decreasing drug release rate, LMW PEO showed the opposite effect. These results can be explained by different mechanisms of drug release from different grades of PEO. As drug diffusion through swollen gel layer take a major role in drug release from high molecular weight PEOs, higher polymer concentration leads to stronger gel formation which slows drug diffusion rate. On the contrary, low molecular weight PEOs form weak gel layer, which is more susceptible to erosion. As drug diffusion are not the major factor determined drug released rate from low molecular weight PEOs, increasing polymer concentration and consequently increasing gel strength and viscosity are not of great importance. Maggi et al revealed that incorporation of water soluble drug can cause dilution of gel layer and accelerate dissolution of LMW PEO, while the effect on HMW PEO is less evident [6]. All of these results suggest that there is no general rule for selection of appropriate polymer concentration that should be optimized taking into account the formulation composition, polymer molecular weight and drug solubility.

3.2. Swelling behavior of matrix tablets

In order to elucidate the mechanisms that contribute to the drug release, it is necessary to examine the swelling behavior and erosion of the matrix. Results of this testing (Figure 2A and 2B) confirmed different swelling behavior of LMW PEOs compared with HMW PEOs. During the first hour of testing formulation containing LMW PEO swells in great extent with water uptake level even above 600 % for formulation F7, prepared by wet granulation with 30 % Polyox® WSR N-12K. But, after 1.5-2 hours water uptake capacity began to decrease as



(A)



(B)

Figure 3. Water uptake capacity of paracetamol matrix tablets F1-F4 (A), F5-F8 (B)

erosion began to prevail over swelling. HMW PEO exhibit slower swelling rate compared with LMW PEO, but water uptake level tend to increase during testing. It is well established that necessary requirement for polymer swelling is reaching water threshold concentration in

the matrix, when water-polymer interactions are preferred over polymer-polymer interactions that hold polymer chains together, and polymer begin to swell [12]. Lower swelling rate of HMW PEO can be explain with its longer chain length with greater degree of entanglement and greater viscosity of gel layer that all hinder water diffusion into the matrix. Thus it takes some time for water diffusion in the matrix and the triggering of swelling process. HMW PEOs require higher amount of water for swelling that last much longer compared with LMW PEOs. Therefore we assume that swelling of tablets prepared with HMW PEO lasted much longer than 8 hours as swelling testing was lasted for. Tablets prepared with LMW PEO showed high tendency to matrix erosion with greater degree of erosion for lower polymer concentration (Figure 3.). Formulation F8 exhibited the highest tendency to erosion with more than 90 % eroded matrix after 8 hours. Tablets prepared with HMW PEO showed much lower liability to erosion. The degree of erosion not exceeded 35 % after 8 hours for all formulation with HMW PEO. These results reveal that LMW PEO has almost 3 times higher tendency for matrix erosion than HMW PEO.

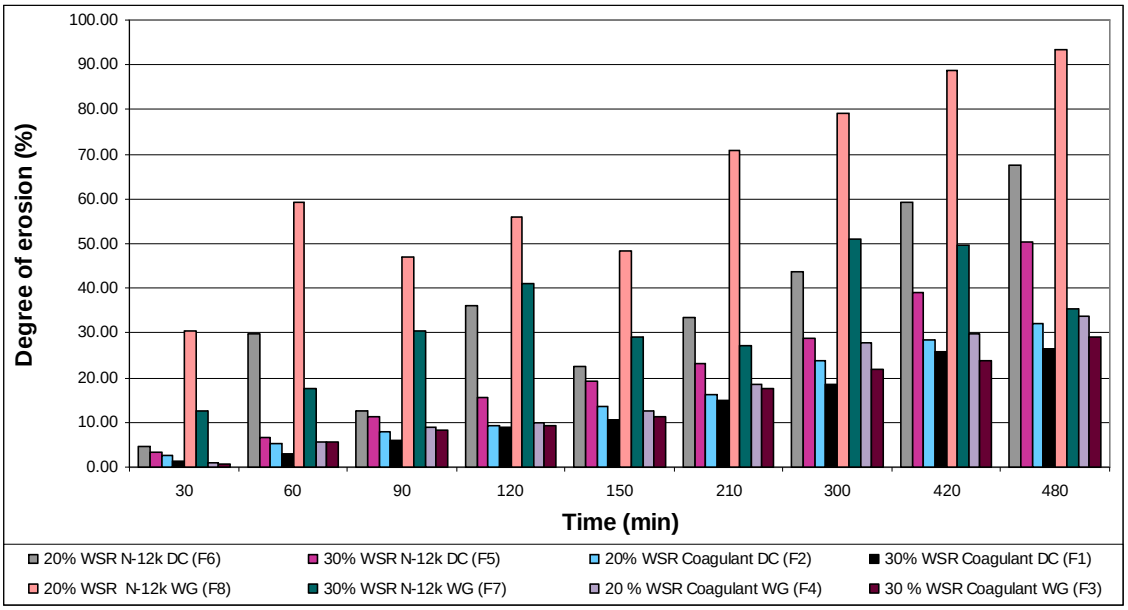


Figure 4. Degree of erosion of paracetamol matrix tablets (F1-F8)

This is confirmed with measuring changes in tablets diameter during swelling testing that are illustrated in Table 3. Larger diameter of formulations F7 and F8 after 30 minutes is a consequence of faster swelling of LMW PEO matrices. Starting from 1 hour tablets prepared with HMW PEO showed greater increase in diameter during the entire duration of the test, which is in agreement with swelling behavior, mentioned above (Figure 5.). After initial increasing of diameter for tablets with LMW PEO, their diameter started to decrease as

erosion process progressed, with the greatest decrease in diameter with formulations prepared by wet granulation with LMW PEO. Measurement of tablet diameter for F7 formulation, which was the most susceptible to erosion, was not possible after 7 hours because of complete tablet disintegration. Erosion diagram revealed that tablets made with high polymer concentration were less liable to erosion due to formation of stronger gel structure on the outer surface of the tablet.

Table 3. Changes in tablet diameter during swelling testing in different time points

Formulation	d_{30} (%)	d_{210} (%)	d_{480} (%)
F1	133.85	154.62	166.15
F2	133.85	148.46	165.38
F3	134.62	156.92	170.77
F4	129.23	144.62	164.
F5	124.62	140.00	117.69
F6	129.23	140.77	95.38
F7	147.69	139.23	83.08
F8	141.54	83.08	0.00

d_{30} – change in tablets diameter after 30 minutes

d_{210} – change in tablets diameter after 210 minutes

d_{480} – change in tablets diameter after 480 minutes

Figure 5. Photographs of different tablets prepared with Polyox® WSR Coagulant as swelling testing progress

The results of swelling testing confirmed well established drug release mechanism from matrix tablets containing swellable polymers such as PEOs. Drug released from HMW PEO tablets is controlled mainly by diffusion through swollen matrix, until releasing from LMW PEO tablets include both diffusion and matrix erosion. HMW PEO tablets exhibited higher swelling capacity and both water uptake and degree of erosion was increasing during the entire duration of the test. The thickness of gel layer that governed the drug release rate is determined by the balance between swelling and erosion. Thus, for achieving controlled drug releasing it is necessary to provide constant gel thickness. LMW PEO tablets exhibited high water uptake capacity, but only at the beginning of the testing afterwards both swelling capacity and tablets diameter decreased. Balance between swelling and erosion is established in a short time interval so these polymers are not suitable for formulation tablets intended for drug delivery over extended time period.

3.3. Analysis of in vitro drug released kinetics

Results of analysis drug release kinetics are shown in Tables 4 and 5. As LMW PEO was not proven suitable for formulation of extended release matrix systems, analyzing of dissolution profiles for formulations F5-F8 was not performed. According to the coefficient of determination (r^2) values, formulations F1 and F2 show the best fitting in first order kinetics model while F3 and F4 best fitted in Ritger-Peppas equation (Table 4.). The diffusional exponent (n) values indicate anomalous release kinetics for formulations F1 and F2 and diffusion controlled releasing for formulation F3. High value of constant k for formulation F4 can indicate initial burst release [13]. Observing dissolution profiles, it can be seen that this formulation exhibited the highest initial burst release among formulation F1-F4.

Table 4. In vitro drug release kinetic for paracetamol extended release tablets with HMW PEO (F1-F4)

Formulation	Zero order		First order		Ritger Peppas		
	k_0	r^2	k_1	r^2	k	n	r^2
F1	0.177	0.975	0.003	0.997	0,830	0.742	0.994
F2	0.215	0.963	0.004	0.996	0,826	0.784	0.970
F3	0.138	0.940	0.002	0.966	3,334	0.449	0.997
F4	0.182	0.875	0.003	0.923	13,366	0.260	0.983

Table 5. Zero order kinetics parameters for formulation F1-F4 in different time intervals

Formulation	Zero order		
	k_0	r^2	Observed time period
F1	0.218	0.990	30-300 min
F2	0.331	0.987	60-180 min
F3	0.184	0.957	30-270 min
F4	0.276	0.928	30-270 min

These results could be expected knowing the complexity of the release mechanisms from hydrophilic matrix systems. An ideal zero order kinetics should be represented only in the cases where swelling and erosion processes are synchronized resulting in maintaining a constant gel layer thickness. Although none of studied formulations showed the best fit in zero order kinetics model, some linear regions indicating zero order release can be observed in dissolution curves (Table 5.). The best fit in zero order model was achieved with formulation F1 (r^2=0.990) between 30 and 300 minutes. A relatively long time interval with constant drug delivery rate makes this formulation a promising candidate for extended release therapeutical systems. Observing the swelling diagram (Figure. 3.), it can be seen that this formulation exhibited relatively narrow range of water uptake level during this time interval which increased significantly after 300 minutes. It is obvious that for HMW PEO tablets zero order kinetics shouldn't be expected during the entire time of drug released. Certain time is needed for polymer swelling and formation of constant gel layer thickness that provides constant drug release rate. In the case of formulation F1, after zero order region between 30 and 300 minutes, the drug release was slowed due to new wave of polymer swelling that increase gel layer thickness and consequently decrease drug diffusion rate. Other formulations also exhibit some region with zero order kinetics, with the statement that formulation prepared by wet granulation showed poorer fitting in zero order model.

4. Conclusion

Drug release from hydrophilic matrix tablets showed the dependence on both polymer concentration and its molecular weight as well as tablet preparing method. HMW PEO (Polyox® WSR Coagulant) showed better suitability for formulation of extended release hydrophilic matrix tablets compared with LMW PEO (Polyox® WSR N-12K). Higher

polymer concentration decrease drug release rate in HMW PEO tablets, while opposite effect was observed in LMW PEO tablets. Swelling testing confirmed well established mechanism of drug release from hydrophilic matrix tablets which include swelling and/or erosion depending on the polymer molecular weight. Both direct compression and wet granulation have proven to be suitable for preparing extended release tablets. Although tablets prepared by wet granulation showed lower overall drug releasing, control drug delivery rate which partially follows zero order kinetics was better achieved using direct compression method. From the results of this study we can conclude that direct compression is still the method of choice for preparing matrix tablets due to its simplicity, low costing and providing relatively controlled drug delivery rate from obtained tablets.

Acknowledgements

This work was done under the project No. TR 34007, supported by the Ministry of Education and Science, Republic of Serbia. The authors gratefully acknowledge to Colorcon Limited for supply polyethylene oxides as gift samples.

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