Hindawi
International Journal of Polymer Science
Volume 2017, Article ID 3486384, 8 pages
https://doi.org/10.1155/2017/3486384

Research Article

Influence of Hydrophilic Polymers on the β Factor in Weibull Equation Applied to the Release Kinetics of a Biologically Active Complex of *Aesculus hippocastanum*

Justyna Kobryń, Sandra Sowa, Monika Gasztych, Andrzej Dryś, and Witold Musiał

Department of Physical Chemistry, Faculty of Pharmacy, Wroclaw Medical University, ul. Borowska 211A, 50-556 Wroclaw, Poland

Correspondence should be addressed to Witold Musiał; witold.musial@gmail.com

Received 27 October 2016; Accepted 26 December 2016; Published 29 January 2017

Academic Editor: Chao Lin

Triterpenoid saponins complex of biological origin, escin, exhibits significant clinical activity in chronic venous insufficiency, skin inflammation, epidermal abrasions, allergic dermatitis, and acute impact injuries, especially in topical application. The aim of the study is the comparison of various hydrogel formulations, as carriers for a horse chestnut seed extract (EH). Methylcellulose (MC), two polyacrylic acid derivatives (PA1 and PA2), and polyacrylate crosspolymer 11 (PC-11) were employed. The release rates of EH were examined and a comparison with the Weibull model equation was performed. Application of MC as the carrier in the hydrogel preparation resulted in fast release rate of EH, whereas in the case of the hydrogel composed with PC-11 the release was rather prolonged. Applied Weibull function adhered best to the experimental data. Due to the evaluated shape parameter β, in the Weibull equation, the systems under study released the active compound according to the Fickian diffusion.

1. Introduction

The horse chestnut (*Aesculus hippocastanum*) seed extract (extractum hippocastani, EH) is a biological source of escin and its derivatives. Various substances are included in the composition of EH: triterpenoid saponins, flavonoids, tannins, coumarins, vitamins C and B, essential oils, and other substances [1, 2]. The extract is used in numerous preparations both internally and externally in patients suffering from chronic venous insufficiency and other inflammatory states of the veins, lower leg varicose veins, hemorrhoids, the treatment of burns, frostbite, skin inflammation, and epidermal abrasion [3]. The main active component of EH is escin. The molecule consists of protoescigenin with carbohydrate and acyl groups (see Figure 1). It occurs as a mixture of triterpenoid saponins, which exist in two forms, α and β, characterized by different melting point, specific rotation, water solubility, and hemolytic index. β-Escin is the main active component and at temperature of 100°C is converted to the α-escin, and consequently the hydroxide groups at C21, C22, and C28 migrate [4]. The saponins of β-escin from the EH contain mainly escin Ia, 24%, escin Ib, 17%, escin IIa, 13.5%, escin IIb, 6%, and escin IIIa, 1.5% [5].

β-Escin is an antagonist to 5-HT and histamine and meliorates entry of ions into channels, raising venous tension. However, the mechanisms of escin activity have not yet been shown [6, 7]. According to recent study, escin induces apoptosis and may decrease pancreatic cancer cell survival, suppressing the NF-κB signal transduction pathway. This phenomenon may result in the sensitization of pancreatic cancer cells to chemotherapeutics agents [8]. Antifungal properties of escin were described; however, results are limited and need to be developed [9]. Escin has high potential of application. Numerous pharmaceutical and cosmetic products containing EH or escin alone are available on the market; however, there is a shortage of kinetic data connected with the release rate of escin from different formulations. The ionic effect between the escin and the functional groups of the polymeric carriers may be utilized for the prolongation of the activity of escin on the skin surface or directly beneath it. There are several biocompatible, biodegradable, and hydrophilic polymers, which are recognized as good

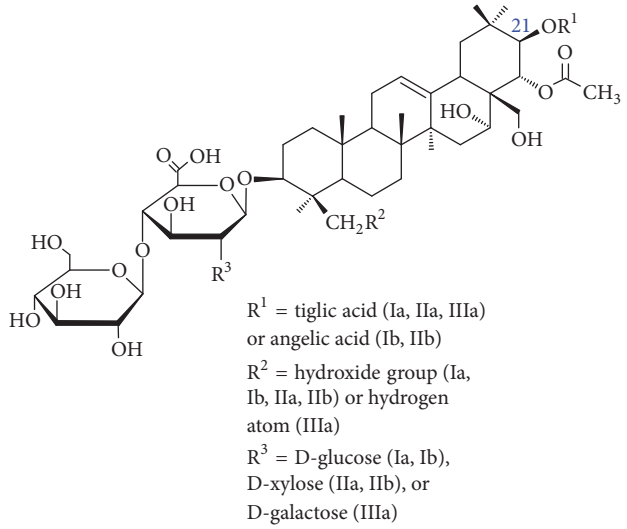

Figure 1: The schematic model of β-escin molecule.

carriers for various active compounds [10]. The applied polymers, as drug carriers, may affect the escin release; thus the selection of a suitable polymeric carrier is essential for controlling the release rate. In the present study, the evaluation of escin release from the hydrogel formulations was performed according to selected kinetic models, that is, zero-order kinetics, first-order kinetics, second-order kinetics, and the Weibull equation. In the zero-order kinetics reaction, the rate is constant and independent of concentration, whereas in first-order kinetics, the process depends on the concentration. The second-order kinetics expands the dependency on the concentrations of two substrates. The mathematical Weibull model enabled the comparison of release profiles of various formulations, using the distribution function, with shape and scale parameters [11]. The present study presents release patterns of formulations with EH, which contain methylcellulose (MC), polyacrylic acid derivatives (PA1 and PA2), and polyacrylate crosspolymer 11 (PC-11) (Figure 2).

The aim of the study is to compare the release rate constants of escin, amongst the formulations containing various hydrophilic polymers, applying various kinetic models, including the Weibull model with the specific β factor.

2. Materials and Methods

2.1. Materials. The hydrogels used in the release study were prepared from the following polymers: methylcellulose (MC, Sigma-Aldrich, Poznan, Poland), Carbopol 980 NF (PA1, Lubrizol, Wickliffe, USA) and polyacrylate crosspolymer 11 (PC-11, Aristoflex Velvet, Clariant, Muttenz, Switzerland). As a reference, a marketed dermatological gel, Venescin, containing EH and Carbopol 5984 (PA2), was used (WZZ Herbapol, Wroclaw, Poland). The composition of the prepared gels is presented in Table 1. EH (7.08 g) was dissolved in 51.72 g (P1) or 52.02 g (P2, P3) of distilled water. In the case of formulation P1, the water of 80°C was applied. The mixtures were complemented by 1.20 g of MC or 0.90 g of PA1 or PC-11. 50.00 mg of 50% of NaOH was added to formulation P2. The formulations were conditioned in a refrigerator at 8°C for 48 hours and equilibrated to the experiment temperature before further evaluation.

Table 1: The composition of the prepared gels comprising EH and different polymers.

Formulation	Composition [%]					
	EH	MC	PA1	PC-11	PA2	W
P1	11.80	2.00	—	—	—	86.20
P2	11.80	—	1.50	—	—	86.70
P3	11.80	—	—	1.50	—	86.70
P4	11.80	—	—	—	qs	qs

EH, extractum hippocastani; MC, methylcellulose; PA1, polyacrylic acid 980 NF; PA2, Carbopol 5984; PC-11, modified polyacrylic acid; W, water; qs, quantum satis: according to the declaration of the manufacturer.

2.2. Methods. The release study was performed using a synthetic membrane applied on the extraction cells. The release study was performed by using a paddle apparatus following the pharmacopoeial method, at 50 rpm. The weighed gel samples were placed in the extraction cells (Perspex, Pharma Test Apparatebau, Germany) and a dialysis tubing cellulose membrane with MWCO of ca. 14000 Da (Sigma-Aldrich, USA) was used for tapping. Drug Dissolution Tester ERWEKA GmbH DT 700 (Heusenstamm, Germany) was utilized in the experiment, with purified water as an acceptor fluid in a volume of 900 ml at 37°C. The experiments were conducted at 37°C, based on the contemporary studies of transdermal absorption using an artificial semipermeable membrane [12–15]. Three collateral measurements proceeded in extraction cells by sampling the acceptor fluid volume of 3 mL every 5, 10, 15, and 20 minutes for over 7 hours. Acceptor fluid was not supplemented. Analysis of taken samples was performed spectrophotometrically (UV/VIS Jasco V-530, Tokyo, Japan) at 265 nm, due to the standard curve according to the available bibliography; the wavelength was selected in accordance with the measured absorption spectrum of escin in aqueous solution [16]. Standard curve was based on three independent series of assessments, with six measurement points at concentrations between 59.00 and 236.00 μg/mL. Statistica software was used to perform statistical tests on the results. The obtained data were evaluated according to zero-order kinetics, first-order kinetics, and second-order kinetics models [17, 18], as well as applying the Weibull model (Table 2) [11].

3. Results

The initial amount of EH in the evaluated formulations is given in Table 1. Due to the course of the plot in Figure 3(a), the largest quantity of EH was released from formulation P1, based on the MC. There was 44.43% of released EH from the MC preparation after 420 min. Comparable amount of EH, that is, 44.03%, was released from the reference formulation P4 after 420 min of the process. Intermediate value of EH, 34.23%, after the same time, was released from the preparation P2 containing the PA1 polymer. The lowest amount

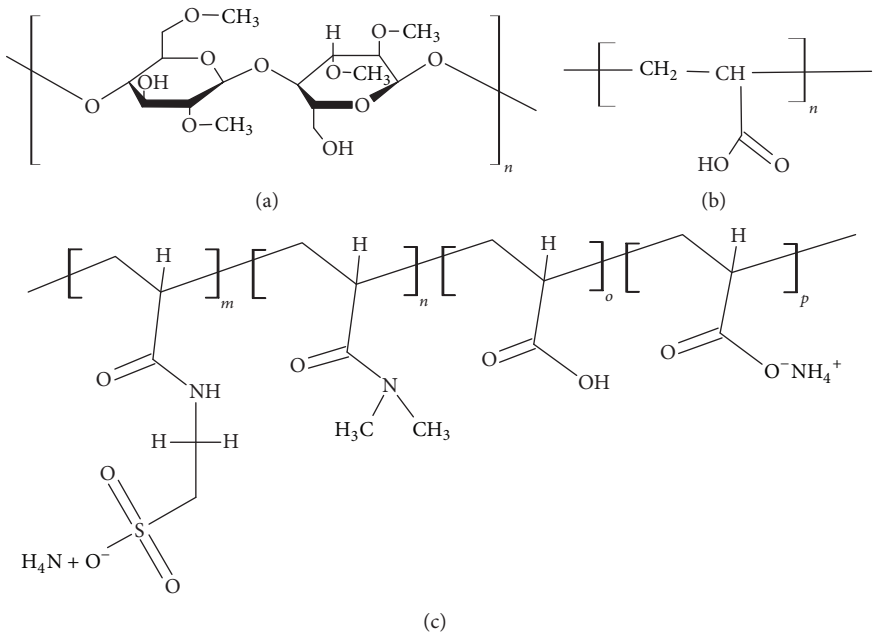

Figure 2: Schematic representation of applied hydrophilic polymers with various functional groups: (a) methylcellulose (MC), (b) polyacrylic acid derivatives (PA1 and PA2), and (c) polyacrylate crosspolymer 11 (PC-11).

Table 2: Kinetic models applied for evaluation of obtained data.

Applied model	General equation	Parameters	
Zero-order	$Q_t = Q_0 - K_{(0)}t$	$K_{(0)} = \frac{Q_0 - Q_t}{t}$	$t_{0.5} = \frac{Q_0}{2K_0}$
1st-order	$Q_t = Q_0 e^{-K_{(I)}t}$	$K_{(I)} = \frac{1}{t}\ln\frac{Q_0}{Q_t}$	$t_{0.5} = \frac{0.693}{K_{(I)}}$
2nd-order	$Q_t^{-1} = Q_0^{-1} + K_{(II)}t$	$K_{(II)} = \frac{Q_0 - Q_t}{Q_0 Q_t}\frac{1}{t}$	$t_{0.5} = \frac{1}{K_{(II)}Q_0}$
Weibull	$Q_t = (100 - Q_0)\left[1 - e^{-(t/T_d)^\beta}\right]$	$\beta = \log_{(-t/T_d)}\left(\ln\left(1 - \frac{Q_t}{(100 - Q_0)}\right)\right)$	$T_d = e^{-b/a}$

K is rate constant, respectively, for zero-order kinetics ($K_{(0)}$), 1st-order kinetics ($K_{(I)}$), 2nd-order kinetics ($K_{(II)}$), and Higuchi model ($K_{(H)}$); t, time; $t_{0.5}$, half release time; Q_0, initial percentage of the released drug; Q_t, percentage of the released drug after time t; T_d, time after release of 63.2% of drug from the formulation; β, a shape parameter in the Weibull model; a, b, slope and intersection of the graph representing the release process.

of released EH was observed in the case of formulation P3, containing PC-11; only 30.48% of EH was released after 420 min. According to Figure 2(a), the release processes did not follow the linear course of the zero-order kinetics function. The release rate constants of the extreme formulations P3 and P1 were $6.72 \cdot 10^{-2}\%\cdot\text{min}^{-1}$ and $9.50 \cdot 10^{-2}\%\cdot\text{min}^{-1}$, respectively. The calculations executed in compliance with first-order kinetics revealed low adherence of the results to the model (Figure 3(b)); the release rate constants were in the range of $8.19 \cdot 10^{-4}\ \text{min}^{-1}$ to $1.29 \cdot 10^{-3}\ \text{min}^{-1}$. Analyzed formulations exhibited the best match for the second-order kinetics equation, as it is seen in Figure 3(c). The range of the release rate constants in boundary formulations P3 and P1 was between $1.00 \cdot 10^{-5}\ \text{min}^{-1}\cdot\%^{-1}$ and $1.80 \cdot 10^{-5}\ \text{min}^{-1}\cdot\%^{-1}$. In comparison, as it is seen in Figure 3(d), the formulation P2 exhibited the best fit to the Weibull model. Additionally, calculated values of a shape parameter β were between 0.6426 and 0.6764 in preparations P3 and P1, respectively, as depicted in Figure 4. The constants and regression coefficients are shown in Table 3. The range of the regression coefficients from 0.95224 to 0.99840 indicated the best matching for second-order kinetics equation and departing from zero-order process model for all formulations. According to the Weibull model, the range of regression coefficients was 0.99134–0.99801.

Figure 5 presents the half-release times for the kinetics models and 63.2%-release time for the Weibull model for all formulations. The range of half-release time in the zero-order model was $5.28 \cdot 10^2$ min to $7.44 \cdot 10^2$ min for formulations P1 and P3, respectively. For the first-order kinetics, the maximal

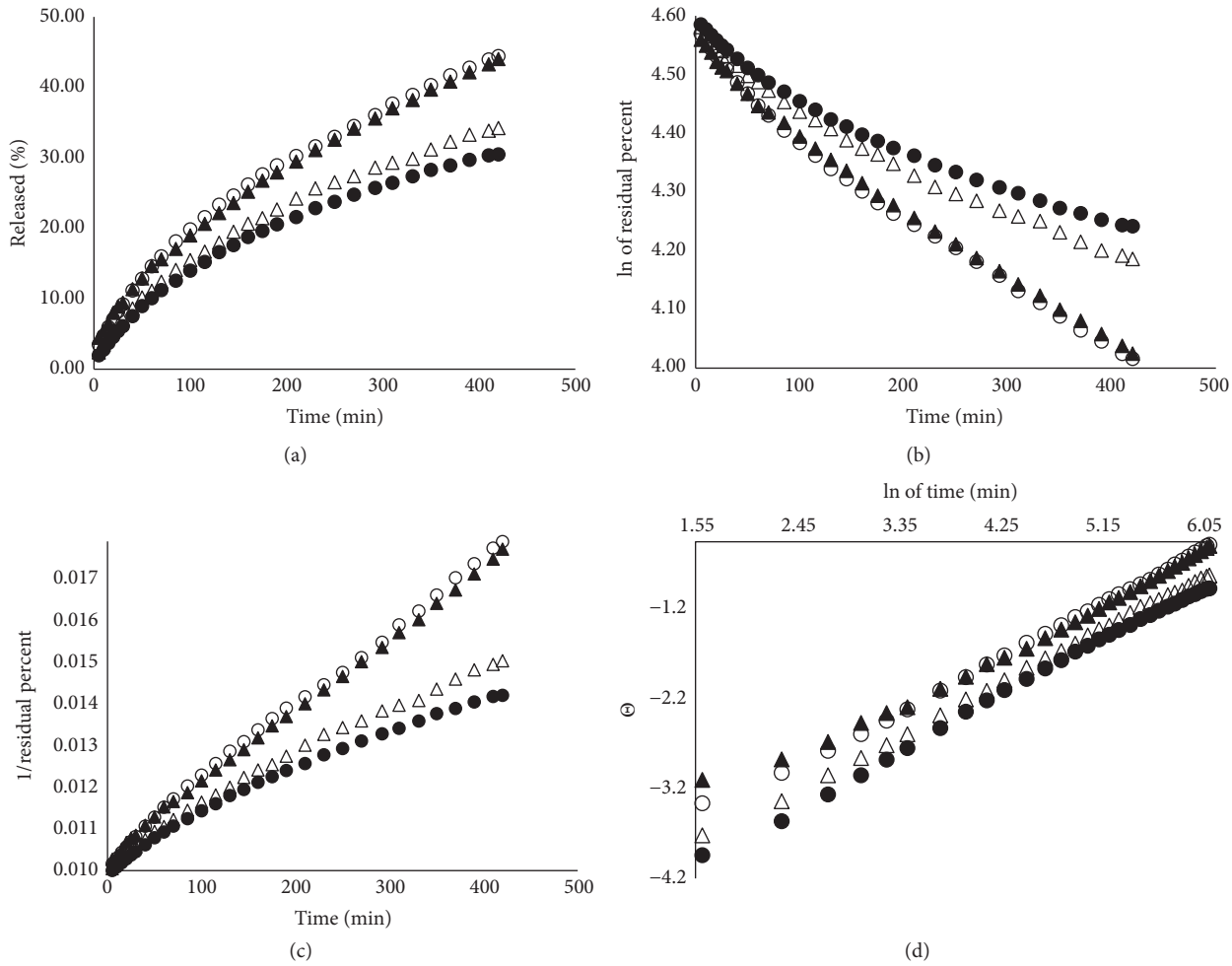

Figure 3: Presentation of release kinetics of EH from various hydrophilic gels according to specified release models. (a) Zero-order kinetics, (b) first-order kinetics, (c) second-order kinetics, and (d) Weibull model. ○, MC; △, PA1; ●, PC-11; ▲, reference gel, PA2; $n = 6$; Θ, ln [−ln(1 − (released percent/100%))].

Table 3: The parameters determined in the course of release kinetics evaluation of gel formulations P1, P2, P3, and P4.

Parameter	Kinetics model								BF
	Zero-order		1st-order		2nd-order		Weibull		
	$K_{(0)}$ [%·min^{-1}]	SD	$K_{(1)}$ [min^{-1}]	SD	$K_{(II)}$ [min^{-1} · %$^{-1}$]	SD	β [−]	SD	
Formulation type: P1 (MC formulation)									
Constant	$9.50 \cdot 10^{-2}$	$6.59 \cdot 10^{-3}$	$1.29 \cdot 10^{-3}$	$1.23 \cdot 10^{-4}$	$1.80 \cdot 10^{-5}$	$2.26 \cdot 10^{-6}$	$6.76 \cdot 10^{-1}$	$3.01 \cdot 10^{-2}$	II
r^2	0.96380	0.01246	0.98490	0.00791	0.99500	0.00216	0.99584	0.00327	
Formulation type: P2 (PA1 formulation)									
Constant	$7.42 \cdot 10^{-2}$	$3.89 \cdot 10^{-3}$	$9.30 \cdot 10^{-4}$	$5.38 \cdot 10^{-5}$	$1.18 \cdot 10^{-5}$	$7.58 \cdot 10^{-7}$	$6.47 \cdot 10^{-1}$	$3.75 \cdot 10^{-2}$	II
r^2	0.95712	0.00802	0.97493	0.00657	0.98776	0.00464	0.99801	0.00063	
Formulation type: P3 (PC-11 formulation)									
Constant	$6.72 \cdot 10^{-2}$	$1.73 \cdot 10^{-3}$	$8.19 \cdot 10^{-4}$	$2.27 \cdot 10^{-5}$	$1.00 \cdot 10^{-5}$	$3.11 \cdot 10^{-7}$	$6.43 \cdot 10^{-1}$	$2.46 \cdot 10^{-2}$	II
r^2	0.95224	0.00464	0.96941	0.00356	0.98286	0.00256	0.99632	0.00129	
Formulation type: P4 (PA2, reference formulation)									
Constant	$9.25 \cdot 10^{-2}$	$3.25 \cdot 10^{-3}$	$1.25 \cdot 10^{-3}$	$4.79 \cdot 10^{-5}$	$1.73 \cdot 10^{-5}$	$7.75 \cdot 10^{-7}$	$6.70 \cdot 10^{-1}$	$3.71 \cdot 10^{-2}$	II
r^2	0.97479	0.00131	0.99155	0.00110	0.99840	0.00027	0.99134	0.00516	

K represents release rates for respective models: zero-order kinetics ($K_{(0)}$), 1st-order kinetics ($K_{(1)}$), and 2nd-order kinetics ($K_{(II)}$); β, a shape parameter in Weibull model; r^2, correlation coefficient for the regression fit describing the course of the release as the first-order process; MC, methylcellulose; PA1, polyacrylic acid derivative Carbopol 980P NF; PC-11, modified polyacrylic acid; PA2, polyacrylic acid derivative Carbopol 5984.

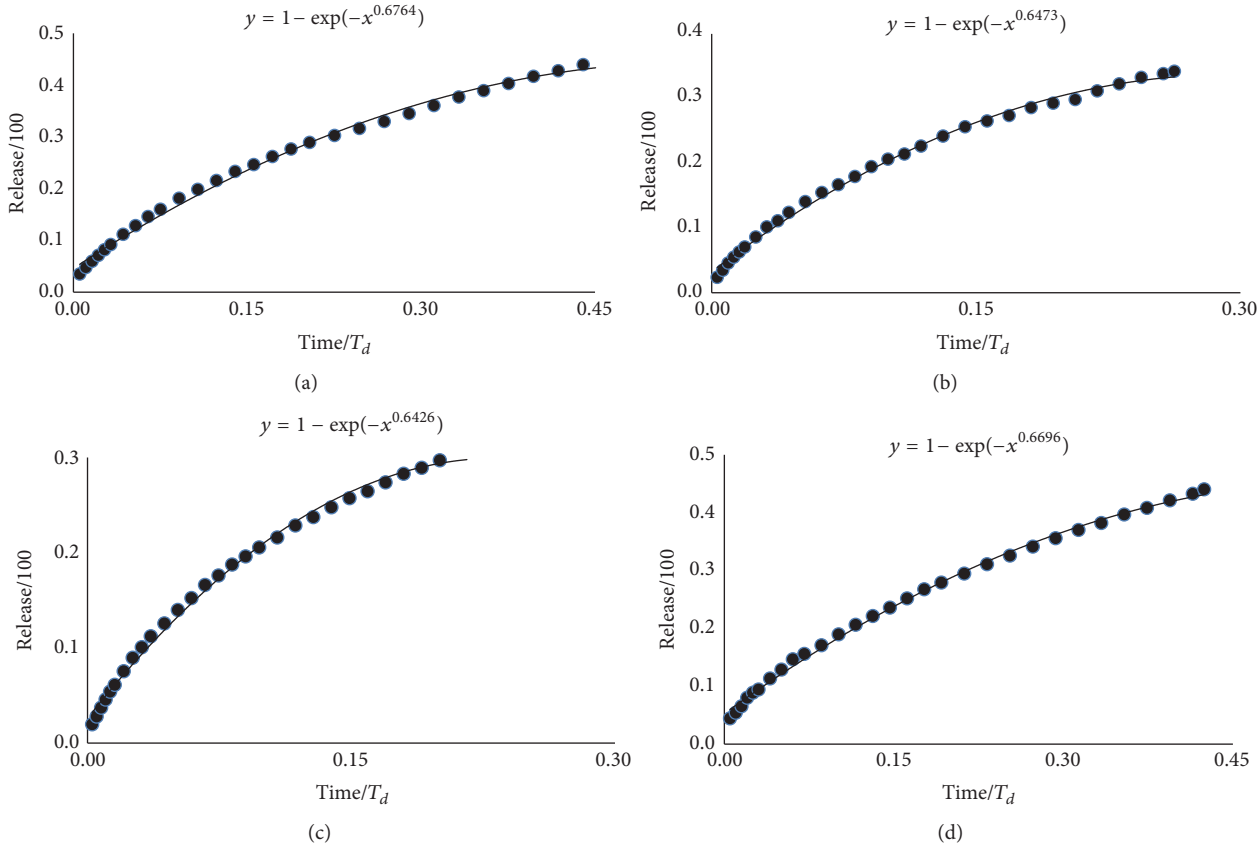

Figure 4: Courses of EH release in Weibull model applied for formulation: (a) MC, (b) PA1, (c) PC-11, and (d) PA2.

half-release time of EH was $8.47 \cdot 10^2$ min and the minimal half-release time was $5.39 \cdot 10^2$ min. For the second-order equation, the half-release times range was between $5.64 \cdot 10^2$ min and $9.96 \cdot 10^2$ min. The Weibull model showed the shortest release time (63.2% of EH) after $9.49 \cdot 10^2$ min and the longest after $19.47 \cdot 10^2$ min. The plots (Figure 5) exhibited the fastest release of EH for the zero-order kinetics model and the slowest release for the Weibull model.

4. Discussion

The most adhering kinetic models were ascribed to the respective assessed samples of hydrogels, according to the high correlation coefficients. The most appropriate model for all the samples studied was the second-order kinetics model (vide data presented in Table 3). The less fitting kinetics belong to the zero-order kinetics model. In the case of second-order kinetics, the change of concentration of two substrates influences the process rate. MC was applied in the P1 hydrogel. The methyl groups in MC are substituted by hydroxyl groups at C2, C3, and/or C6 of glucose (see Figure 2(a)). This molecule is nonionic and has an amphiphilic character. It is water-soluble and organo-soluble, depending on the number of substitutions and distribution of the methoxy groups [19]. Degrees of substitution larger than 1.3 and a heterogeneous distribution of the methyl groups facilitate hydrophobic interactions of the polymer [20]. There are few recent studies based on a MC as a drug carrier [12, 13]. The highest quantity of model active compound (calcium dobesilate, CD) was released from the hydrogel based on a hydroxypropyl methylcellulose (HPMC), 82% after 250 min, and similarly in the case of MC and PC-11 the gels released around 81% after 250 min [13]. Comparatively, in another study, 51% of CD was released from HPMC gel, and 68% was released from MC-based hydrogel. For the PC-11-based preparation, the largest amount of CD was released, that is, 88%, after 250 minutes [12]. However, it must be stressed that the porcine ear skin was utilized in the second study as a way of active components transport. The variability between release rates of active substances in our studies might depend on their structure and properties. EH mostly contains a complex of escin with free carboxyl groups, which might interact with cations. Because of complex character of escin, few interactions have been examined [21]. PA1 and PA2 were used in hydrophilic gels in preparations P2 and P4, respectively. Polyacrylic acid derivatives are anionic polymers, which have the ability to create complexes with cationic residues of other compounds [22]. The bulky structural form of PA1 and PA2, as a net of polyalkene polyether, may immure the EH components and interrupt the active compounds diffusion [23]. Formulation P3 consisted of cationic polymer which may interact with anionic compounds into complexes. Additionally, ammonium groups enable binding of carboxyl

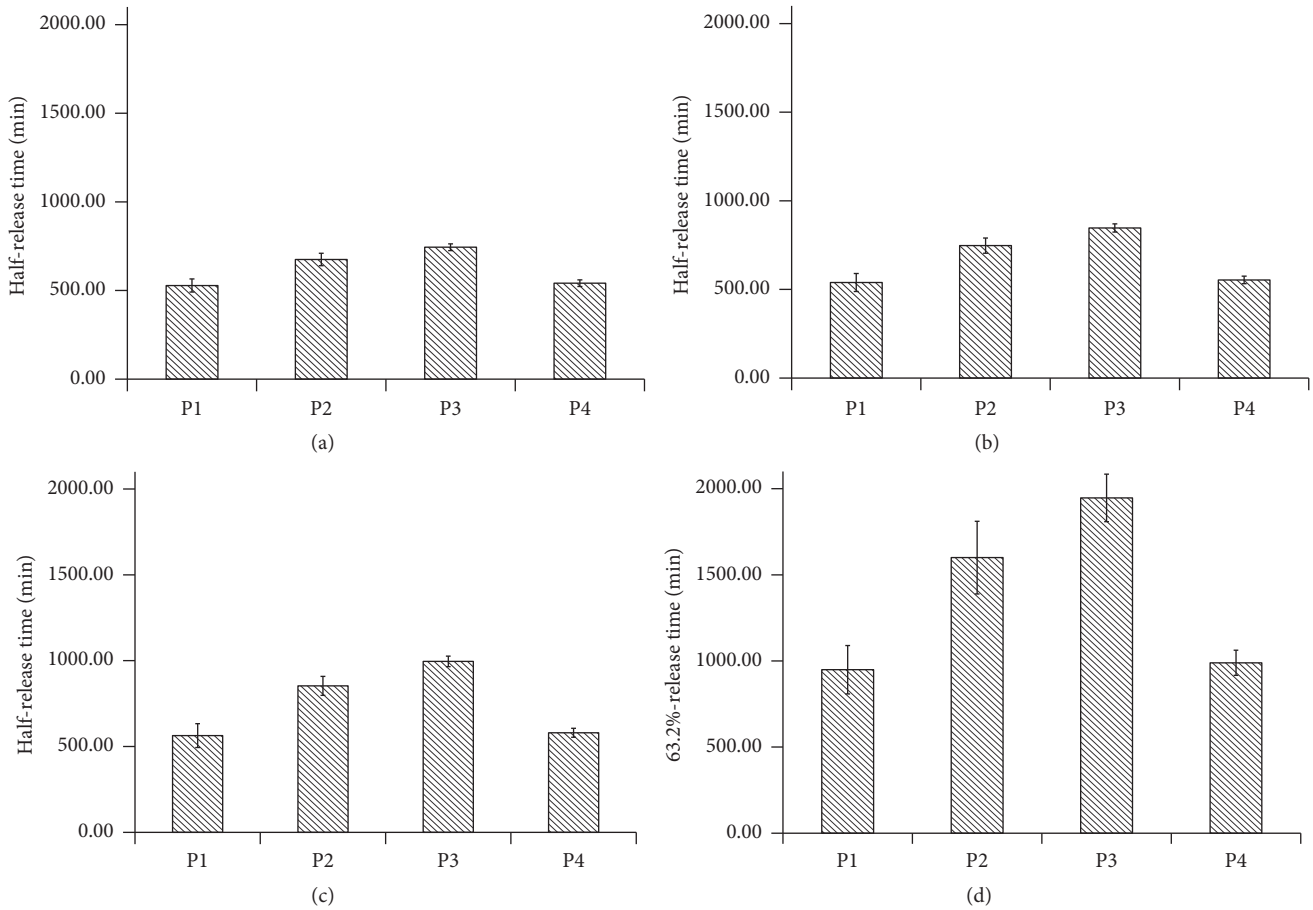

Figure 5: Histograms of half-release times and 63.2%-release time of EH for various hydrogels prepared with the use of MC (P1), PA1 (P2), PC-11 (P3), and PA2 (P4), evaluated according to the kinetics models: (a) zero-order kinetic equation, (b) first-order kinetic equation, (c) second-order kinetic equation, and (d) Weibull model; the Y-bar represents SD; $n = 6$.

groups, for example. Moreover, a cross-structure of the PC-11 may influence the release rate of diffusing components [23].

The release rates, as presented in Table 3, were between $6.72 \cdot 10^{-2}$%·min^{-1} and $9.50 \cdot 10^{-2}$%·min^{-1} for the zero-order kinetics, between $8.19 \cdot 10^{-4}$ min^{-1} and $1.29 \cdot 10^{-3}$ min^{-1} for the first-order kinetics, and between $1.00 \cdot 10^{-5}$ min^{-1} · %$^{-1}$ and $1.80 \cdot 10^{-5}$ min^{-1} · %$^{-1}$ for the second-order kinetics. The highest values of release rate were observed in the case of formulation with MC (P1), and the lowest one was in the case of the preparation with PC-11 (P3). The detailed insight into the variability of the processes was confirmed by the half-release time values presented in Figure 5. The amphiphilic properties of MC may positively influence the solubility of the assessed active complex. On the other hand, ammonium groups of PC-11 may bond to the carboxyl groups of escin (see Figure 6). The ability of ionic cross-linking with other polymers groups was indicated in the case of chitosan hydrogel structure by Berger et al. [24].

According to the Weibull model, the range of a shape parameter β was 0.6426–0.6764 (see Figure 4). The dependency between β value and the release mechanism of substances has been established by several authors. Fickian diffusion was estimated for processes with $\beta \leq 0.75$. In β range between 0.75 and 1.0, the Fickian diffusion is combined with case II transport. For β value more than 1.0, the complex mechanism of drug transport has been reported [25]. Monte Carlo simulation techniques were used for the evaluation of drug release via Fickian diffusion, applying Euclidean matrix. Kosmidis et al. pointed to the Weibull function as a general form appropriate for drug release studies [26]. Similarly, Papadopoulou et al. proved a successful use of the Weibull model in drug release, based on the formulations of diltiazem and diclofenac [25]. Moreover, in the present study, the Weibull equation gave better adherence of processed data, compared to the standard kinetics model equations, with the exception of PA2 system. The good adherence of release data to the Weibull model was confirmed in previously reported studies [25, 26].

5. Conclusions

Application of the nonionic polymer, MC, as a carrier in the hydrogel preparation results in a fast release rate of EH. The release pattern of EH from the hydrogel, composed of PC-11, results in a rather prolonged release. This may be ascribed to the presence of the carboxylic groups interacting with the

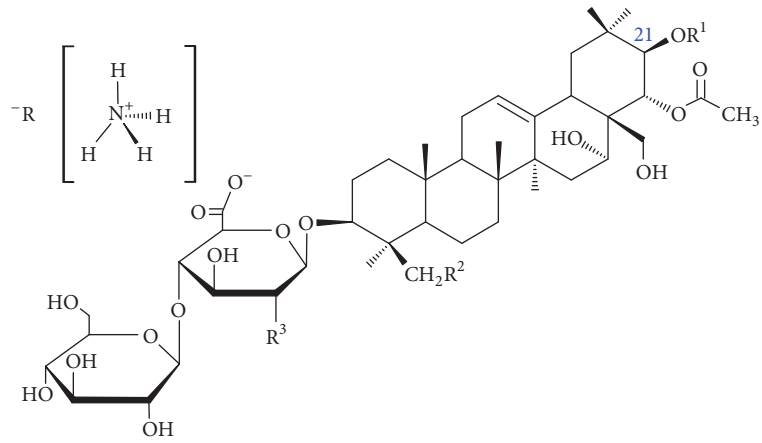

Figure 6: The scheme of possibility of ionic binding ammonium group of polymer with the carboxyl group of escin.

active compound. The Weibull function adheres best to the experimental data. Due to the evaluated shape parameter β, the studied systems released the active compound according to the Fickian diffusion.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

The work was supported by Wroclaw Medical University (Grant ST-847). The horse chestnut extract was supplied by the WZZ Herbapol, Wroclaw, Poland.

References

[1] F. Bahri, R. Harrak, N. Achak, and A. Romane, "Chemical composition and antibacterial activities of the essential oils isolated from Juniperus thurifera L. var. Africana," *Natural Product Research*, vol. 27, no. 19, pp. 1789–1794, 2013.

[2] I. Cvetkovikj, G. Stefkov, J. Acevska et al., "Polyphenolic characterization and chromatographic methods for fast assessment of culinary Salvia species from South East Europe," *Journal of Chromatography A*, vol. 1282, pp. 38–45, 2013.

[3] M. Dudek-Makuch and I. Matławska, "Flavonoids from the flowers of Aesculus hippocastanum," *Acta Poloniae Pharmaceutica—Drug Research*, vol. 68, no. 3, pp. 403–408, 2011.

[4] C. R. Sirtori, "Aescin: pharmacology, pharmacokinetics and therapeutic profile," *Pharmacological Research*, vol. 44, no. 3, pp. 183–193, 2001.

[5] M. Yoshikawa, E. Harada, T. Murakami et al., "Escins-Ia, Ib, IIa, and IIIa, bioactive triterpene oligoglycosides from the seeds of Aesculus hippocastanum L.: their inhibitory effects on ethanol absorption and hypoglycemic activity on glucose tolerance test," *Chemical & Pharmaceutical Bulletin*, vol. 42, no. 6, pp. 1357–1359, 1994.

[6] F. E. Koehn and G. T. Carter, "The evolving role of natural products in drug discovery," *Nature Reviews Drug Discovery*, vol. 4, no. 3, pp. 206–220, 2005.

[7] A. Gurib-Fakim, "Medicinal plants: traditions of yesterday and drugs of tomorrow," *Molecular Aspects of Medicine*, vol. 27, no. 1, pp. 1–93, 2006.

[8] A. Rimmon, A. Vexler, L. Berkovich, G. Earon, I. Ron, and S. Lev-Ari, "Escin chemosensitizes human pancreatic cancer cells and inhibits the nuclear factor-kappaB signaling pathway," *Biochemistry Research International*, vol. 2013, Article ID 251752, 9 pages, 2013.

[9] R. Franiczek, M. Gleńsk, B. Krzyzanowska, and M. Włodarczyk, "β-Aescin at subinhibitory concentration (sub-MIC) enhances susceptibility of *Candida glabrata* clinical isolates to nystatin," *Medical Mycology*, vol. 53, no. 8, pp. 845–851, 2015.

[10] S. Anlar, Y. Capan, and A. A. Hincal, "Physico-chemical and bioadhesive properties of polyacrylic acid polymers," *Pharmazie*, vol. 48, no. 4, pp. 285–287, 1993.

[11] P. Costa and J. M. Sousa Lobo, "Modeling and comparison of dissolution profiles," *European Journal of Pharmaceutical Sciences*, vol. 13, no. 2, pp. 123–133, 2001.

[12] D. Wojcik-Pastuszka, A. Lisik, M. Twarda, R. Berkowski, and W. Musial, "The influence of hydrophylic polymers on the release rate of calcium dobesilate in hydrogel formulation assessed in vitro using porcine ear skin," *Current Issues in Pharmacy and Medical Sciences*, vol. 28, no. 4, pp. 225–230, 2015.

[13] A. Lisik, D. Wojcik-Pastuszka, M. Twarda, R. Berkowski, and W. Musial, "Effect of standard and reversible arrangements of Ph.Eur./USP extraction cells during dissolution tests of calcium dobesilate in hydrogel formulation," *Current Issues in Pharmacy and Medical Sciences*, vol. 28, no. 2, pp. 136–141, 2015.

[14] D. Reddy, D. Swarnalatha, S. Ramanjulu, B. Karthik, S. Kumar, and S. Ussain, "Design, development and characterization of clopidogrel bisulfate transdermal drug delivery system," *Asian Journal of Pharmaceutical and Clinical Research*, vol. 8, no. 2, pp. 2–5, 2015.

[15] H. Hamishehkar, M. Khoshbakht, A. Jouyban, and S. Ghanbarzadeh, "The relationship between solubility and transdermal absorption of tadalafil," *Advanced Pharmaceutical Bulletin*, vol. 5, no. 3, pp. 411–417, 2015.

[16] B. Sanjivkumar, D. Rajkumar, P. Mallikarjun, B. Karankumar, and K. S. Rao, "Development and method validation of Aesculus hippocastanum extract," *International Research Journal of Pharmacy*, vol. 3, no. 7, pp. 324–328, 2012.

[17] S. Dash, P. N. Murthy, L. Nath, and P. Chowdhury, "Kinetic modeling on drug release from controlled drug delivery systems," *Acta Poloniae Pharmaceutica*, vol. 67, no. 3, pp. 217–223, 2010.

[18] J. Siepmann and F. Siepmann, "Modeling of diffusion controlled drug delivery," *Journal of Controlled Release*, vol. 161, no. 2, pp. 351–362, 2012.

[19] P. L. Nasatto, F. Pignon, J. L. M. Silveira, M. E. R. Duarte, M. D. Noseda, and M. Rinaudo, "Methylcellulose, a cellulose derivative with original physical properties and extended applications," *Polymers*, vol. 7, no. 5, pp. 777–803, 2015.

[20] N. Sarkar, "Structural interpretation of the interfacial properties of aqueous solutions of methylcellulose and hydroxypropyl methylcellulose," *Polymer*, vol. 25, no. 4, pp. 481–486, 1984.

[21] Y. Huang, S.-L. Zheng, H.-Y. Zhu, Z.-S. Xu, and R.-A. Xu, "Effects of aescin on cytochrome P450 enzymes in rats," *Journal of Ethnopharmacology*, vol. 151, no. 1, pp. 583–590, 2014.

[22] M. Milanović, V. Krstonošić, L. Dokić, M. Hadnađev, and T. Dapčević Hadnađev, "Insight into the interaction between carbopol® 940 and ionic/nonionic surfactant," *Journal of Surfactants and Detergents*, vol. 18, no. 3, pp. 505–516, 2015.

[23] G. Z. Abdullah, M. F. Abdulkarim, C. Mallikarjun et al., "Carbopol 934, 940 and Ultrez 10 as viscosity modifiers of palm olein esters based nano-scaled emulsion containing ibuprofen," *Pakistan Journal of Pharmaceutical Sciences*, vol. 26, no. 1, pp. 75–83, 2013.

[24] J. Berger, M. Reist, J. M. Mayer, O. Felt, N. A. Peppas, and R. Gurny, "Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 57, no. 1, pp. 19–34, 2004.

[25] V. Papadopoulou, K. Kosmidis, M. Vlachou, and P. Macheras, "On the use of the Weibull function for the discernment of drug release mechanisms," *International Journal of Pharmaceutics*, vol. 309, no. 1-2, pp. 44–50, 2006.

[26] K. Kosmidis, P. Argyrakis, and P. Macheras, "A reappraisal of drug release laws using Monte Carlo simulations: the prevalence of the Weibull function," *Pharmaceutical Research*, vol. 20, no. 7, pp. 988–995, 2003.