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Pilot Formulation Study of Ph-sensitive Gels

Special Issue Article

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Abstract Drugs remain for a short time on mucus membranes, such as oral, ocular, or nasal mucus, which are washed with physiological fluids. One of the possibilities to overcome this obstacle is the application of solutions that, due to the physiological environment or stimulus, turn into more viscous gels. These gels often also have mucoadhesive properties and the drug is released from them for a longer period. Carbomer 940 (C940), polycarbophil (PCP), and chitosan (CH) are gel-forming excipients, and the consistency of their solutions changes due to the concentration of protons (pH); therefore, they are referred to as pH-sensitive gelling agents. The aim of this study was to prepare pH-sensitive solutions that form gels in the pH of the oral cavity. We prepared water solutions with various concentrations of gel-forming excipients and evaluated the appearance, pH of the solution, injectability of the solution, and pH of gelation. By determining the pH of gelation, suitable concentrations (w/w) of the used polymers were found, namely, 0.1% C940, 0.225% PCP, and 2.5% CH with medium molecular weight (CHM). The 0.1% C940 and 0.225% PCP solutions were injectable through the syringe with the smallest 0.5 mm needle diameter. The 2.5% CHM solution was not injectable even through the syringe with the largest 0.8 mm needle diameter. Solgels prepared at the determined concentrations were evaluated by a dissolution test in a pH 6.8 phosphate buffer using methylene blue (MB) as a model substance. After 60 min of dissolution, 77.04% ± 5.94%, 48.85% ± 5.74%, and 77.35% ± 4.98% of MB were released from samples with C940, PCP, and CHM, respectively. The dissolution of the C940 and CHM samples took place according to the Korsmeyer–Peppas kinetic model (R2 0.999 ± 0.001, 0.978 ± 0.003) and of the PCP samples took place according to the first-order model (R2 0.994 ± 0.001). The 0.225% PCP pH-sensitive gel showed the most advantageous properties in terms of injectability, pH gelation, and prolonged release of MB.

Keywords *in situ – pH-sensitive – gel – polycarbophil – chitosan – carbomer 940*

INTRODUCTION

pH-sensitive (responsive) gels are a subgroup of *in situ* gels that respond to physiological stimuli because they change their consistency, making it possible to achieve prolonged release of the active pharmaceutical ingredient (API). pH-responsive polymers have an ionizable group in their structure that can accept or release a proton. The increased electrostatic charge increases the hydrophilicity of the polymer, and it can cause an electrostatic impulse between the polymer chains, which can cause extension or opening of the polymer chains. The pH at which such conformational or structural changes occur is called the transition pH. The transient pH value is related to the pKa value of the polymer. As a rule, ionizable polymers that have a pKa value of 3–10 act as a pH-responsive system (Mutalabisin et al., 2018). In addition to the ionization of the functional group, the rate of API release is also influenced by the hydrophobicity of the main chain of the polymer and the conformation of the polymer, which is closely related to the cross-linking density of the polymer chain (Aguilar et al., 2007). Carbomer 940 (C940) and polycarbophil (PCP) belong to polyacids (polyanions). They swell in a neutral to alkaline environment and increase their volume several times. C940 and PCP are high-molecular-weight acrylic acid polymers, whereas C940 is cross linked with allyl ethers and pentaerythritol and PCP with polyalkenyl ethers or divinylglycol (Gajdziok & Vetchý, 2012). Chitosan (CH) is one of the polybases (polycation) which swells at reduced pH, when it ionizes by accepting a proton (Livovská et al., 2021).

METHODS

Chemicals: PCP was generously donated by The BFGoodrich Company (USA). C940 was purchased from Dr. Kulich Pharma (CZ), CH with low molecular weight (CHL) and medium molecular weight (CHM) from Sigma-Aldrich (USA),

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Table 1. Composition of polymeric solutions (in grams).

Formulation	C940	PCP	CHL	CHM	PW	AA 1%
C940-0.10	0.100	-	-	-	99.900	-
C940-0.70	0.700	-	-	-	99.300	-
C940-1.30	1.300	-	-	-	98.700	-
PCP-0.200	-	0.200	-	-	99.800	-
PCP-0.225	-	0.225	-	-	99.775	-
PCP-0.250	-	0.250	-	-	99.750	-
PCP-0.300	-	0.300	-	-	99.700	-
PCP-0.400	-	0.400	-	-	99.600	-
PCP-0.600	-	0.600	-	-	99.400	-
PCP-1.000	-	1.000	-	-	99.000	-
CHL-3000	-	-	3.000	-	-	97.000
CHL-3.50.	-	-	3.500	-	-	96.500
CHM-200.	-	-	-	2.000	-	98.000
CHM-2.50	-	-	-	2.500	-	97.500
CHM-30.0	-	-	-	3.000	-	97.000

C940: carbomer 940, PCP: polycarbophil, CHL: chitosan low molecular weight, CHM: chitosan medium molecular weight, PW: purified water, AA 1%: acetic acid water solution 1% (1%)

Table 2. Process parameters of preparation for individual polymers.

Polymer	Primary stirring (rpm)	Secondary stirring (rpm)	Homogenization time (min)
Carbomer	300	330	30
Polycarbophil	300	350	45
Chitosan	500	700	45

methylene blue (MB) and potassium dihydrogen phosphate from Centralchem (SR), acetic acid from Salvus (SR), sodium hydroxide from Lachema (CZ), and purified water (PW) and phosphate buffer (pH 6.8) were prepared at the University of Veterinary Medicine and Pharmacy in Košice (SR).

Preparation of polymeric solutions was carried out at room temperature. Composition of the polymeric solutions is shown in Table 1. C940 and PCP were dispersed in PW. CHL and CHM were dispersed in an acetic acid solution (1% w/w). Weighed polymers were gradually added to the weighted solvent under constant stirring (primary stirring); with increasing viscosity, the speed was increased (secondary stirring) and the mixture was homogenized for a specified time (Witeg Labortechnik, DE). Table 2 shows the process parameters of preparation for individual polymers.

Appearance of sols and gels was visually evaluated against a black and white background. According to the appearance, the samples were characterized by the following signs: (+) turbid – turbidity is present; (++) transparent – minimal turbidity or opalescence is present; (+++) glassy – without turbidity or opalescence.

The pH of the polymeric solutions was evaluated using a pH meter Seven Compact S220 (Mettler Toledo, USA) calibrated by standard solutions with pH 4.01, 7.0, and 11.0. Samples were measured in triplicate.

Injectability was checked using a 5-ml syringe with injection needles of various diameters (0.5, 0.6, 0.7, 0.8 mm). We tried to squeeze out 1 ml of the polymer solution smoothly. The polymeric solutions were evaluated as injectable (+) or noninjectable (-).

Gelation pH

The C940 and PCP formulations were tempered at 37 °C ± 1 °C in a tube. 1 M NaOH was added dropwise with continuous stirring. The pH was checked using a pH meter Seven Compact S220 (Mettler Toledo, USA). Gel formation was indicated by the lack of movement of meniscus on tilting the tube. It was not possible to determine the gelation pH of the CH samples in this way because a gel-like precipitate was formed after the addition of NaOH, which could not be homogenized. Therefore, the following procedure was chosen. Five hundred microliters of the CH sample colored with MB (1 drop/1 g of sample) were added to the buffer with a pH range of 3–14 tempered at 37 °C ± 1 °C, which was followed by vortexing (VELP Scientifica, IT) for 10 s at 800 rpm. The presence of the gel was observed immediately after the addition of sol. The gelation pH was evaluated as the pH of the buffer with the

Table 3. Appearance of polymeric solutions and gels, pH of polymeric solutions, and pH of the gelation.

Formulation	Appearance		pH	
	polymeric solution	gel	polymeric solution	gelation
C940-0.10	++	+++	3.57 ± 0.05	6.74 ± 0.47
C940-0.70	++	+++	2.93 ± 0.10	3.01 ± 0.14
C940-1.30	++	+++	2.66 ± 0.03	2.81 ± 0.02
PCP-0.200	+	-	3.68 ± 0.02	-
PCP-0.225	+	+++	3.59 ± 0.05	6.61 ± 0.21
PCP-0.250	+	+++	3.56 ± 0.03	6.02 ± 0.06
PCP-0.300	+	+++	3.39 ± 0.03	5.36 ± 0.30
PCP-0.400	+	+++	3.35 ± 0.04	4.19 ± 0.33
PCP-0.600	+	++	3.26 ± 0.04	4.03 ± 0.08
PCP-1.000	+	+	3.32 ± 0.24	3.36 ± 0.37
CHL-3000	+	np	4.62 ± 0.09	7.00 ± 0.00
CHL-3.50.	+	np	5.05 ± 0.02	6.50 ± 0.00
CHM-200.	++	np	4.33 ± 0.02	9.00 ± 0.00
CHM-2.50	+	np	4.52 ± 0.01	6.00 ± 0.00
CHM-30.0	+	np	4.85 ± 0.01	6.00 ± 0.00

(+): turbid, (++): transparent, (+++): glassy, (-): the gel was not formed, np: not provided, AA 1%: acetic acid water solution 1% (1%)

lowest pH at which the gel formed and remained visible even after vortexing. Samples were evaluated in triplicate.

Dissolution test was carried out using a paddle apparatus (50 rpm) in phosphate buffer with pH 6.8 tempered at 37 °C ± 0.5 °C (Ph. Eur. 10.4, 2021). Ten samples were collected for 60 min (SR8 Plus; Hanson Research, Los Angeles, CA, USA).

RESULTS AND DISCUSSION

The prepared sols showed a transparent to turbid appearance (Table 3). In this state, the polymers are coiled and form clumps that block the passage of light. By increasing the pH, the system turns into a gel and the polymers expand (Gupta et al., 2019). There are enough gaps between the polymer fibers that are filled with solvent and light passes more easily through the system arranged in this way. Therefore, most of the gels had a glassy appearance, except for PCP-1, where the gel was turbid. With PCP-0.2, we did not notice the formation of a gel, and with the CH formulations, gel-like clusters were formed, the appearance of which could not be determined.

Since C940 and PCP are polyacids (polyanions), with increasing concentration of polymer solutions, the pH decreased slightly (Table 3): for C940 from 3.57 ± 0.05 (C940-0.1) to 2.66 ± 0.03 (C940-1.3) and for PCP from 3.68 ± 0.02 (PCP-0.2) to 3.32 ± 0.24 (PCP-1). The higher the concentration of anionic polymers, the lower was the pH needed to form a gel: 2.81 ± 0.02 (C940-1.3), 3.36 ± 0.37 (PCP-1). On the contrary, the lower the concentration, the higher was the pH needed to form a gel: 6.74 ± 0.47 (C940-0.1), 6.61 ± 0.21 (PCP-0.225). A higher concentration of polymer increases the viscosity and mucoadhesive strength of formulations (Singh et al., 2018). The low pH of 1% acetic acid (2.62 ± 0.01) was gradually increased by adding CH (Table 3), since CH is a polybase. Fig. 1 shows the change in the consistency of polymer solutions from liquid to gel form when the gelation pH is reached. At the same time, the difference in the appearance of sols and gels can be seen.

For convenient application of *in situ* gels, it is necessary that they pass through an injection needle. When injecting a liquid drug, it is necessary to use a force that (1) overcomes the resistance force of the syringe plunger; (2) imparts kinetic energy to the liquid; and (3) forces the liquid through the needle (Chien et al., 1981). Additional force is also required when the medicine is administered to the subcutaneous tissue or muscle (Rungseevijitprapa & Bodmeier, 2009). As the polymer concentration increases, the viscosity of the sols increases, which can lead to application problems. All PCP concentrations (0.2–0.6) were injectable. For the C940 formulations, only the lowest concentration (0.1) was injectable, while the other concentrations, as well as all the CH formulations were not injectable (Table 4).

For dissolution evaluation, we chose formulations that were injectable or the most liquid and had a gelation pH close to the pH of the oral cavity. The formulations C940-0.1, PCP-0.225, and CHM-2.5 were selected for dissolution.

We monitored the amount of MB released by dissolution in phosphate buffer of pH 6.8 for 60 min. According to the adjusted coefficient of determination (R^2_{adj}), which takes into

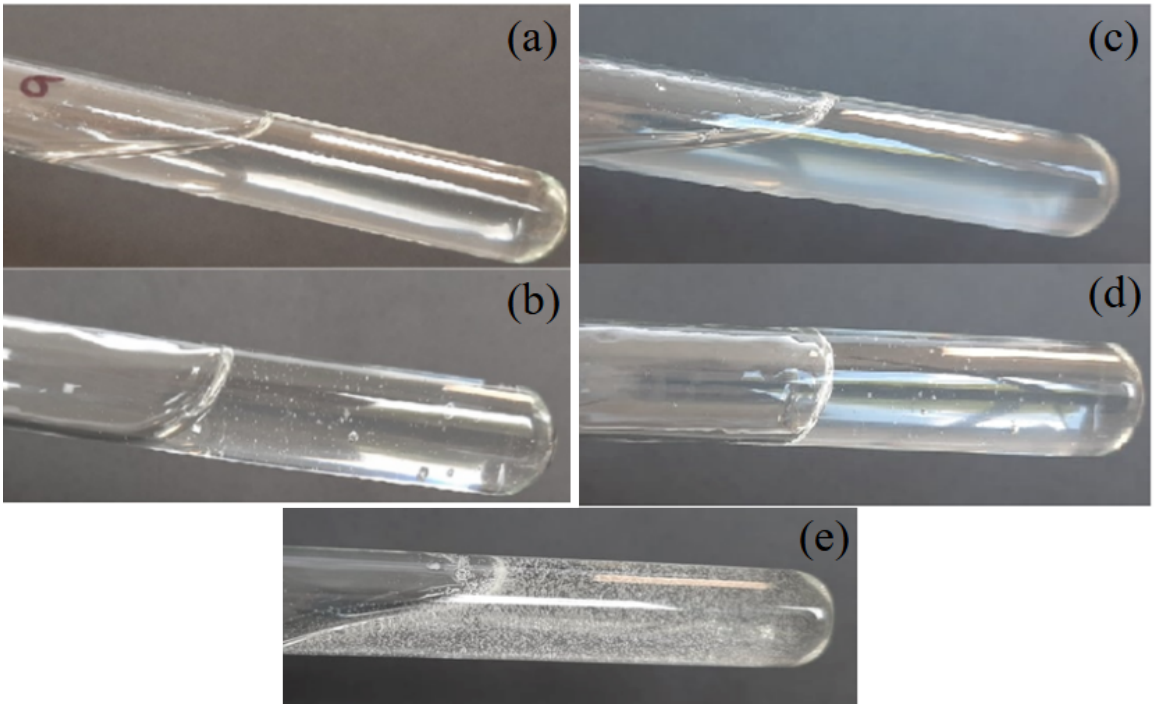

Figure 1. Appearance of formulation C940-0.1 (a) solution, (b) gel, PCP-0.225 (c) solution, (d) gel, CHM-2.5 (e) solution.

Table 4. Injectability of polymeric solutions.

Formulation	Injection needle diameter			
	0.5	0.6	0.7	0.8
C940-0.10	+	+	+	+
C940-0.70	-	-	-	-
C940-1.30	-	-	-	-
PCP-0.200	+	+	+	+
PCP-0.225	+	+	+	+
PCP-0.250	+	+	+	+
PCP-0.300	+	+	+	+
PCP-0.400	+	+	+	+
PCP-0.600	+	+	+	+
PCP-1.000	+	+	+	+
CHL-3000	-	-	-	-
CHL-3.50.	-	-	-	-
CHM-200.	-	-	-	-
CHM-2.50	-	-	-	-
CHM-30.0	-	-	-	-

(+): injectable, (-): not injectable

account the number of parameters (Costa & Sousa Lobo, 2001), the release of MB followed the first-order kinetic (Gibaldi & Feldman, 1967) in the case of the PCP-0.225 formulation (0.993 ± 0.002) and the Korsmeyer–Peppas model (Korsmeyer et al., 1983) in the case of C940-0.1 (0.999 ± 0.001), and CHM-2.5 (0.969 ± 0.004) (see Table 5). Since the difference of R^2_{adj} of the first-order model and Korsmeyer–Peppas is minimal (0.993 ± 0.002 vs. 0.990 ± 0.003) for the PCP-0.225 sample, we can compare the dissolution of MB from individual formulations using the Korsmeyer–Peppas model (see Table 6). Although the Korsmeyer–Peppas release constant (k_{KP}) for the PCP-0.225 sample is not the lowest (19.70 ± 2.86), MB release is prolonged, as only 48.85 ± 5.74% of MB is released in 60 min. Decisive is the low value of the diffusion exponent (n), which is less than 0.5 for all samples, indicating that there was no Fickian diffusion. According to the Korsmeyer–Peppas model, 50% of MB (T_{50}) was released from C940-0.1, PCP-0.225, and CHM-2.5 in 16.54 ± 5.37, 61.01 ± 20.48, and 19.29 ± 4.88 min, respectively. Fig. 2 shows the dissolution curves.

Table 5. Calculated adjusted coefficient of determination (R^2_{adj}) of different mathematical models, fitted to released data in whole dissolution time (0–60 min).

Formulation	R^2_{adj} of mathematical models		
	Zero order	First order	Korsmeyer–Peppas
C940-0.10	0.741 ± 0.046	0.975 ± 0.003	0.999 ± 0.001
PCP-0.225	0.637 ± 0.077	0.993 ± 0.002	0.990 ± 0.003
CHM-2.50	0.792 ± 0.032	0.956 ± 0.008	0.969 ± 0.004

In conclusion, we have prepared colloidal solutions with various concentrations of pH-sensitive polymers to determine

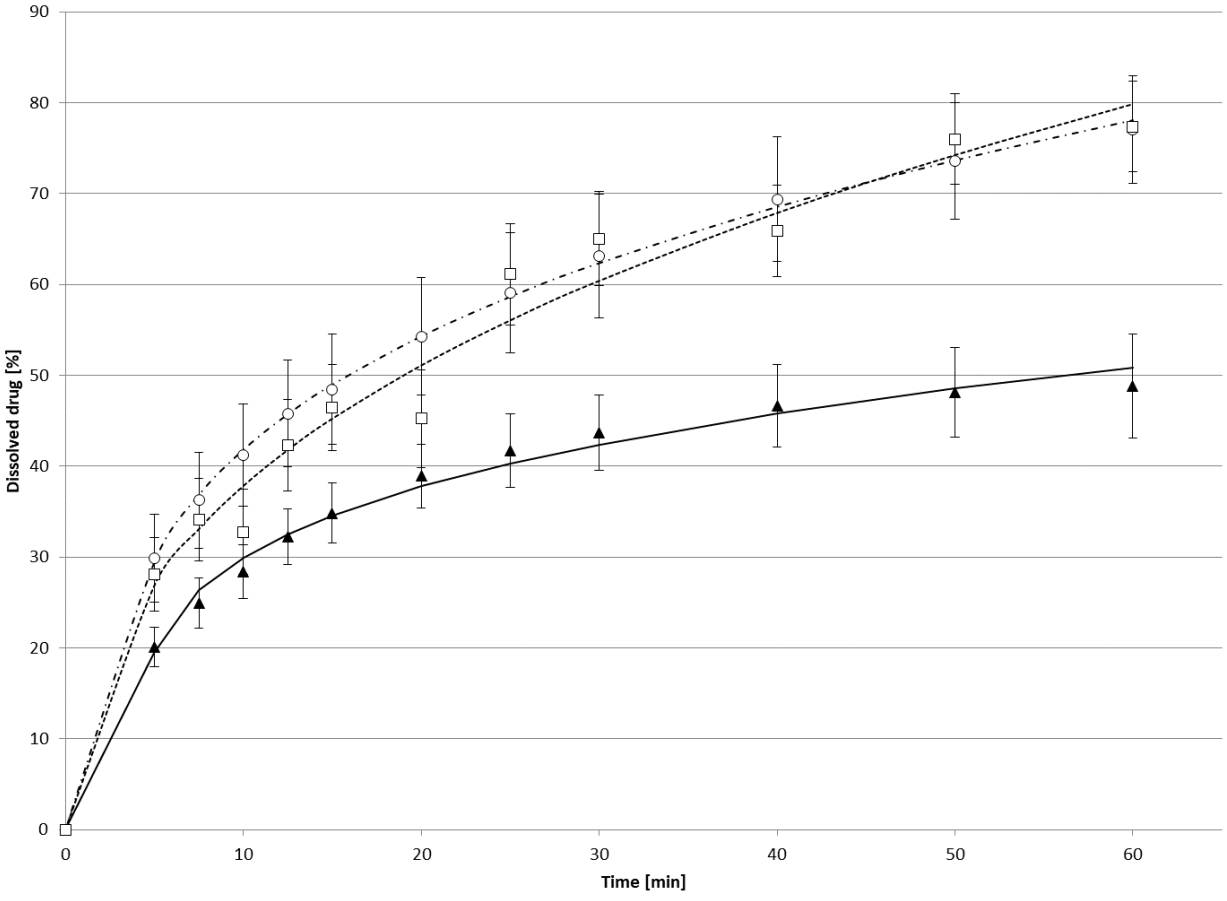

Figure 2. Dissolution profiles and Korsmeyer-Peppas fitting lines of formulations C940-0.1 (○, – • –), PCP-0.225 (▲, ——) and CHM-2.5 (□, - - -).

Table 6. Dissolution parameters of the Korsmeyer–Peppas model and released amount of the drug after 60 min dissolution.

Formulation	k_{KP}	n	T_{lag}	T_{50}	Q_{60}
C940-0.10	22.98 ± 4.95	0.31 ± 0.03	2.72 ± 0.21	16.54 ± 05.37	77.04 ± 5.94
PCP-0.225	19.70 ± 2.86	0.24 ± 0.04	4.04 ± 0.27	61.01 ± 20.48	48.85 ± 5.74
CHM-2.50	16.52 ± 3.42	0.39 ± 0.04	1.45 ± 0.61	19.29 ± 04.88	77.35 ± 4.98

k_{KP} is the Korsmeyer–Peppas release constant, n is the diffusional exponent, T_{lag} is the lag time before drug release, T_{50} is the time (min) when 50% of the drug is released, Q_{60} is the quantity (%) of drug released after 60 min of dissolution

the basic properties as a preliminary study. PCP-0.225 showed the best properties according to injectability, pH gelation, and prolonged release from all prepared compositions and could be used as a dosage form for oromucosal application.

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