Immobilization of 2,5-Dimethyl-4-benzoyl-oxypiperidine Succinate over Polyacrylic Acid (PAA) Gels. II. Study of Quantitative Characteristics of Immobilization of Succinate of 2,5-Dimethyl-4-benzoyl-oxypiperidine over PAA

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ABSTRACT: By use of a spectrophotometric method the quantity of binding of medicinal compound [succinate of 2,5-dimethyl-4-benzoyl-oxypiperidine (AK-29)], over gels of polyacrylic acid, and liberation of medicinal compound (MC) from the gel phase were investigated. It was established that both concentration and pH dependency of AK-29 sorption over PAA gels pass through a maximum and increase with increasing degree of gel crosslinking. The yield of MC from the gel phase, depending on the conditions, reaches 80% and accelerates at the change of the aqueous phase to a physiological one. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 96: 1187–1192, 2005

Key words: hydrogels; swelling; crosslinking; drug delivery systems; networks

INTRODUCTION

An effective way to immobilize a medicinal compound (MC) is to blend it into a gel.[1] There are two basic methods to immobilize medicinal compounds: (1) introduction of MC into an aqueous solution of monomer with the following polymerization; as a result the polymer gel, including molecules of the medicine, is formed; (2) sorption of MC into a prepared gel.[2,3] Each method has its own advantages as well as disadvantages. A chief disadvantage of the first method is the difficulty of washing the gel containing medicine because the main portion of medicine is lost during this procedure. To prevent this loss it is necessary to wash the gel in solution of MC with the following MC regeneration, although this is a rather laborious method. A disadvantage of the second method is a limitation of medicine binding attributed to the complex formation over the gel's surface, thus making it difficult for the next portion of medicine molecules to be sorbed. Nevertheless, this method has an advantage because the medicine is immobilized over the entire preliminarily washed and clean gel. In this article the study of conditions for immobilization of 2,5-dimethyl-4-benzoyl-oxypiperidine succinate (AK-29) over PAA by the second method is reported.

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EXPERIMENTAL

For study of AK-29 sorption by PAA gels the previously dried gels were immersed in an aqueous solution with a definite MC content. The concentration of AK-29 in the external solution was determined over a period of 5–6 days.

The gel containing MC was added to aqueous or physiological solutions. Then the amount of medicinal compound, liberated from the gel phase into the external solution, was determined for 3–4 days.

The concentration of MC in the external solution was determined by an SF-26 spectrophotometer (Lomo, St. Petersburg, Russia) at wavenumbers of 232 and 274 nm, which are typically attributed to pyridine rings and the carbonyl group of a complex ether bond.

RESULTS AND DISCUSSION

The knowledge of quantitative characteristics of binding in the system containing a polymer medicinal compound is significant for both theory and practice, and is absolutely necessary for regulation of properties and composition of polymer derivation and content of medicine.

For this reason, the quantity of both binding of AK-29 with PAA gels and liberation of MC from gel were determined by a spectrophotometric method. The study of sorption of AK-29 medicinal compound over PAA hydrogels shows that the sorption ability of AK-29 over the polyelectrolytic network depends on the concentration of the low-molecular compound

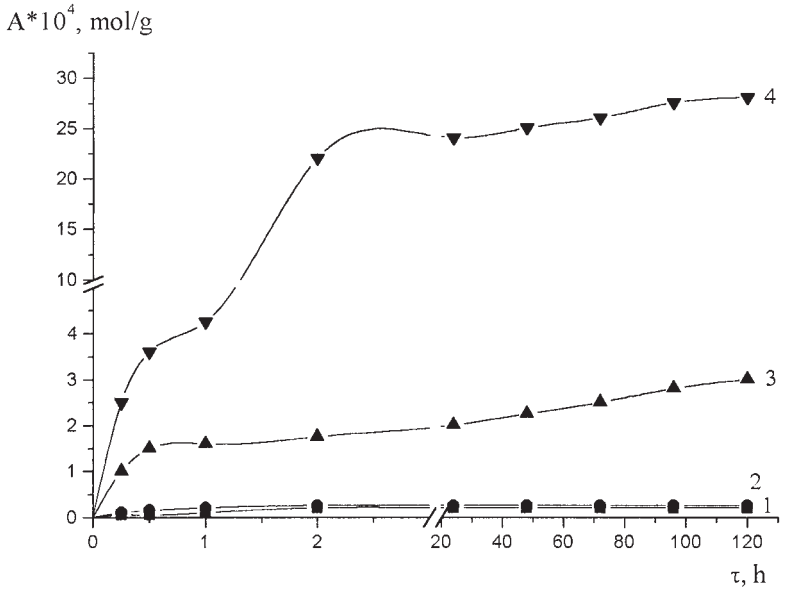

Figure 1 Sorption kinetics of AK-29 over PAAG with 0.1 mol % MBAA content. AK-29 concentrations (in *M*): (1) 5×10^{-5}; (2) 1×10^{-4}; (3) 1×10^{-3}; and (4) 1×10^{-2}.

(Figs. 1 and 2). If, at the low concentration of AK-29 (curves 1 and 2), the amount of sorbed compound monotonously grows with time and relatively quickly ($\approx$ 2 h) reaches the equilibrium value, then as the concentration increases (10^{-3} *M*, curve 3) the sorption degree increases by a few orders. The sorption kinetic curve attracts attention because it is characterized by intensive and stepped growth with time, indicating polymolecular sorption.[4] Evidently, this occurs as a result of PAA–MC complex formation, which initiates the addition of the next molecules of the sorbing compound.[5] According to the turgescence data, collapse of the polymer network is observed in this field of AK-29 concentration because the complex formation and action of ionic forces have occurred.[1]

A comparison of AK-29 sorption by gels with different crosslinking degrees yields interesting results (Figs. 1 and 2). As shown, a significant increase of sorption degree is observed as the crosslinking degree varies from 0.1 to 0.25 mol %, which may be explained by the following reasons. A gel with a content of crosslinking agent of 0.1 mol % does not significantly

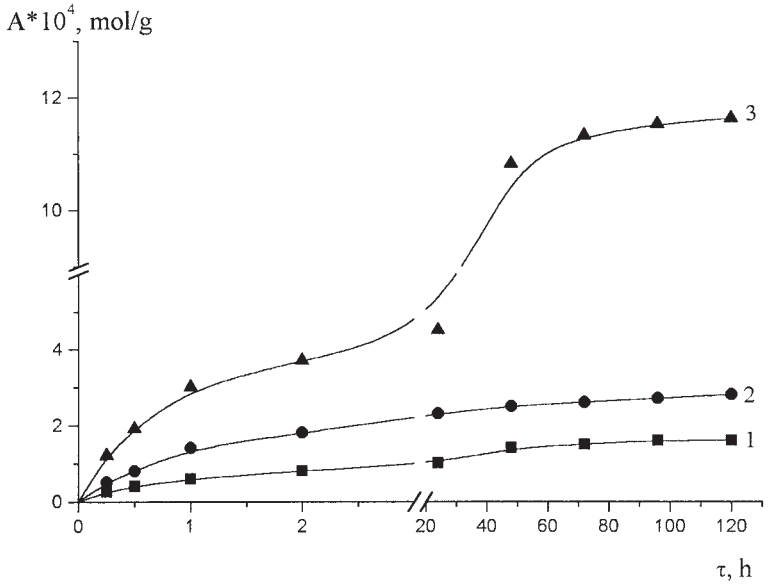

Figure 2 Sorption kinetics of AK-29 over PAAG with 0.25 mol % MBAA content. AK-29 concentrations (in *M*): (1) 5×10^{-5}; (2) 1×10^{-4}; and (3) 1×10^{-3}.

TABLE I
Percentage Amount of AK-29 Adsorbed by PAAG with 0.1 mol % Content of Crosslinked Agent

C_{AK-29} (M)	τ (h)						
	0.3	0.5	1	2	24	48	72
5×10^{-5}	8.0	12.0	24.0	32.0	40.0	28.8	36.6
1×10^{-4}	13.7	21.6	29.4	35.3	43.1	49.0	51.0
1×10^{-3}	11.4	29.5	36.6	43.2	43.5	44.5	56.4
1×10^{-2}	25.0	30.2	37.3	44.5	47.6	49.5	49.5

differ from its linear analogue. The increase of crosslinking degree up to 0.25 mol % is accompanied by the greatest degree of complex formation ability of the network polymer.

In Table I the values of the percentage amount of sorbed PAAG–MC are presented. It has been shown that the gel sorbs 40–60% MC, depending on concentration, over a period of 3 days. Analogous data were obtained for PAAG with 0.25 mol % MBAA (Table II).

The constants of AK-29 distribution between the gel and water phases may be calculated from the known amounts of sorbed MC and gel turgescence. The effectiveness of binding is characterized by these constants.[7] The values of distribution constants (K_D) are presented in Tables III and IV. The K_D values are high, indicating the high affinity of medicinal compound to PAAG. The values of the distribution constant pass through a maximum at the concentration change, thus contributing to the most effective sorption of MC molecules from solution. The highest values of distribution constants were achieved at a content of crosslinking agent of 0.25 mol % compare with that at 0.1 mol %.

As mentioned in a previous study,[1] pH has a substantial influence on the behavior of polymer acids. At the same time it supports the ability of a polyelectrolyte to form a complex. In fact, the sorption of AK-29 by PAA gels is significantly increased and passes through a maximum at pH $\approx$ 7 (Fig. 3). Such an increase of sorption ability is probably caused by the expansion of a spatial network gel. In this case the penetration of MC molecules into the gel phase becomes easier. The increase of AK-29 content in the system implies an increase of the amount of sorption, which agrees with above-mentioned data for the con-

TABLE II
Percentage Amount of AK-29 Adsorbed by PAAG with 0.25 mol % Content of Crosslinked Agent

C_{AK-29} (M)	τ (h)							
	0.2	0.3	0.7	1.0	2.0	24.0	48.0	72.0
5×10^{-5}	5.3	12.3	19.3	26.3	33.3	49.0	56.0	66.7
1×10^{-4}	7.5	11.3	16.9	24.3	33.9	39.6	45.3	50.9
1×10^{-3}	—	—	—	—	—	9.7	24.6	33.3

TABLE III
Constant of AK-29 Distribution in Gel–Water for PAAG with 0.1 mol % Content of MBAA

C_{AK-29} (M)	τ (h)						
	0.3	0.5	1	2	24	48	72
5×10^{-5}	201.2	408.2	1395.4	1975.3	1870.8	2631.6	2870.8
1×10^{-4}	289.0	1547.6	2051.3	2702.7	3333.3	3458.2	3433.5
1×10^{-3}	454.0	1368.0	1778.0	2375.0	2860.2	2785.7	3289.0
1×10^{-2}	1272.7	2586.0	1860.0	2200.0	2895.0	2600.0	2921.3

TABLE IV
Constant of AK-29 Distribution in Gel–Water for PAAG with 0.25 mol % Content of MBAA

C_{AK-29} (M)	τ (h)							
	0.2	0.3	0.7	1	2	24	48	72
5×10^{-5}	267.9	673.0	1122.0	1666.7	2317.1	3888.9	5000.0	6800.0
1×10^{-4}	400.0	618.6	957.0	1511.6	2368.4	2763.0	3428.6	4000.0
1×10^{-3}	—	—	—	—	—	474.2	1586.7	1987.0

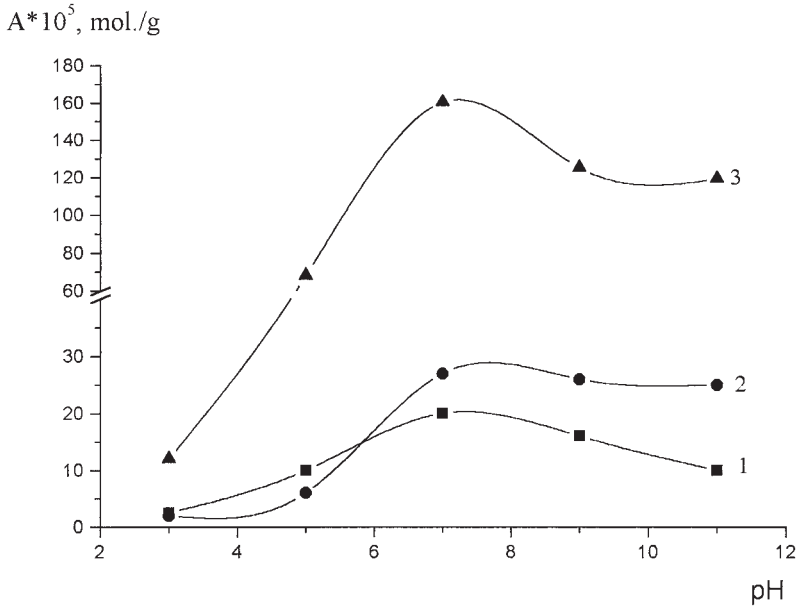

Figure 3 Dependency of sorption of AK-29 over PAAG with 0.25 mol % MBAA content on pH at n values of (1) 0.06, (2) 0.12, and (3) 0.52.

centration dependency of sorption. Curves 3 and 4 demonstrate that with increasing n (n = [AK-29]/[PAAG]), the curves' descending branch is gradually smoothed, indicating the formation of stable PAAG–MC complexes with respect to the values of n and pH.

For practical use, study of the rules of MC liberation from gels has been of great interest. In this connection the kinetics of AK-29 liberation from the gel phase into aqueous and physiological solutions was studied by a spectrophotometric method. Figure 4 demonstrates that the amount of liberated MC with time increases proportionally to its quantity in gel. The relative equilibrium amount of MC in solution is established after about 1 h, although the gradual liberation of AK-29 into external solution continues after this period.

The percentage expression of the MC amount liberated into solution is demonstrated by the liberation pattern. The analysis of data from Figures 5 and 6

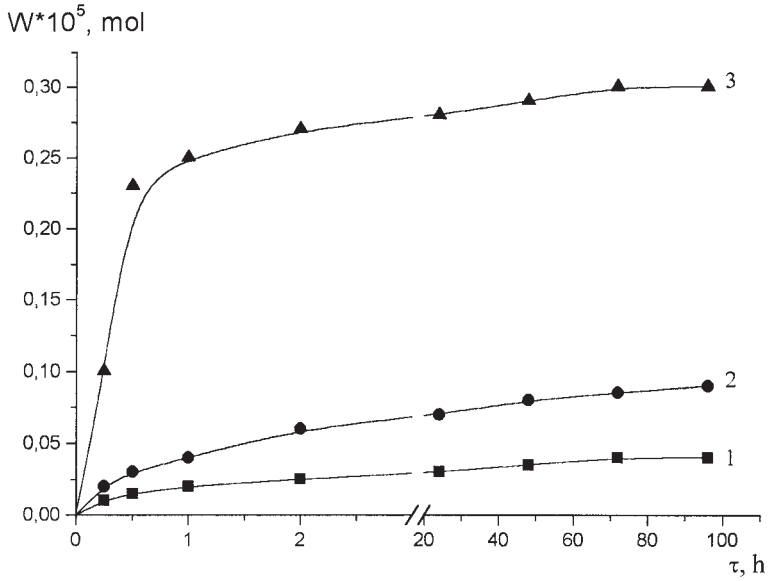

Figure 4 Kinetics of liberation of AK-29 from PAAG into water. MBAA content: 0.25 mol %; content of AK-29 (in moles): (1) 0.2×10^{-5}; (2) 0.33×10^{-5}; and (3) 1.65×10^{-5}.

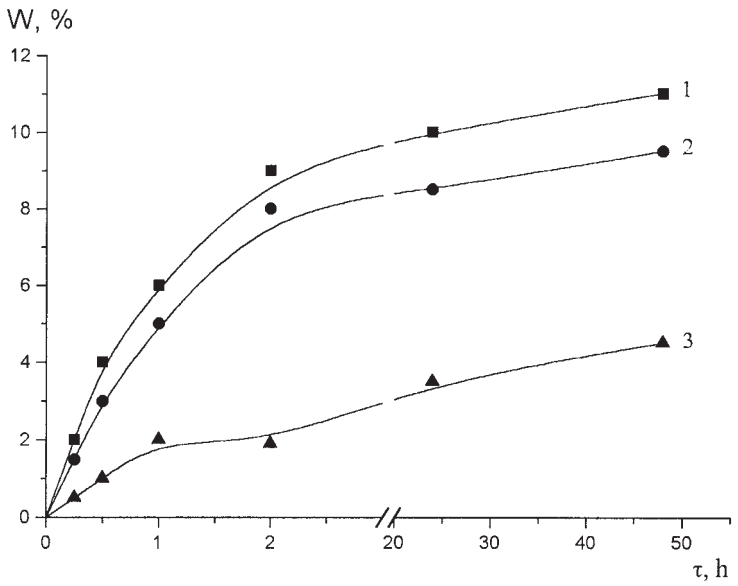

Figure 5 Kinetics of liberation of AK-29 from PAAG into water. MBAA content: 0.1 mol %; content of AK-29 (in moles): (1) 0.23×10^{-5}; (2) 0.3×10^{-5}; and (3) 3.2×10^{-5}.

shows that the MC liberation into physiological solution is much higher than that into an aqueous one. For example, the liberation of AK-29 into a physiological solution reaches about 80%, depending on MC concentration, whereas the value for the aqueous solution is about 10%. Obviously, it occurs as a consequence of the competitive binding of ions of NaCl with PAAG, which increased the osmotic pressure inside the gel and liberation of AK-29 from the gel phase.[5,7] This reason is important for the practical use of gel–AK-29 complexes. It is clear that, by extraction of a medicinal compound from the external solution, it is possible to reach a high yield.

CONCLUSIONS

This article has reported on investigation of the rules of both the binding between the medicinal compound with analgesic action (AK-29) and gels of polyacrylic acid and the liberation of MC from gel phase as an object of immobilization.

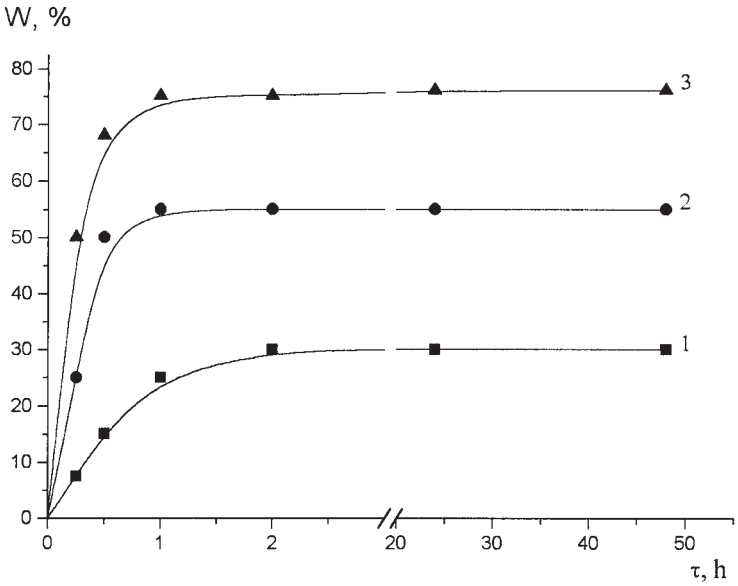

Figure 6 Kinetics of liberation of AK-29 from PAAG into physiological solution. MBAA content: 0.1 mol %; content of AK-29 (in moles): (1) 0.36×10^{-5}; (2) 3.76×10^{-5}; and (3) 28×10^{-5}.

The potential creation of polymer derivations of AK-29 with regulated liberation of medicine was demonstrated.

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