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pH RESPONSE CHARACTERISTICS OF PA1Am-G-PIPA MICROSPHERES

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ABSTRACT

Poly (N-isopropylacrylamide) (PIPA) was grafted to polyallylamine hydrochloride (PAlAm • HCl) by amide formation under the influence of water soluble carbodiimide 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). The graft polymer was made into microspheres (MS) by chemical cross-linking. The pH responsive drug release of the graft polymer microspheres was examined by releasing phenobarbital natrium (PN) which was carried on the microspheres by physical adsorption. A dynamic dialysis technique was used in the drug release experiment and the drug release rate constants reflecting the drug release characteristic of polymer microspheres were obtained by constituting a mathematical model. The results indicated that the homopolymer PAlAm microspheres and the copolymer PAlAm-g-PIPA microspheres are both pH responsive to release PN and in neutral pH condition the release rate is the slowest.

INTRODUCTION

Poly (N-isopropylacrylamide)[1] has demonstrated noticeable thermo-sensitivity in terms of water swelling. Changes in swelling states of the PIPA gels can influence the diffusion of solutes from within the gels to the outside aqueous media. Okahate[2] had ever used a large nylon capsule membrane with a surface grafted poly (N-isopropylacrylamide) to regulate reversily the permeation of NaCl and dyes by ambient temperature change. Recently, Schild[3] reported a detailed review about the PIPA gels. The review reported also a novel extension[4] of the PIPA system in which acrylic acid as a comonomer was introduced, consquently th copolymer possessed not only thermal response but also pH sensitivity. Yan[5] had reported a graft copolymer polyallylamine (PAlAm) with PIPA (PAlAm-g-PIPA) which was influenced not only by the temperature but also by the pH of the dissolution medium on phase transition. If the graft PAlAm-g-PIPA has not on-

ly thermo-sensitivity but also pH respovsive properties, it would be very valuable in the study of the controlled drug release. The properties of the thermo-sensitive controlled drug release of the graft PAlAm-g-PIPA microspheres had already been investigated[6] by us. Extensively, we carried out drug release experiments with PAlam-g-PIPA as a drug carrier at various pH' s. The pH responsive drug release of the homopolymer PAlAm was also carried out for comparing and discussing the mechanism of the pH responsive drug release of the PAlAm-g-PIPA. A mathematical model proposed by Gupta[7] is quoted to quantitate the drug release of the polymer microspheres in this paper.

EXPERIMENTAL

Materials

PIPA was synthesised in our laboratory with a molecular weight 3053. PAlAm • HCl(Mw=60,000) was purchased from Nittobo Co. , Tokyo, Japan. Other reagents were commercially available. All water used in the experiments was double distilled.

Preparation of graft polymer.

Both PAlAm • HCl and PIPA were dissolved in water. Soluble carbodiimide EDC was added into the solution. Graft reaction was carried out under stirring at 10℃ over night and the products were purified by dialysis against distilled water. The structures of the final products were confirmed by infrared spectrum (Nicolet,MX-1,Nicolet Co. ,England) and the graft ratio was determined by elements analysis.

Preparation of the microspheres

0. 2g graft copolymer PAlAm-g-PIPA was dissolved in 0. 8 ml H_2O. The copolymer aqueous solution was then added dropwise into the mixture of 1 g Span 80, 5 ml toluene and 5 ml chloroform. The water/oil mixture was emulsified with a vortex mixer for 5 min, then, transferred into a triangle shape bottle with 60 ml mixture of toluene/chloroform (3/1) and 4 g Span 80. Glutaraldehyde (25%)-saturated toluene solution (2 ml) was added into the emulsion. The chemical cross-link reaction was carried out under stirring for 5 hrs followed by adding 1 ml ethanoamine into the reaction mixture to close the aldehyde groups and the reaction went on again for 1 hr. The resultant microspheres were washed by centrifuge with organic solvent and distilled water and then incubated with dimethylamine-borane solution (7%) for 12 hrs to reduce Shiff base in the microspheres and washed again. The size of the microspheres was detected with a photomicroscope. The resultant microspheres were lyophilized for story. Microspheres were also prepared with PAlAm without graft chains for comparison.

Drug carrying of the microspheres

Dried microspheres accurately weighted were added into the phenobarbital natrium solution with a concentration of 10 mg/ml. The microspheres suspension was

stirred at ambient condition for 24 hrs and incubated in warm water of 45℃ for 1 hr. Drug-carrying microspheres were washed with water. The washing supernatant was determined with ultraviolet spectrophotometer (Shimadzu, UV-120-02) at 239 nm for PN content. Drug content of drug-carrying MS was calculated following the equation:

$$Cm = \frac{A_0 - A_1}{W} (ug/mgMS)$$

Cm: drug content in microspheres
A_0: total amount of drug added initially
A_1: drug amount of supernatant
W: total amount of microspheres

Drug contents of various drug-carrying MS as follow:
PA1Am-g-PIPA-MS (graft ratio 10%) 156 ug/mg;
PA1Am-g-PIPA-MS (graft ratio 5%) 118.7 ug/mg;
PA1Am-MS (graft ratio 0) 193 ug/mg

Release of PN

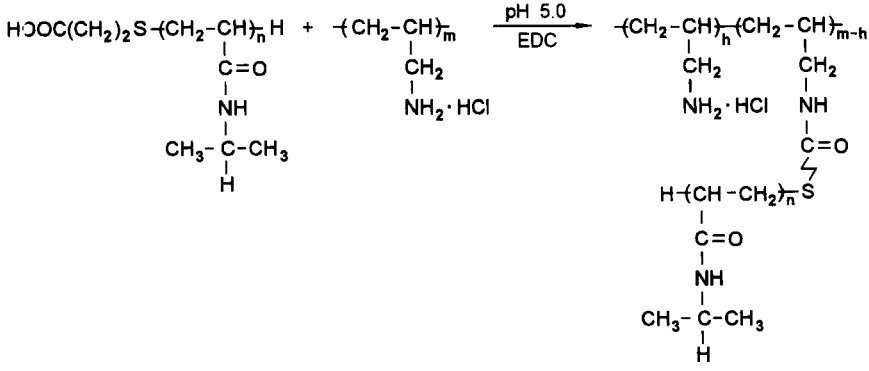
Drug-carrying microspheres of both PA1Am and PA1Am-g-PIPA matrix were used for studying drug-release behavior. 30 mg of drug-carrying polymer microspheres suspended in 5 ml glycine buffer (GB, 0.05M) was placed in a dialysis bag. The microsphere suspension was then dialysised against 100 ml of GB at 37℃ under oscillating condition. 3 ml of the outer dialysis medium were taken at regular time of 20 min over 8 hrs. Then the sample was taken once per hour. The samples were immediately assaied for the drug content with ultravoilet spectrophotometer (Shimadzu UV-120-02). Drug release of free drug were carried out at the same condition as above to estimate the drug permeability constant of the dialysis membrane.

RESULTS AND DISCUSION

Synthesis and characterization of the graft copolymer microspheres

Because β—mercatopropionic MPA as chain transfer reagent joined in the synthesis of the PIPA, the PIPA chain carried in end carboxyl groups. It was the end carboxyl groups COOH of the PIPA that made the PIPA be grafted on the main chain of the PA1Am • HCl with the amine groups $-NH_2$ by amide formation when water soluble EDC was added in the reaction system (Scheme A).

The graft reaction above was confirmed by infrared spectrum analysis (Fig. 1). By comparing the infrared spectra of the three polymer PA1Am • HCl, PIPA and PA1Am-g-PIPA, it can be seen that on the spectrum of graft copolymer PA1Am-g-PIPA, the absorbance peak of carboxyl groups —COOH (1719 cm^{-1}) of PIPA spectrum disappeared the stretching vibration absorbance of hydrogen-chloride bond HCl (720 cm^{-1}) of PA1Am • HCl weadened and the carkonyl peak (1651 cm^{-1}) of the amide groups strengthened. This fact confirmed clearly that a part



Scheme A

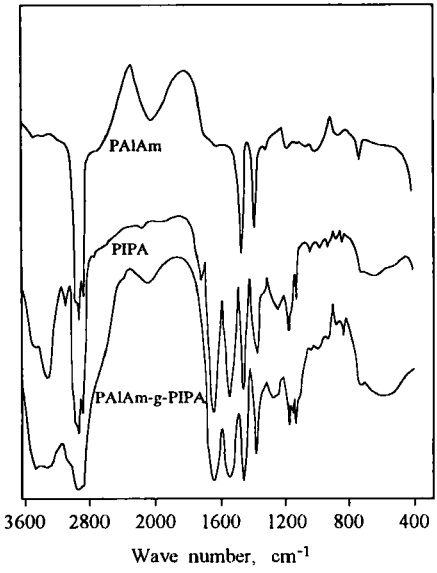


Fig. 1 IR spectra of various polymers

of amino groups of the PA1Am and the carboxyl groups of the PIPA had formed into amide groups. The graft products PA1Am-g-PIPA was obtained.

Graft percent of the graft polymer were controlled by the molar ratio of the PIPA and the PA1Am-HCl used in the reaction. Actual graft percent of the graft polymer was estimated by elemental analysis. The experimental date in Table I indicated that actual graft percent of the graft copolymer were almost equal to predeterminate value of the graft ratio.

The graft copolymer PA1Am-g-PIPA was made into microspheres with particle size 5-20 μm (Fig. 2) in W/O emulsion system. Glutaraldehyde was added into the system to stabilize the microspheres by chemical cross-link reaction because of a large number of amine groups on the main chain PA1Am • HCl which were easy to react with aldehyde groups.. The Schiff base produced from the aldehyde-amine reaction was reduced by dimethylamineborane to stabilize the cross-linking bonds.

Drug release experiments of the microspheres at various pH

Drug release experiment results showed that the drug delivering of the microspheres was the first order kinetic characteristic and the drug release behavior of both PA1Am microspheres and PA1Am-g-PIPA microspheres were affected by pH of the dissolution medium. According to Gupta' s[6] first-order kinetic matkhematic equation of drug release from a drug carrying microsphere

$$\ln\left(C_1-\frac{C_2^0V_2}{V_t}-\frac{Q_m^0}{V_t}\right)=-K_mt+\ln\frac{K_{cv}Q_m^0}{(K_m-K_{cv})V_1V_2}$$

the drug release rate constant K_m of the microspheres can be estimated by the slope of the polt of In $(C_1-C_2^0V_2/V_t-Q_m^0/V_t)$ vs t. where, 1,2 represent the dissolution media outside and inside the dialysis bag, respectively. C, V represent the concentration and volume of the dissolution medium, respectively. $V_t=V_1+V_2$. C_2^0 and Q_m^0 are the drug concentration of the dissolution medium inside the dialysis bag and the drug amount of the microspheres at time 0, respectively. K_{cv} was a constant representing the drug permeability of the dialysis membrane which can be determined by free drug release. Fig. 3 shows the representative plots of In $(C_1-C_2^0V_2/V_t-Q_m^0/V_t)$ vs. t. From the plots, the process was a biphasic release of the drug and has two constants, the initial release rate constant K_{m1} and the terminal release rate constant K_{m2}.

Table II are the K_{cv} of the dialysis membrane, the initial K_{m1} and terminal K_{m2} of the microspheres at different pH. The Table I shows clearly that the drug release rate of whether the grafted microspheres or not grafted microspheres are both affected by the pH of the dissolution medium. When the dissolution was neutral, the drug release rate would be the slowest. With the increase of the acidity or the alkaline of the dissolution, the release rate would increase. However, the drug release rate of the grafted microspheres was decreasing with the increase of the alkaline of the dissolution in the later period of drug release.

TABLE I
GRAFT RATIO OF THE PAlAm-g-PIPA FROM ELEMENTAL ANALYSIS AND THEORY

	PIPA	PAlAm	Elemental analysis			Graft ratio, %	
	g	g	C%	N%	H%	Theoritcal	Experimental
I	4	2.450	57.38	12.56	9.56	5	5.30
II	4	1.225	52.08	11.71	10.26	10	9.1

Mw: PIPA, 3053, detemined by conductometric titration; AlAm, 93.5

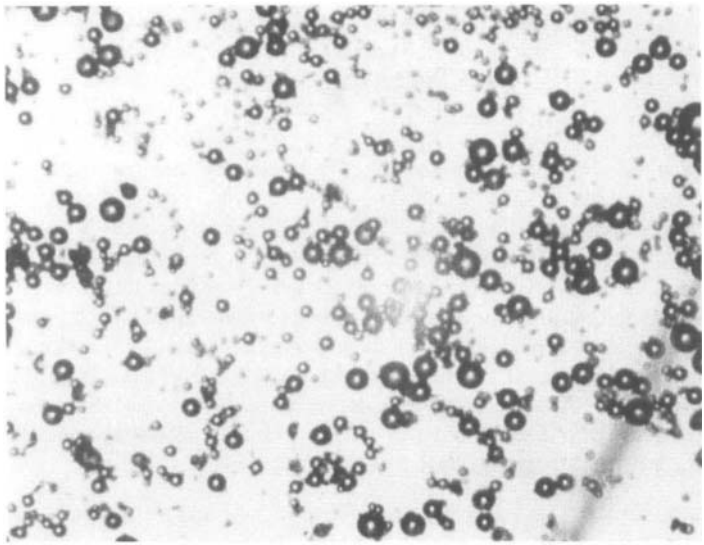


Fig.2 The optical micrograph of the PAlAm-g-PIPA microspheres. Magnification 250X.

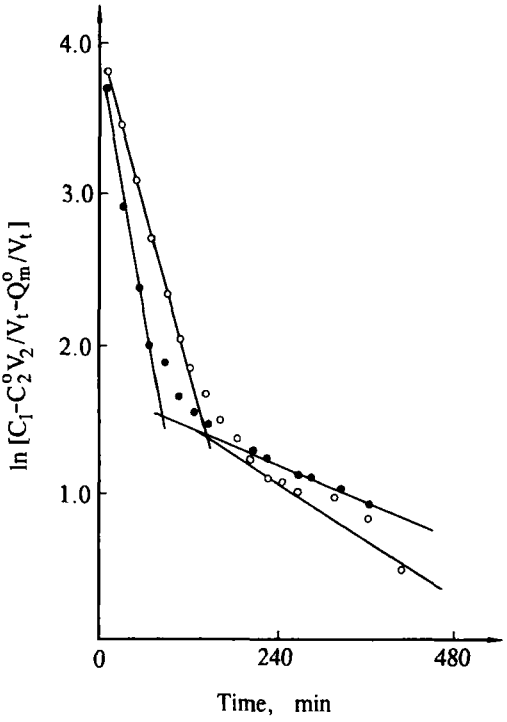
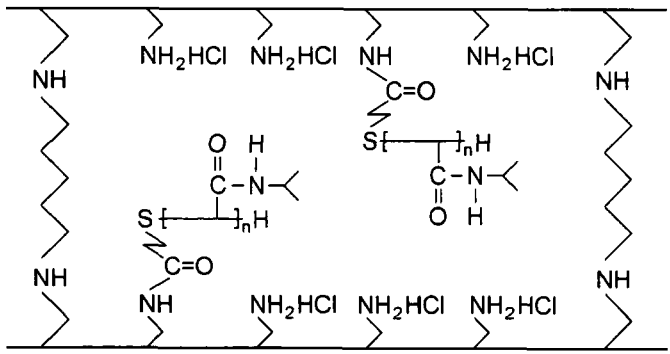


Fig. 3 Typical plots of logarithem $\ln(C_1 - C_2^0 V_2/V_t - Q_m^0/V_t)$ versus dialysis time t.

TABLE I
THE DRUG PERMEABILITY CONSTANTS K_{ov} OF THE DIALYSIS MEMBRANE AND THE DRUG RELEASE RATE CONSTANTS K_m OF THE MICROSPHERES AT VARIOUS PH

pH		3	5	7	9	11
$K_{ov} \times 10^3$ of the dialysis memberane		22.41	25.63	21.02	20.66	23.37
Initial drug release rate constant $K_{m1} \times 10^3$	PA1Am-MS	20.01	5.33	4.22	6.70	17.60
	PA1Am-g-PIPA-MS	15.50	9.33	5.54	7.51	9.00
Terminal drug release rate constant $K_{m2} \times 10^3$	PA1Am-MS	2.0	0.25	0.22	1.15	3.33
	PA1Am-g-PIPA-MS	0.75	1.17	0.70	0.36	0.07



Scheme B

Analysis of the pH responsive drug release,

In the pH responsive changes of the swelling states of the polymer, the ionic groups on the polymer were thought of main reason of the phase transition. The PAIAm • HCl has a large amount of NH_2H^+ which ionicity could change from weak to strong with the pH change from high to low in the dissolution. After grafting PIPA chains and cross-linked, the main chain PAIAm of the graft copolymer has still many residual NH_2H^+ groups as scheme B shows. So the hydrophility and the phase state of the copolymer are still influenced by the pH in the dissolution. The cross-linked polymer network should swell or shrink when the dissolution was acidic or alkaline.

Because of having a $pKa_1=7$ and $pKa_2=9.5$, the carried drug PN would change from hydrophilic to hydrophobic with change of pH in solution. When pH was in acidic region, the PN was charged and the pores of the polymer network were open because of swelling. So the drug release rate is fast. When pH was in alkaline region, though the polymer matrix network shrunk and the pores of the polymer network contracted, the release rate of the PN was still fast due to its negative charge and excellent hydrophility. In addition, the process suggested by Hoffman et al[3] may be a cause that was the pressure generated during the polymer network collapse to squeeze out the drug. In a neutral solution, the polymeric matrix would be partially positively charged and the drugs should be partially negatively charged. The strongest ionic interaction between PN and the polymer matrix would occur in this case, leading to the slowest release rate. The reason of that the terminal drug release rate of the graft copolymer MS decreased with the increase of pH in the dissolution now is unclear because of many factors affecting the drug release in the later period of drug release. Usually, the initial release behavior is the most representative for the drug release process.

CONCLUSION

When Polyallylamine hydrochloride was introduced in the poly (N-isopropyiacrylamide) system as a copolymerization component, the copolymer would be pH-responsive on controlled drug release. In the case of strong-base weak-acid salt as phenobarbital natrium as carried drug, the release of drug from the polymer matrix would increase with the acidity or alkaline of the dissolution medium. In the neutral solution, the drug release rate was the slowest.

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