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Investigation of stability and activity of poly(ethylene-alt-maleic anhydride) copolymer at different pHs and in simulated body fluids

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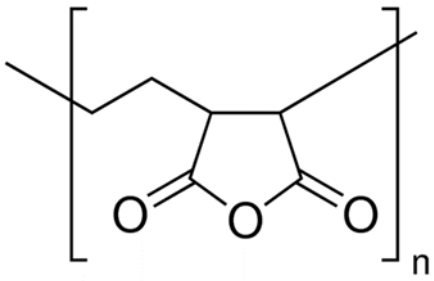
Poly(ethylene-alt-maleic anhydride) copolymers are used in various applications as emulsion stabilizers, detergent compositions, viscosity modifiers and drug delivery systems. This work aimed at determining the stability and activity of poly(ethylene-alt-maleic anhydride) copolymer (PEAMA) as drug carrier candidate at different pHs and in various artificial body fluid media such as 5% dextrose solution, PBS solution and 0.9% isotonic NaCl solution. To determine the stability of PEAMA, the polydispersity, particle size, mobility and zeta potential of PEAMA were measured at different pH values and in various artificial body fluid media *via* zetasizer. The activity of PEAMA was investigated at different pH values and in various artificial body fluid media based on the time effect by UV/VIS measurements. According to the obtained results, the optimum conditions of stability and activity of PEAMA copolymer were determined.

Keywords: Poly(ethylene-alt-maleic anhydride) copolymer, zeta potential, particle size, stability, activity, simulated body fluids

INTRODUCTION

Maleic anhydride (MA) copolymers have often been used as reactive macromolecules displaying various biological activities, such as direct antitumor effectors. The antitumor activity of these copolymers has been demonstrated to be dependent upon the amount of hydrogen bonding between carboxyl groups and the nature of their distribution on side chains. MA-containing copolymers, also known as polyanhydrides, the highly reactive anhydride ring on the MA portion can be bound by the ring-opening reaction to amino or hydroxyl groups of nucleophilic reagents resulting in either ester/carboxylic acid or amide/carboxylic acid structures. When the drug conjugate is being released, the carrier copolymer might display its own biological activity, in an increasing fashion, via the carbonyl groups that are freed [1-5]. The important copolymer of MA is poly(ethylene-alt-maleic anhydride) copolymer. Poly (ethylene-alt-maleic anhydride) (Scheme 1) is a nontoxic polyanhydride. It is a synthetic copolymer of maleic anhydride and is used as viscosity modifier for solution, suspension or emulsion, dispersing aid for insoluble solids and a wide variety of purposes in biotechnological applications. It is soluable in DMSO+water mixture [6]. Physicochemical properties such as particle size, surface charge and zeta potential of polymer-drug delivery systems are important parameters by the means of their interactions with plasma proteins [7-10].



Scheme 1. Chemical structure of poly(ethylene-alt-maleic anhydride)

In the present work, zetasizer and UV/VIS measrements were used to determine the activity and stability of poly(ethylene-alt-maleic anhydride) at different pHs and in simulated body fluids.

EXPERIMENTAL

Poly(ethylene-alt-maleic anhydride, M_w =100,000-500,000 g/mol; T_g=235 °C), DMSO and phosphate buffer saline tablets (PBS) were purchased from Sigma-Aldrich. Dextrose 5 % and NaCl 0.9 % solutions were biological grade. The particle size and zeta potential of poly(ethylene-alt-maleic anhydride) at different pHs and in simulated body fluids such as % 5 dextrose, 0.9 % isotonic NaCl and PBS solutions were measured *via* Brookhaven 90 Plus/BI-MAS (Multi Angle Particle Sizing) and Brookhaven Zeta Potential Analyzer. The controlling activity of poly(ethylene-alt-maleic anhydride) at different pHs and in simulated body fluids such as 5 % dextrose, 0.9 % isotonic NaCl and PBS solutions were checked by Shimadzu UV mini-

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1240 spectrometer. PEAMA forms a gel in water. Because of this, to prepare homogenous solutions, PEAMA solutions were prepared by dissolving in 5 % DMSO (v/v) and diluting with water.

RESULTS AND DISCUSSION

The stability and activity of PEAMA solutions, prepared at different pH values, were measured with a Zetasizer and a UV/Vis spectrophotometer, respectively.

Zetasizer measurements of polydispersity, particle size, mobility and zeta potential of PEAMA give the stability information in aqueous solution and were done *via* Zetasizer at different pHs. The zetasizer measurements results of PEAMA at different pHs are given in Table 1.

Table 1. Zetasizer measurements of PEAMA at different pHs

pH	PDI	Particle size (nm)	Mobility	Zeta Potential (mV)
2	0.333	350	-2.99	-38.24
3	0.361	465	-3.03	-38.79
4	0.372	900	-2.99	-38.30
5	0.467	880	-2.98	-38.11
6	0.377	1220	-3.00	-38.38
7	0.385	1370	-2.95	-37.78
8	0.395	1110	-2.97	-38.06
9	0.320	1425	-2.99	-38.22
10	0.354	1300	-3.03	-38.76
11	0.422	1170	-3.02	-38.60
12	0.385	1100	-3.02	-38.62

The particle size distribution of PEAMA at different pHs was found to be between 0.3 and 0.4. It means that PEAMA particles at different pHs are monodisperse and show homogenous dispersion. The particle size of PEAMA varies between 300 and 1400 nm with increasing pH. The PEAMA particles at different pHs were negatively charged and preserved their stability because of higher zeta potential values as about 39 mV. No aggregation or coagulation of PEAMA particles in solutions of different pH was seen.

The activity and stability of PEAMA at different pHs were checked by UV/VIS spectrometry and the spectrum is given in Fig. 1.

The activity and stability of PEAMA particles at the studied pHs were controlled at 230 nm. The activity and stability of PEAMA particles did not change and they continued their activity and stability at all pHs.

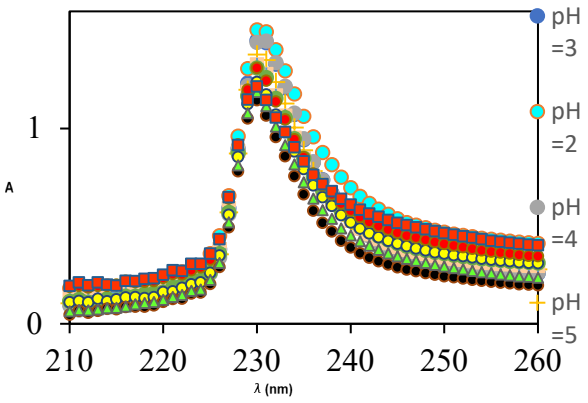

Fig. 1. UV/VIS spectrum of PEAMA at different pHs

The zetasizer measurement results of PEAMA in 5 % dextrose solution as a function of time are given in Table 2.

Table 2. Zetasizer measurements of PEAMA in 5 % dextrose solution as a function of time

Time	PDI	Particle size (nm)	Mobility	Zeta Potential (mV)
0	0.190	595	-3.03	-38.79
15 min	0.314	465	-2.99	-38.24
30 min	0.268	500	-2.99	-38.31
1 h	0.311	480	-2.98	-38.11
2 h	0.277	520	-3.00	-38.38
3 h	0.290	465	-2.95	-37.78
1 d	0.179	630	-3.03	-38.79
2 d	0.154	610	-2.95	-37.78
1.w	0.226	615	-3.03	-38.79
2.w	0.207	570	-3.03	-38.79
3.w	0.265	585	-3.03	-38.79
4.w	0.246	575	-3.03	-38.79

PEAMA particles in 5 % dextrose solution were highly monodisperse because of PDI values between 0.1 and 0.2. The particle size of PEAMA changed between 400 and 600 nm with time. The PEAMA particles in 5 % dextrose solution were negatively charged and preserved their stability because of higher zeta potential values as about 39 mV. No aggregation or coagulation of PEAMA particles in %5 dextrose solution as a function of time was seen.

The activity and stability of PEAMA in 5 % dextrose solution were monitored by UV/VIS and the spect The activity and stability of PEAMA particles in 5 % dextrose solution were checked by consideration of the 230 nm peak. The activity and stability of PEAMA particles did not change and they continued their activity and stability in 5 % dextrose solution up to 4 weeks.

The activity and stability of PEAMA in 5 % dextrose solution were monitored by UV/VIS and the spectrum is given in Fig. 2.

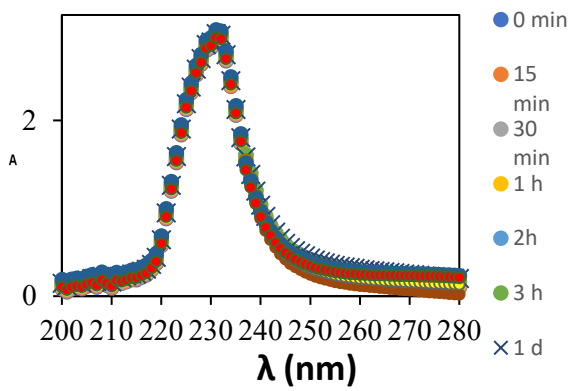

Fig. 2. UV/VIS spectrum of PEAMA in 5 % dextrose solution as a function of time

The zetasizer measurement results of PEAMA in PBS solution as a function of time are given in Table 3.

Table 3. Zetasizer measurements of PEAMA in PBS solution as a function of time

Time	PDI	Particle size (nm)	Mobility	Zeta Potential (mV)
0	0.409	740	-3.03	-38.79
15 min	0.419	1100	-2.99	-38.24
30 min	0.400	1080	-2.99	-38.31
1 h	0.392	1045	-2.99	-38.11
2 h	0.434	1035	-2.95	-38.78
3 h	0.404	925	-2.98	-37.10
1 d	0.391	825	-3.03	-38.79
2 d	0.398	470	-3.03	-37.79
1.w	0.377	440	-3.03	-38.79
2.w	0.414	580	-2.98	-38.19
3.w	0.404	645	-2.95	-38.79
4.w	0.375	665	-3.03	-38.79

PEAMA particles in PBS solution as a function of time were monodisperse because of PDI changing between 0.3 and 0.4. The particle size of PEAMA changed and bigger particles started to form after 15 min. After 2 h, the size of the PEAMA particles started to decrease from 3 h to 4 w. The PEAMA particles in PBS solution were negatively charged and preserved their stability because of higher zeta potential values as about 39 mV. No aggregation or coagulation of PEAMA particles in PBS solution was seen as a function of time.

The activity and stability of PEAMA in PBS solution were monitored by UV/VIS and the spectrum iss given in Fig. 3.

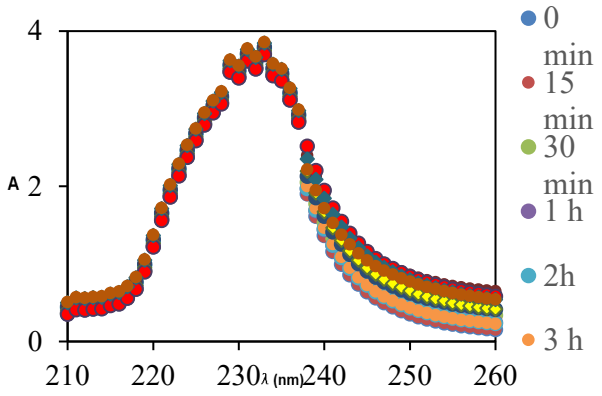

Fig. 3. UV/VIS spectrum of PEAMA in PBS solution as a function of time

The activity and stability of PEAMA particles in PBS solution were checked by consideration of the 230 nm peak. The activity and stability of PEAMA particles did not change and they continued their activity and stability in PBS solution up to 4 weeks.

The zetasizer measurement results of PEAMA in isotonic NaCl solution (0.9 %) as a function of time are given in Table 4.

Table 4. Zetasizer measurements of PEAMA in isotonic NaCl solution as a function of time

Time	PDI	Particle size (nm)	Mobility	Zeta Potential (mV)
0	0.342	185	-3.00	-38.42
15 min	0.344	200	-2.99	-38.30
30 min	0.311	175	-3.03	-38.79
1 h	0.346	240	-2.99	-38.24
2 h	0.361	250	-2.98	-38.13
3 h	0.366	250	-2.97	-37.98
1 d	0.343	200	-3.03	-38.79
2 d	0.363	240	-2.98	-38.11
1.w	0.339	250	-2.99	-38.25
2.w	0.362	255	-2.99	-38.24
3.w	0.359	245	-2.98	-38.11
4.w	0.354	250	-3.03	-38.79

PEAMA particles in isotonic NaCl solution as a function of time were monodisperse. The particle size of PEAMA in isotonic NaCl solution was about 200 nm. The PEAMA particles in isotonic NaCl solution were negatively charged and preserved their stability because of higher zeta potential values as about 39 mV. No aggregation or coagulation of PEAMA particles in isotonic NaCl solution as a function of time was seen.

The activity and stability of PEAMA in isotonic NaCl solution were monitored by UV/VIS and the spectrum is given in Fig. 4.

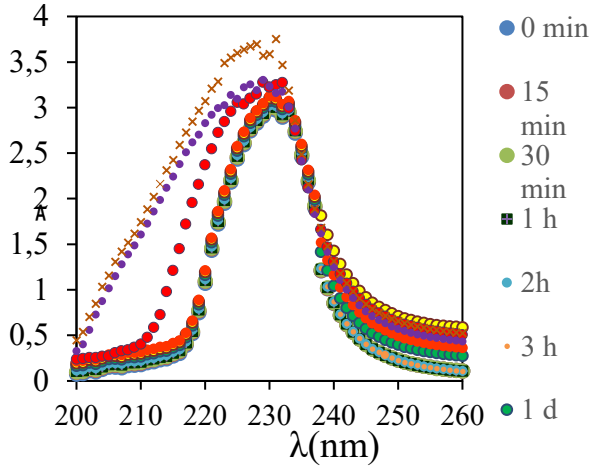

Fig. 4. UV/VIS spectrum of PEAMA in isotonic NaCl solution as a function of time

The activity and stability of PEAMA particles in isotonic NaCl solution was checked by consideration of the 230 nm peak. The activity and stability of PEAMA particles did not change and they continued their activity and stability in isotonic NaCl solution up to 4 weeks.

CONCLUSIONS

The stability and activity of PEAMA particles at different pHs and in simulated body fluids were determined *via* zetasizer and UV/VIS measurements. It was determined that PEAMA particles at different pHs and in simulated body fluids were negatively charged, monodisperse and preserved their activity and stability up to 4 weeks without any aggeragation and coagulation. According to the obtained results, it was concluded that PEAMA copolymer was a suitable candidate for drug delivery systems in all pH ranges and simulated body fluids.

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