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# Investigation of poly(ethylene-alt-maleic-anhydride)-pregabalin (1:1) ratio controlled drug delivery system synthesized in catalyst-free media: stability and activity at different pHs

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The controlled release of pregabalin drug active material covalently bound to poly(ethylene-alt-maleic anhydride) (PEAMA) copolymer was aimed in order to prevent the drug leaving the polymer matrix. Also, it was proposed to increase stability and activity of the drug, thus reducing frequent drug intake. Poly(ethylene-alt-maleic anhydride) (PEAMA) and pregabalin (PRG) at a (1:1) ratio copolymer-drug delitvery system (PEAMA-PRGI) was synthesized in catalyst-free media and was characterized by $^1$H NMR and FTIR/ATR. The stability and activity of PEAMA-PRGI copolymer-drug delivery system were determined in different pH environments at 37 $^o$C *via* zetasizer measurements and UV/VIS spectroscopy, respectively.

**Keywords:** Controlled drug delivery system, poly(ethylene-alt-maleic-anhydride), pregabalin, stability and activity

## INTRODUCTION

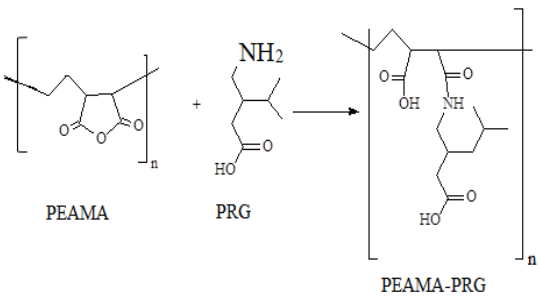
The main purpose of controlled drug delivery systems is to release the drug to the target tissue or organ. The system offers a release with maximum therapeutic effect by controlling the amount of the drug and the duration of treatment. Maleic anhydride can be used in drug delivery systems *via* the maleic anhydride-copolymer formula. Amide, ester and carboxylic structures containing amino and hydroxyl groups can be bounded with a covalent bound to maleic anhydride group by ring-opening of the maleic anhydride [1-3]. Pregabalin is a medication commonly used to treat epilepsy, fibromyalgia, pain, and anxiety. Pregabalin has a half-life of approximately 6 hours. After oral intake of PRG, the drug reaches peak blood levels in 1.5 hours and it can be taken frequently. This reason can lead to the development of a controlled drug delivery system through conjugating with polymers [4-6].

To overcome halflife problem of PRG in body circulation, the PRG drug active substance was covalently bonded with PEAMA at (1:10) ratio. The synthesized PEAMA-PRGI copolymer-drug delivery system was structurally characterized and the stability (controlling polydispersity, particle size, mobility, zeta potential) and activity (checking maximum and minimum absorption) were determined at different pHs *via* zetasizer and UV/VIS, respectively.

## EXPERIMENTAL AND INTRUMENTAL PART

Poly(ethylene-alt-maleic anhydride) (PEAMA) (Mw≃100,000-500,000, LOT: #MKCC4605) was purchased from Sigma-Aldrich. Pregabalin (PRG) was a gift from Bilim Phar- maceuticals, (purity 99.5 %). N,N-dimethylformamide (DMF) (≥99.8%) and dimethyl sulfoxide (DMSO) (≥99.9%) were purchased from Merck and used as solvents.

PEAMA-PRG controlled drug delivery system was synthesized by functionalization of PEAMA copolymer at (1:1) molar ratio with pregabalin in dimethylformamide (DMF) for 72 h at 60 °C [7]. The reaction mechanism is given in Scheme 1.




**Scheme 1**. Reaction mechanism of PEAMA-PRGI copolymer-drug delivery system [7].

Synthesized PEAMA-PRG controlled drug delivery system was characterized *via* FTIR-ATR (Thermo Fisher Scientific Nicolet iS10 FT-IR spectrometer which has an attenuated total reflection (ATR) apparatus) and $^1$H NMR (Agilent Varian 400 MHz NMR spectrometer in DMSO-d6 at 25 °C). The results were discussed and details given in the master thesis of Ozge Eslek [7].

Particle size, polydispersity, mobility and zeta potential measurements for stability checking were done with Brookhaven Instruments Corporation 90Plus zetasizer. SR-542 probe was used for zeta

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potential measurements. pH measurements were taken with Sentek P14/BNC electrode; Shimadzu UVmini-1240 spectrometer was used for controlling activity of samples using Hellma 100-QS cuvette at different pHs, at 37 °C.

## RESULTS AND DISCUSSION

Structural characterization of the synthesized PEAMA-PRG (1:1) copolymer-drug delivery system was done by FT-IR/ATR and $^{1}$H NMR [7].

In order to determine the stability and activity of the synthesized drug delivery systems in solution, aqueous sample solutions were prepared at different pH values, and measured with both zetasizer and UV/VIS spectrophotometer, respectively.

Zetasizer measurements of polydispersity, particle size, mobility and zeta potential of PEAMA, PRG and PEAMA-PRG (1:1) copolymer-drug delivery system gave information on the stability in aqueous solution and were done at different pH values.

The polydispersity index values of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pH values are given in Table 1.

**Table 1**. Polydispersity index values of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pHs

| pH | PRG | PEAMA | PEAMA-PRG I |
|---|---|---|---|
| 2 | 0.312 | 0.405 | 0.188 |
| 3 | 0.744 | 0.485 | 0.267 |
| 4 | 0.716 | 0.341 | 0.379 |
| 5 | 0.757 | 0.321 | 0.333 |
| 6 | 0.638 | 0.564 | 0.322 |
| 7 | 0.510 | 0.429 | 0.398 |
| 8 | 0.623 | 0.583 | 0.474 |
| 9 | 0.547 | 0.612 | 0.456 |
| 10 | 0.568 | 0.664 | 0.437 |
| 11 | 0.591 | 0.595 | 0.452 |

Polydispersity index (PDI index) defines the width or spread of particle size distribution. It is expressed as a dimensionless number extrapolated from the autocorrelation function in photon correlation spectroscopy. The value of polydispersity index may vary from 0.01 (mono dispersed particles) to 0.5-0.7, whereas, PDI index value > 0.7 indicated broad particle size distribution of the formulation [8].

The PDI values of PEAMA, PRG and PEAMA-PRG I at different pHs were smaller than 0.7 and these results implied that the sample particles at different pHs showed monodisperse particle size distributions. If comparing the distribution of PRG and PEAMA particles with the distribution of PEAMA-PRGI particles, we will see that PEAMA-PRGI particles have a narrower distribution and uniform particles at different pHs (PDI=0.2-0.4) than PEAMA and PRG particles.

The particle sizes of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pH values are given in Table 2.

**Table 2.** Particle sizes (nm) of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pHs

| pH | PRG | PEAMA | PEAMA-PRGI |
|---|---|---|---|
| 2 | 1690 | 300 | 190 |
| 3 | 1460 | 290 | 240 |
| 4 | 1700 | 250 | 390 |
| 5 | 1880 | 225 | 230 |
| 6 | 1560 | 330 | 380 |
| 7 | 470 | 320 | 630 |
| 8 | 590 | 340 | 860 |
| 9 | 650 | 385 | 860 |
| 10 | 680 | 440 | 830 |
| 11 | 700 | 360 | 855 |

PRG swelled and had larger particle size values at acidic pHs compared to basic pHs, whereas PEAMA particle sizes were unaffect by pH changes. The particle size change trend of PEAMA-PRGI copolymer-drug delivery system was different from yhst of PRG and PEAMA. With increasing pH, particles of PEAMA-PRGI were 4 times swollen at basic pHs, from 190 to 855 nm and large particles were obtained after pH 6.

The mobility of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pH values is given in Table 3.

It is seen from Table 3 that PRG, PEAMA and PEAMA-PRGI are negatively charged over the studied pH ranges.

The zeta potential of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pH values is given in Table 4.

**Table 3.** Mobility of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pHs

| pH | PRG | PEAMA | PEAMA-PRG I |
|---|---|---|---|
| 2 | -0.28 | -1.17 | -1.58 |
| 3 | -0.38 | -1.87 | -3.58 |
| 4 | -1.93 | -3.72 | -4.03 |
| 5 | -2.69 | -4.13 | -5.64 |
| 6 | -2.80 | -5.14 | -5.57 |
| 7 | -3.81 | -5.61 | -4.94 |
| 8 | -4.35 | -6.73 | -6.54 |
| 9 | -3.92 | -7.16 | -6.84 |
| 10 | -5.10 | -7.61 | -6.12 |
| 11 | -4.09 | -7.34 | -4.65 |

**Table 4.** Zeta potential (mV) of PEAMA, PRG and PEAMA-PRGI copolymer-drug delivery system at different pHs.

| pH | PRG | PEAMA | PEAMA-PRG I |
|---|---|---|---|
| 2 | -2.87 | -12.15 | -16.96 |
| 3 | -3.90 | -19.07 | -37.10 |
| 4 | -19.93 | -38.46 | -41.47 |
| 5 | -25.41 | -42.79 | -58.42 |
| 6 | -28.98 | -53.17 | -57.63 |
| 7 | -39.40 | -58.05 | -51.09 |
| 8 | -45.06 | -69.92 | -67.72 |
| 9 | -40.58 | -74.06 | -70.76 |
| 10 | -52.77 | -78.80 | -63.34 |
| 11 | -42.39 | -75.92 | -48.15 |

The stability of PRG, PEAMA and PEAMA-PRGI increased with increasing pH. They were more stable at basic pH than at acidic pH.

Absorption spectra for checking activity and cumulative release of PRG from PEAMA-PRGI at different pH values are given in Figure 1 for PRG, Figure 2 for PEAMA and Figure 3 for PEAMA-PRGI.

According to the absorption spectrum, Fig. 1, PRG shows maximum activity at pH 11 (A=0.68), minimum activity at pH 6 (A=0.4) at 235 nm and PRG activity decreased by 59% from pH 11 to pH 6.

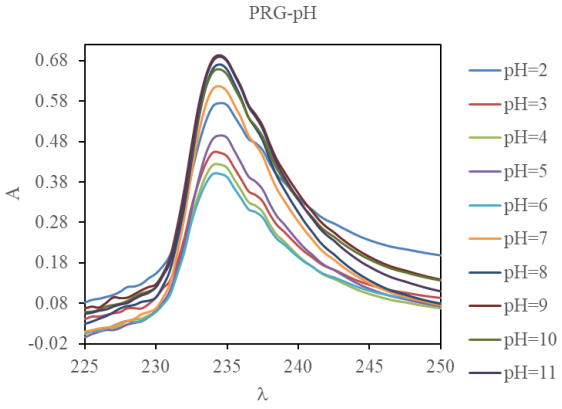


**Figure 1.** Absorption spectrum of PRG at different pHs

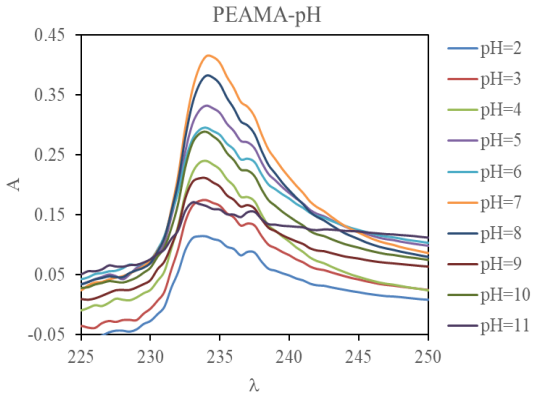


**Figure 2.** Absorption spectrum of PEAMA at different pHs

According to the absorption spectrum, Fig. 2, PEAMA shows maximum activity at pH 7 (A=0.4), minimum activity at pH 2 (A=0.11) at 234 nm and PEAMA activity decreased by 28% from pH 7 to pH 2.

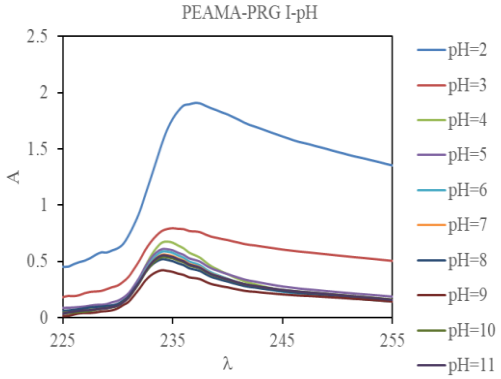


**Figure 3.** Absorption spectrum of PEAMA-PRGI at different pHs

According to Fig. 3, PEAMA-PRGI has maximum activity at pH 2 (A=1.9), minimum activity at pH 9 (A=0.4) at 234 nm and PEAMA-PRG I activity decreased by 21% from pH 2 to pH 9.

## CONCLUSION

In the present study, the pH effect on the stability and activity of the synthesized PEAMA-PRGI copolymer-drug system was determined. The pH effect on the activity of PEAMA-PRGI was different from that on PRG and PEAMA. The activity of PEAMA-PRGI increased four times at acidic pH whereas maximum activity of PEAMA and PRG was obtained at pH 7, and pH 11, respectively. The maximum stability of PEAMA, PRG and PEAMA-PRGI was observed at basic pH 10, pH 10, and pH 9, respectively. PEAMA, PRG and PEAMA-PRGI were negatively charged over the studied pH ranges.

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