Radiation Synthesis and Characterization of Polystyrene/ Methacrylic Acid Microcomposite for Drug Delivery uses

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ABSTRACT

Polystyrene/methacrylic acid microcomposites (PSty/MAA) with different metal particles; Ni, Fe or Cu have been entrapped in the copolymer matrix by using gamma rays. Effects of time, pH and type of metal particles on the swelling behavior of microcomposites were investigated in aqueous solution. It was observed that, the swelling capacity of all investigated microcomposites increases with an increase in the pH of the medium and the optimum pH is 7. The prepared microcomposites were investigated by using ultraviolet-visible (UV-Vis) spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), dynamic light scattering (DLS), thermo gravimetric analysis (TGA) and Fourier transform infrared spectroscopy (FTIR). TGA demonstrated that PSty/MAA microcomposites exhibited higher thermal stability compared to PSty/MAA hydrogel. The amount of metal particles in PSty/MAA microcomposites is about 11.70, 7.75, and 12.37 wt% for PSty/MAA-Ni, PSty/MAA-Fe and PSty/MAA-Cu, respectively. The data of DLS indicate that the average particle sizes obtained of different investigated microcomposites are ordered in sequence of PSty/MAA-Ni > PSty/MAA-Fe > PSty/MAA-Cu. The in vitro Chlortetracycline HCl release studies from PSty/MAA-Ni, PSty/MAA-Fe and PSty/MAA-Cu microcomposites at pH 7 are 58, 68 and 83%, respectively, after 7h. Complete release of Chlortetracycline HCl (100%) was reached after 10h from PSty/MAA-Cu microcomposite. The obtained microcomposites can be successfully used as drug delivery and PSty/MAA-Cu microcomposite was found to be the most effective one.

Key words: γ-radiation; microcomposite; characterization; drug delivery

INTRODUCTION

Micro/nano structures as fibers and spheres are known to have a large surface to volume ratio (¹). This characteristic is important for many applications such as sensors (gas or biological) and drug delivery (²). The main attraction of using sub-micron sized particles in drug delivery, particularly those under 260 nm in size, is the observation that such small particles tend to escape the detection systems of alveolar macrophages and remain long enough to release their contents in a controlled manner (³⁻⁹).

The potential of combining radiation effects with micro/nanomaterials has been recognized from the very early stages of nano-science research. In many uses of nanoparticles, radiation can play a significant role for catalysis, bio sensing, nano-electronics, magnetic applications including separations, mechanic-chemical conversion and to molecular computing. The use of radiation is clearly central to the fabrication of the nanostructured systems. Metal and salt–polymer composites are synthesized by this method (¹⁰).

The formation of amphiphilic copolymers consisting of hydrophilic and hydrophobic monomer units leads to hydrogel structures. Amphiphilic copolymers consist of polar and nonpolar monomeric

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units and are able to stabilize diverse interfaces in aqueous systems \(^{(11)}\). Due to the different polarities, such systems are, however, not easy to make and it is still a great challenge to control the relative incorporation of each monomer in the resulting polymer chain, as well as the homogeneity of the obtained structures. Radical copolymerization reactions in solvents like dimethyl formamide or butanone allows the preparation of some amphiphilic copolymers that can also be suitable for the formation of hydrogels \(^{(12, 13)}\). However, due to solubility problems, the limited range of accessible polymers and control of the monomer sequence are major problems.

Stimulus-responsive polymer gels undergo sharp volumetric transitions under small changes of external conditions, such as ionic strength, pH, temperature, the action of electric current, mechanical force, etc. \(^{(14-16)}\). These features of smart gels make them increasingly attractive for biotechnology and medicine, as well as for the development of new devices, for example, artificial muscles \(^{(17)}\). The incorporation of diverse particles in the gels often imparts new properties. Gels with entrapped magnetic particles are responsive to a magnetic field \(^{(18, 19)}\), and gels containing clays have improved mechanical and adsorption properties \(^{(20, 21)}\). Gels having isolated pores filled with water effectively trap linear macro-molecules \(^{(22)}\) and low molecular weight multicharged ions \(^{(22)}\).

In the present study PSty/MAA microcomposites containing Cu, Ni or Fe particles were prepared using gamma irradiation as initiator. The prepared microcomposites were characterized by the ultraviolet-visible (UV-Vis) spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), dynamic light scattering (DLS), thermo gravimetric analysis (TGA) and Fourier transform infrared spectroscopy (FTIR). The suitability of such microcomposites as drug delivery using Chlortetracycline HCl as a drug model has been investigated.

**MATERIALS AND METHODS**

1. **Materials:**

   The monomers, styrene (Sty) and methacrylic acid (MAA) were all purchased from (Merck, Germany). Chlortetracycline HCl was purchased from (Sigma chemical Co., USA) and used as received. All other chemicals were purchased from El-Nasr Co, Egypt.

2. **Synthesis of P(Sty/MAA) microcomposites:**

   The microcomposites were prepared by dissolving (20 wt %) Sty in methanol/water (60/40) and mixed with MAA (20 wt %) at different compositions. Then add 100 mg/L of Ni(II), Fe(II) or Cu(II), then the solution mixture was vortex mixed. Transfer the solution into test tube and purging nitrogen gas for 5 min to make the solution free from oxygen. The solution was irradiated using \(^{60}\)Co gamma cell at radiation dose 30 kGy. After copolymerization, the polymeric cylinder were removed by broken the test tubes and washed in excess methanol/water to remove the un-reacted component then air-dried at room temperature. Finally, this material was reduced to a powder with particle sizes ranging from 300 to 425 mm.

3. **Fourier Transform Infrared Spectroscopy (FTIR):**

   IR spectra of powdered discs were recorded over the range 400–4000 cm\(^{-1}\), in a Mattson 1000, Unicom infrared spectrophotometer (Cambridge, England) using the potassium bromide pellet technique.

4. **X-ray diffraction (XRD):**

   X-ray diffraction measurements were recorded using a D8-advance XRD apparatus (Bruker, Darmstadt, Germany). All the diffraction patterns were done at room temperature and under constant operating conditions.
5. Thermogravimetric analysis (TGA):

A Shimadzu TGA-50 TGA system was used to study the thermal stability of the prepared copolymers under a nitrogen atmosphere. The temperature range was from ambient temperature to 600°C at a heating rate of 10°C/min.

6. The swelling measurements:

The clean, dried, sample of known weight was immersed in a varying pH medium for different intervals time durations up to 24 h. HNO$_3$ of 0.2M was used to prepare solutions of low pH; while 0.1 M CH$_3$COONa / 0.1 M CH$_3$COOH were used to prepare buffer solution ranged from 3 -8 at room temperature for 24 h. The sample was removed and the excess solvent on the surface was removed by blotting quickly with absorbent paper and weighed. The water uptake was calculated as follows:

$$\text{Swelling (g/g)} = \frac{W_s - W_d}{W_d}$$

Where $W_d$ and $W_s$ are the weights of dry and wet samples, respectively.

7. Morphological studies:

Surface morphology of the PSty/MAA microcomposites was studied by means of a Field emission scanning electron microscope (QVANTA FEG 250, Netherlands) at an acceleration voltage of 20 kV. The Particle sizes of Sty/MAA microcomposites were analyzed by dynamic light scattering nano-particle size analyzer (LB-550, Horiba, Japan).

8. Drug Loading to the Polymer Matrix:

The loading of Chlortetracycline HCl drug onto P(Sty/MAA) microcomposite was carried out by swelling equilibrium method. The hydrogel was allowed to swell in the drug solution of known concentration for 24 h at 37°C and then dried to obtain the release device. The concentration of the rejected solution was measured to calculate percent entrapment of the drug in the polymer matrix. The mass of adsorbate per unit mass of adsorbent ($q_e$) was calculated as follows:

$$q_e (mg/g) = \frac{C_i - C_e}{m} \times V_i$$

Where $C_i$ and $C_e$ are the initial and equilibrium concentrations of adsorbate solution in mg/ml, $V_i$ is the volume of the treated solution in ml, and $m$ is the mass of dry adsorbent, in g.

9. In-vitro release studies:

In vitro release studies of the drug were performed by placing the pre-weighed microcomposite loaded with Chlortetracycline HCl drug in definite volume of releasing medium of buffer at pH 7 at 37°C for 12 h. One milliliter sample was withdrawn on time intervals to follow the release process. The concentration of chlortetracycline hydrochloride drugs was measured by UV spectroscopy (UNICAM UV/Vis Spectrometer. 1000 Model). After the complete release; the hydrogels were immersed in pH 3.0 buffer solutions and then, 0.1mol/L, HCl for 2 days to remove remaining drug may be loaded in the gel system. The total uncertainly for all experiments ranged from 3to 5%.

RESULTS AND DISCUSSION

In this study, microcomposites were prepared from styrene (Sty) and methacrylic acid (MAA) monomers mixed Ni, Fe or Cu particles using gamma irradiation as initiator. Firstly, the two monomers are mixed in the same ratio in methanol/water (60/40) system. 100 mg/L of different metal
ions solutions of Ni$^{2+}$, Fe$^{2+}$ or Cu$^{2+}$ were added, the carboxylic groups have an ability to bind M$^{2+}$ from water. When irradiated with gamma rays, free radical copolymerization was occurred. We also suppose that these process leads to some reorientation of -COOH groups of the polymethacrylic acid chains to more reactive state, enabling mutual interactions of these groups; metals should occupy these regions. Metal ions were bind by -COOH groups and its reduction by gamma rays as shown in Fig. 1.

Figure (1). A proposed mechanism for the synthesis of the PSty/MAA microcomposite

1. FTIR Spectroscopy

The FTIR spectra of PSty, PSty/MAA hydrogel are given in Fig. (2). In the spectrum of [Fig. 2(a)], the characteristic peaks for PSty are: 3050 cm$^{-1}$, originates from aromatic C-H stretching vibrations; peak at 1978 cm$^{-1}$ results from aromatic C-H combination frequency overtones; peak on 1620 cm$^{-1}$ results from aromatic C-C and peak at 1185 cm$^{-1}$ results from C-H stretching vibrations. The peak appears at 654 cm$^{-1}$ corresponds to C-H out of plan.

The spectrum of PSty/MAA [Fig. 2(b)] showed that, the characteristic peaks for poly(methacrylic acid) are: 3158 cm$^{-1}$ originates from stretching O-H vibrations and overlapped with C-H of PSty; peak at 1704 cm$^{-1}$ originates from C=O vibrations of carboxyl group; peak at 1320 cm$^{-1}$ originates from C-C and peak at 1260 cm$^{-1}$ originates from C-O stretching vibrations. From FT-IR results, it can be concluded that the formation of PSty/MAA hydrogel using ionizing radiation was occurred.
2. X-Ray Diffraction (XRD):

The XRD patterns for PSty/MAA hydrogels and different microcomposites are presented in Fig. 3. The Figure indicates that XRD pattern of the PSty/MAA hydrogels show an amorphous nature with peak existed at $2\theta = 19.64^\circ$. For PSty/MAA microcomposites extra peak appears in the patterns of all investigated microcomposites compared to that of PSty/MAA hydrogel at $26.45^\circ$. The intensity of this peak increased in order of Ni > Fe > Cu metals loaded PSty/MAA microcomposites. This means that the intercalation has occurred and the intercalated microcomposites have been formed.
Figure (3): X-ray diffractograms of different compositions of PSty/MAA hydrogels and different microcomposites.

3. Thermal Gravimetric Analysis (TGA)

TGA measurements of microcomposites were done and compared with PSty/MAA hydrogels as a control, and the corresponding thermograms are shown in Fig. 4. The same behavior was observed for all investigated samples. TG curve of PSty/MAA hydrogels reveals three degradation steps. The first degradation step up to 158 °C attributed to the loss of associated water. The second degradation step up to 296 °C attributed to anhydride formation and decarboxylation of carboxylic groups of MAA. The main weight loss in the third degradation step up to 400 °C attributed to the degradation of polymer chains. It can also be noted that the hydrogel composition was highly effect in thermal stability as observed in Fig. 4. Increasing Sty content in the hydrogel was improved the thermal stability due to the resonance effect of benzene ring. For microcomposites, the presence of Fe and Cu particles typically enhances the thermal stability of PSty/MAA hydrogel and little enhancement in thermal stability for PSty/MAA-Ni microcomposites. Thus, TGA experiments demonstrated that PSty/MAA microcomposites exhibited higher thermal stability compared to PSty/MAA hydrogel.

The amount of metal particles inside PSty/MAA hydrogel was determined by comparing PSty/MAA hydrogel with PSty/MAA loaded with Ni, Fe and Cu metals. As shown in Fig. 4, the amount of metal particles in PSty/MAA microcomposites is about 11.70, 7.75, and 12.37% by weight for PSty/MAA-Ni, PSty/MAA-Fe and PSty/MAA-Cu microcomposites, respectively. It is possible
that this weight may not be completely pure metals; some metal oxides can be formed during heating with TGA.

**Figure (4):** TGA thermal diagrams of different compositions of PSty/MAA hydrogels and different microcomposites

4. UV–Vis Analysis:

Figure 5 shows the UV–vis absorbance spectra of PSty/MAA-Ni, PSty/MAA-Fe and PSty/MAA-Cu microcomposites. It can be seen that the UV–vis spectra of microcomposites exhibit some differences result from the difference in loaded metal type. In the curves of PSty/MAA-Ni, PSty/MAA-Fe and PSty/MAA-Cu microcomposites, peaks are observed at around 287, 341 and 211nm, respectively. This result indicates that the different metal loading effect on the morphology of PSty/MAA microcomposite.

**Figure (5):** UV-Vis spectra of PSty/MAA-Ni, PSty/MAA-Fe and PSty/MAA-Cu microcomposites.
5. Morphological Studies:

The surface of the investigated PSty/MAA microcomposites containing Ni, Fe and Cu were evaluated using scanning electron microscopy (SEM) and depicted in Fig. 6(a-c), respectively. It can be noted that the metal ions are not uniformly dispersed in PSty/MAA microcomposite networks and there is no aggregation in the metal particles. MAA contains carboxylic groups, which are ideal for dispersing metal ions through ion exchange (25), thus producing dispersible particles.

The dynamic light scattering technique (DLS) was used to measure the hydrodynamic mean diameter of different investigated microcomposites in order to follow the permanent structural changes caused by changed type of nanoparticles. The relations between a Gaussian distribution and particle diameters of different microcomposites are represented in Fig. 7. The data of Figure indicate that the average particle sizes obtained of different investigated microcomposites are ordered in sequence of PSty/MAA-Ni > PSty/MAA-Fe > PSty/MAA-Cu.

Figure (6): SEM image of PSty/MAA-Ni (a) PSty/MAA-Fe (b) PSty/MAA-Cu (c) microcomposites.
Figure (7): DLS results of PSty/MAA-Ni (a) PSty/MAA-Fe (b) PSty/MAA-Cu (c) microcomposites.
6. The Swelling Properties:

The swelling capacities in water of the investigated microcomposites were carried out at ambient temperature compared with PSTy/MAA hydrogel as shown in Fig. 8. It can be seen that presence of Ni, Fe or Cu particles embedded in the PSTy/MAA hydrogel caused enhancement in the swelling capacity. A considerable variation in the swelling capacity of the PSTy/MAA hydrogel was observed when the hydrogel was loaded with Ni, Fe or Cu particles. The significant increase in the swelling capacity was attributed to the presence of the surface charge of metal colloidal particles. Meanwhile, a little effect in the swelling capacity was observed by changing the type of metal embedded in the hydrogel.

Figure 9 shows the swelling kinetics of different prepared PSTy/MAA microcomposites compared with PSTy/MAA hydrogels as a control. It can be seen that the swelling capacity of all the PSTy/MAA microcomposites increases progressively within the initial time of swelling up to 150 min and then tends to level off up to the equilibrium state.

The effect of pH on the swelling capacity of different microcomposites were studied and shown in Fig. 10. It can be seen that the swelling capacity of all investigated microcomposites is influenced by medium pH. The pH-responsive swelling behavior is basically due to ionization of the functional groups in the gel, which depends on the pH of the surrounding medium. It was observed that, the swelling capacity of all investigated microcomposites increases with an increase in the pH of the medium and the optimum pH was 7. At lower pHs, the network chains are firmly bonded to one another via hydrogen bonding as a result of excess of -COOH groups that restricted mobility and the swelling rate rises slowly \(^{(26)}\). As the pH increased above the pKa value of PAAc which is 4.7 \(^{(27)}\) the carboxylic groups of PAAc are ionized and generate carboxylate ions along the macromolecular chains, the mutual repulsion facilitate the chain relaxation and causing greater swelling.

![Swelling behavior of PSTy/MAA hydrogel, PSTy/MAA-Ni, PSTy/MAA-Fe and PSTy/MAA-Cu microcomposites.](image-url)
Adsorption of Chlortetracycline HCl

Before investigation the release behavior, the microcomposites were initially swollen in Chlortetracycline HCl solution in a concentration range of 0.25 – 1.0 mg/mL at pH 7. The amount of Chlortetracycline HCl adsorbed into 0.1 gm of PSty/MAA microcomposites were measured and given in Fig. 11. It can be seen that the amount of total chlortetracycline HCl taken increased with increasing initial drug concentration. The reason for this increase was attributed to the interactions between positively charged drugs to partially ionized microcomposite and also, to the higher free volume available for diffusion.
Figure (11): Effect of initial concentration of drug (mg/ml) on the amount of drug adsorbed by different microcomposites at 37 °C.

Controlled Drug Release Behaviors

The in vitro drug release was performed in buffer solution of pH 7 which is similar to that of the intestine medium. Figure 12 shows the drug release behavior of the investigated microcomposites loaded with 100 mg/L of the initial drug as a function of time. As can be seen from Fig. 12, the Chlortetracycline HCl release from Psty/MAA-Ni, Psty/MAA-Fe and Psty/MAA-Cu microcomposites are 58, 68 and 83%, respectively, after 7 hr. Complete release of Chlortetracycline HCl (100%) after 10 h from Psty/MAA-Cu microcomposite. The introduced of Cu particles into Psty/MAA microcomposite increases the swelling capacity of Psty/MAA hydrogel. The higher swelling ratio could afford enough space among the polymer chains of the microcomposite, which facilitates migration of Chlortetracycline HCl out of the microcomposites (28).

Figure (12): In vitro release data of Chlortetracycline HCl from different microcomposites at 37 °C and pH 7.
CONCLUSION

In this study, microcomposites from polystyrene/methacrylic acid – nickel, iron or cupper were prepared using gamma irradiation as initiator. It was found that the presence of Fe and Cu particles enhances the thermal stability of PSty/MAA hydrogel and little enhancement for PSty/MAA-Ni microcomposites. The structural morphology of the composite was measured by scanning electron microscope and dynamic light scattering technique which showed the smallest average particle sizes was obtained for polystyrene/methacrylic acid – cupper microcomposite. The presence of Ni, Fe or Cu particles inside the PSty/MAA hydrogel were enhanced its swelling capacity. It was observed that, the swelling capacity of all investigated microcomposites increases with an increase in the pH of the medium and the optimum pH was 7. The prepared microcomposites showed successfully release character of chlortetraycline HCl drug and Psty/MAA-Cu microcomposite was found to be the most effective one.

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