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Drug delivery of graft-copolymers prepared by gamma-radiation graft-copolymerization of acrylic acid onto plasticized starch/ montmorillonite clay blends

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ABSTRACT

Nanocomposite graft-copolymer hydrogels were prepared by gamma-radiation graft-copolymer ization of acrylic acid (AAc) onto plasticized starch (PLST)/ montmorillonite clay (MMT) blends. The effect of irradiation dose and MMT nanoparticle content on the gel fraction and swelling characters of PAAc-co-(PLST/MMT) graft-copolymer were investigated. In addition, the structure-property behavior of the graft-copolymer was characterized by IR spectroscopy, thermogravimetric analysis (TGA) and x-ray diffraction (XRD). The drug uptake-release characters of PAAc-co-(PLST/MMT) graft-copolymer, taking Sulphanilamide as a model drug, were studied. The study showed that the appropriate dose of gamma irradiation to achieve homogeneous nanocomposites hydrogel films and the highest swelling in water was 20 kGy, regardless of composition. The introduction of MMT up to 5 wt % improved the physical properties and enhanced the drug uptake-release characters.

Introduction

Hydrogels are three-dimensional network structures, which are capable of swelling and absorbing large amounts of water or biological fluids allowing a wide range of medical applications [1]. The network structure of hydrogels can be formed by ionizing radiation from one component or two components. Nanocomposite hydrogels has attractted great interest as biomaterials in various applications in the medical and pharmaceutical fields [2]. Polymer/clay nanocomposites have been reported to exhibit unique properties and lead to environmentally friendly and inexpensive plastic composites. The improved flame retardant, increased thermal stability, improved mechanical properties, and decrease in permeability are the most properties can be obtained [3-5]. The dispersion of the clay within the polymer has significant influence on the properties of the material because of the hydro-philicity of clays, which hinders the formation of homogeneous dispersion in organic polymers [6,7]. When clay is not well dispersed, either an intercalated or a delaminated nanocomposite is formed [8]. Intercalated nanocomposites consists of well ordered layers in which registry is maintained between the clay layers on the other hand this registry is lost in delaminated -also known as exfoliated-nanocomposites. The formation of delaminated nanocomposites seems to lead to a greater enhancement of mechanical properties than is observed for intercalated systems. It has been suggested that layered materials may be beneficial to the enhancement of polymer properties.

Sodium montmorillonite (MMT) is a naturally occurring 2:1 phyllosilicate, capable of forming suspension in water. The hydrophilic character of MMT clay allows dispersion of these inorganic crystalline layers in water-soluble polymers such as poly (ethylene oxide) [9] and poly (vinyl alcohol) [10,11].

Sulphanilamide is a synthetic bacteriostatic antibiotic with a wide spectrum against most gram-positive and many gram-negative organisms. Sulfonamides inhibit multiplication of bacteria by acting as competitive inhibitors of p-aminobenzoic acid in the folic acid metabolism cycle. Most sulfonamides are readily absorbed orally. However, parenteral administration is difficult, since the soluble sulfonamide salts are highly alkaline and irritating to the tissues. The sulfonamides are widely distributed throughout all tissues [12].

In previous work, radiation synthesis of pH-sensitive hydrogels from carboxymethyl cellulose/poly(ethylene oxide) blends as drug delivery systems for ketoprofen, as

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a drug model was investtigated [13].

In the present work, nanocomposite graft-copolymer hydrogels were prepared by gamma irradiation graft-copolymerization of acrylic acid monomer (AAc) onto blends composed of plasticized starch (PLST) and nanoparticle montmorillonite clay (MMT).

The formed nanocomposites were characterized by infrared spectroscopy (IR), x-ray diffraction (XRD), thermogravimetric analysis (TGA) and transmission electron microscope (TEM). In addition, the possible application of PAAc-co-(PLST/MMT) nanocomposite graft-copolymers in the field of drug delivery taking Sulphanilamide as model drug was investigated.

Materials and methods
Materials
Acrylic acid (AAc) monomer used in this study was a laboratory grade chemicals purchased from Merck Chemical (Germany), and used as received.

Unmodified commercial grade maize starch was obtained from El-Gomhoria Co. for Chemical Industries, (Egypt), and used as received.
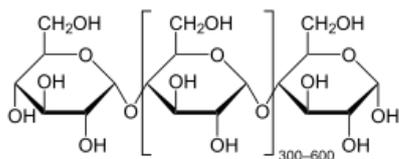
Montmorillonite nano-clay was obtained from Sigma-Aldrich, Germany and used without any treatments.
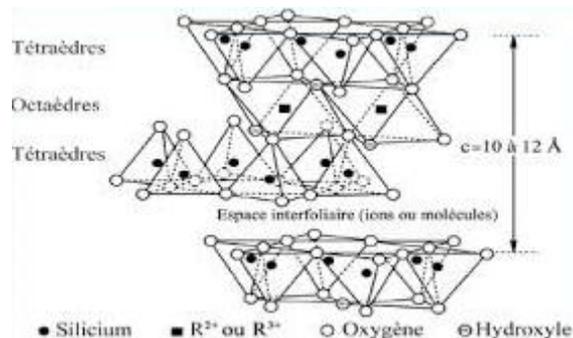
Sulphanilamide drug was purchased from Sigma and the chemical structure is shown below.
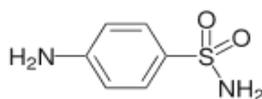
Preparation of plasticized starch (PLST)
PLST was prepared by dissolving maize starch into water under continuous stirring and then heating the solution for 1h at 95°C to obtain a completely gelatinized solution. Subsequently, glycerol (30-wt% based on the weight of the dry starch) was added with continuous stirring and heating for 1 h at >100°C to complete gelatinized solution.

Preparation of PAAc-co-(PLST/MMT) graft-copolymer hydrogels
The gelatinized starch solution containing well-dispersed

nanoparticles montmorillonite (MMT) was prepared by mixing different ratios of clay into PLST gelatinized solution. The weight ratio of montmorillonite clay in the dispersion was (1%, 3%, 5%, 7% and 9%) based on starch weight. The dispersion was magnetically stirred and heated to the gelatinized temperature of starch. The graft-copolymer hydrogels were prepared by dissolving separately different ratios of AAc monomer. The solutions were then mixed with continuous stirring until complete miscibility was achieved. The solutions were casted onto Petri dishes and subjected to gamma irradiation. Irradiation to the required doses was carried out at a dose rate of 2.857 kGy/ h. in the ^{60}Co gamma cell made in Canada. The contents were washed with hot water to get rid of the unreacted monomers.

Characterization of PAAc-co-(PLST /MMT) nanocomposites
Transmission electron microscope (TEM)
The morphology of the MMT nanoparticles was performed using Transmission electron microscopy (TEM), model JEM 100CS, Joel electron microscopy, Japan, working at acceleration voltage of 80 kV.

Gel fraction
Samples of the hydrogels were accurately weighed (W_o), extracted with distilled water using a soxhlet system and then dried in a vacuum oven at 80°C to a constant weight (W_1). The gel fraction was calculated according to the following equation:

Gel fraction (%) = (W_1/W_o) x 100

Swelling properties
Swelling studies were carried out on PAAc-co-(PLST /MMT) nanocompo-site hydrogels as a function of time (0-24 hrs). A known dry weight of insoluble hydrogel (W_d) was immersed in water under different conditions. The samples were then removed and blotted on filter paper to remove excess water and weighed (W_s), in which the percentage swelling under each condition was calculated according to the following equation:

Swelling (%) = [($W_s - W_d$) /Wd] × 100

X-ray diffraction(XRD)analysis
X-ray experiment of the samples was performed at room temperature by a Shimadzu D6000 diffractometer (40 kV, 30mA) with copper target irradiation at a scanning rate of 8 deg/min in a range of 2Θ =4-90°.

Thermogravimetric analysis (TGA)
The TGA studies were carried out on a Shimadzu-50 instrument (Japan) at a heating rate of 10°C min^{-1} under flowing nitrogen of 20 ml min^{-1} over a temperature range from room temperature up to 500°C.

FT-IR spectroscopic analysis
A FTIR spectrometer model Mattson 100, made by Unicam, was used over the range 400-4000 cm^{-1}.

Drug uptake and release studies of PAAc-co-(PLST /MMT) nanocomposites
Dry sample pieces of PAAc-co-(PLST /MMT) nanocomposite hydrogels were loaded with Sulphanilamide drug by immersion into aqueous solutions of drug (100 mg/l) for 24 h. The release of Sulphanilamide from hydrogels was measured by placing

the drug loaded hydrogels in a vessel containing 20 ml of different buffer solutions at a constant shaking rate. At each time interval, aliquots of 3 ml were drawn from the medium to follow the release of Sulphanilamide and returned into the vessel to keep the solution volume constant. Sulphanilamide release was determined by a spectrophotometeric method using a Unicam 8625 UV/Visible spectrophotometer.

Results and discussion
Radiation synthesis of PAAc-co-(PLST/MMT) nanocomposite Hydrogels

Acrylic acid is known to undergo radiation induced polymerization and subsequent crosslinking to form hydrogels. The crosslinking of vinyl monomers in solutions by gamma radiation was early established by Chapiro [14]. The mechanism of graft-copolymerization of AAc in aqueous solution by gamma radiation can be briefly outlined as follows: (1) AAc monomer and the solvent H_2O absorb gamma radiation resulting in the formation of the radicals $–(-CH^\bullet-CH^\bullet-COOH-)_n$, $HO^\bullet$

and $H^\bullet$. The transfer of radicals from water to polymer increases the concentration of AAc radicals and increases the rate of crosslinking and gelation and (2) Two polymer radicals with "n" and "m" repeat units combine to form a crosslinked point. Free radicals will be formed on the backbone of PLST, which will react with the free radicals formed on AAc to form graft-copolymers. An interpenetrating (IPN) type structure hydrogels could be formed, in which MMT clay is physically included in the network.

Characterization of PAAc-co-(PLSt/MMT) graft-copolymer Hydrogels
Transmission electron microscopy (TEM)

The TEM micrographs of PAAc-co-(PLST/MMT clay) graft-copolymer nanocomposite hydrogels containing different ratios of MMT clay prepared by gamma irradiation graft-copolymerization of AAc onto PLST/MMT clay blends is shown in **Fig. 1**. In all cases the ratio of AAc is 50% and the irradiation dose is 20 kGy. The images obtained indicate that the resultant
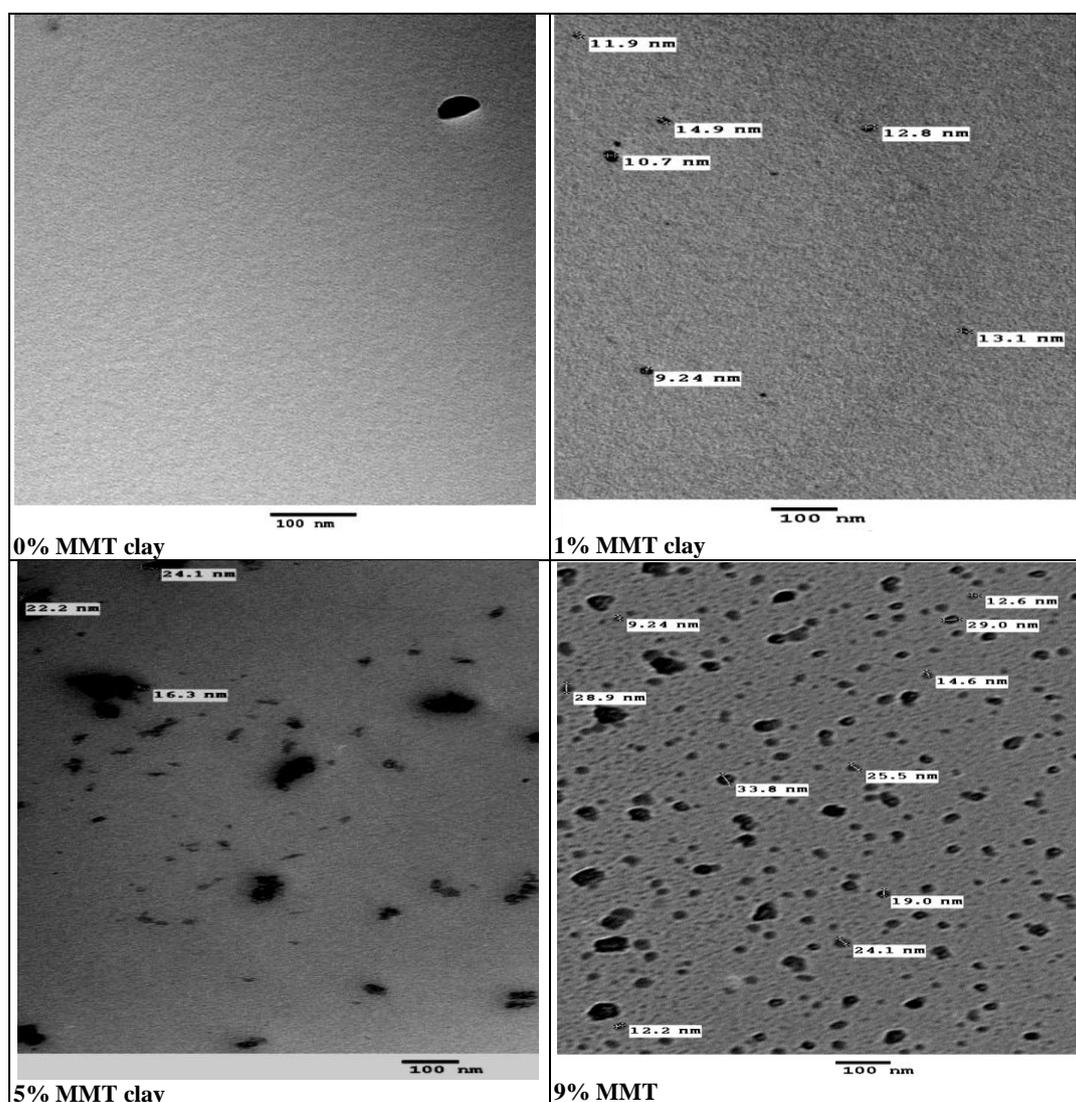
Fig. 1: TEM micrographs of PAAc-co-(PLST/MMT clay) graft-copolymer nanocomposite hydrogels containing different ratios of MMT clay prepared by gamma irradiation graft-copolymer ization of onto PLST/MMT clay blends. In all cases the ratio of AAc is 50% and the irradiation dose is 20 kGy.

product contains well-stabilized nanoparticles with a diameter range of 10–40 nm. The number of MMT clay nanoparticles was found to increase with increasing the ratio of MMT clay indicating the formation of nanocomposite graft-copolymers.

Gel fraction

The effect of irradiation dose on the gel fraction (%) of graft-copolymer hydrogels prepared by gamma-radiation graft-copolymerization of different ratios of acrylic acid (AAc) onto plasticized starch (PLST) is shown in **Fig. 2**. The effect of gamma irradiation dose and nanoparticle clay (MMT) ratio on the gel fraction (%) of PAAC-co-(PLST/MMT) nano-composite graft-copolymer hydrogels prepared at different ratios of AAc is shown in **Figs. 3-5**. It can be seen that the gel fraction has increased by increasing the AAc ratio, irrespective of irradiation dose. However, the gel fraction was found to increase with increasing gamma dose up to 15 kGy and then tends to decrease at high doses. The gel fraction decrease could be explained as due to the degradation of the PLST components.

Fig. 4. Effect of gamma irradiation dose and nanoparticle clay (MMT) ratio on the gel fraction (%) of PAAC-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels. In all cases the AAc ratio is 50%.
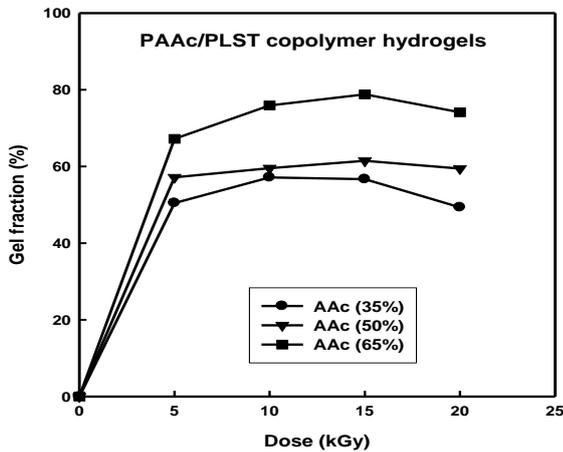
Fig. 2. Effect of irradiation dose on the gel fraction (%) of graft-copolymer hydrogels prepared by gamma-radiation graft-copolymer ization of different ratios of acrylic acid (AAc) onto plasticized starch (PLST).
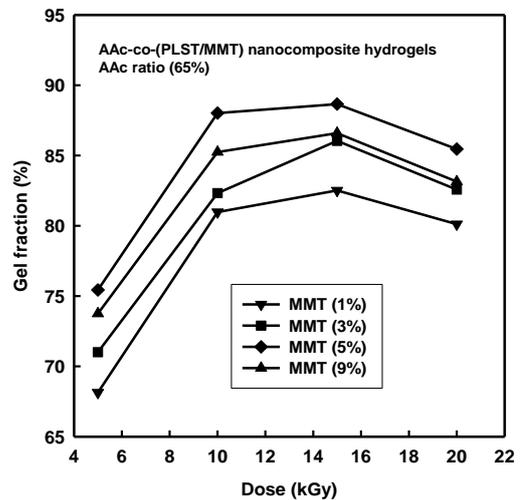
Fig. 5. Effect of gamma irradiation dose and nanoparticle clay (MMT) ratio on the gel fraction (%) of PAAC-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels. In all cases the AAc ratio is 65%.

As shown, MMT nanoparticle clay ratio together with the irradiation dose had a great effect on the gel fraction of PAAC-co-(PLST/MMT) graft-copolymer hydrogels. Apparently, the gel fraction was found to increase with increasing the ratio of MMT clay, regardless of AAc ratio or the irradiation dose. However, the gel fraction was higher in the presence of MMT nanoparticles.

Clay materials are, generally denotes as three-dimensional framework structures with channels and interconnecting cavities of SiO_4 and AlO_4 tetrahedral. Since aluminum is trivalent, the lattice carries a negative charge. This charge is balanced by alkali or alkaline earth cations, which do not occupy fixed position but are free to move in the channels of the lattice framework [15]. The montmorillonite clay is of a 2:1 layered structure whereas; Al^{3+} can isomorphously replace Si^{4+} in a number of silicate structures [two layers of SiO_4 tetrahedral and one AlO_4 tetrahedral.

Fig. 3. Effect of gamma irradiation dose and nanoparticle clay (MMT) ratio on the gel fraction (%) of PAAC-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels. In all cases the AAc ratio is 35%.

The increase in gel fraction resulted from the introduction of MMT may be explained as due the distribution of MMT nanoparticles in the crystalline region of the graft-copolymer that would eventually facilitate the exposure of additional sites to gamma irradiation leading to higher gel fractions than graft-copolymerization of AAc onto pure starch.

Swelling characters

The swelling behavior of polymeric systems is of great importance when it is applied in the biomedical field as its hydration degree influences the surface properties and mobility, mechanical properties and the type of solute transport mechanism through the blends. **Figure 6** shows swelling (%) in water at room temperature and pH 7 of PAAc-co-PLST graft-copolymer hydrogels prepared by gamma irradiation at different doses and different ratios of AAc. It can be seen that swelling decreased with increasing gamma irradiation dose, irrespective of AAc ratio. The structure of PLST at high branched side chains which that limits water to be absorbed by graft-copolymer hydrogel. The swelling was found to decrease with increasing the AAc ratio due to the increased crosslinking density which makes the structure compact so that it prevents the absorption of water in accordance with the gel fraction.
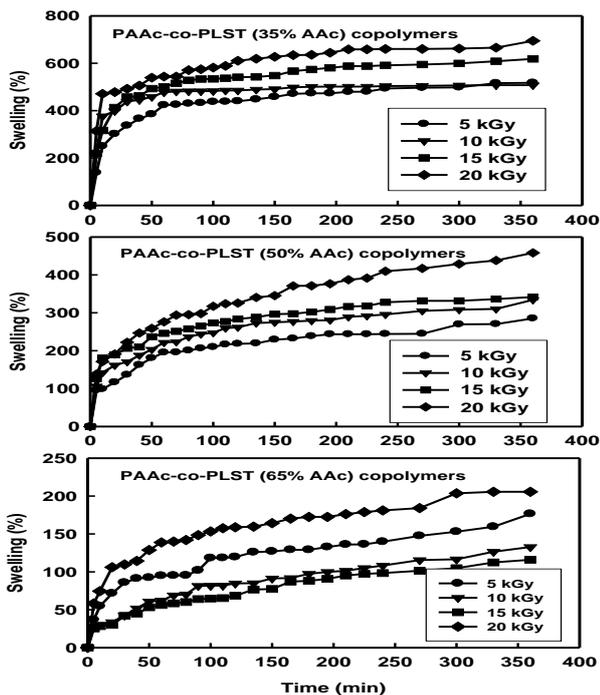
Fig. 6. Swelling (%) in water at room temperature and pH 7 of PAAc-co-PLST graft-copolymer hydrogels prepared by gamma irradiation at different doses and different ratios of AAc.

Figure 7 shows the swelling (%) in water at room temperature and pH 7 of PAAc-co-PLST nanocomposite hydrogels containing different ratios of nanoparticle montmorillonite clay (MMT). An opposite trend can be observed in the relationship between the MMT rato and water swelling of PAAc-co-PLST nanocomposite graft-copolymer hydrogels. The swelling was found to increase

with increasing the MMT clay ratio and then tends to decrease progressively with increasing MMT ratio up to 9%. This decrease in water swelling is due to the strong interaction between MMT and PAAC matrix, which leads to the formation of bound polymer, which is close to the reinforcing filler leading to the restriction of the water absorption.
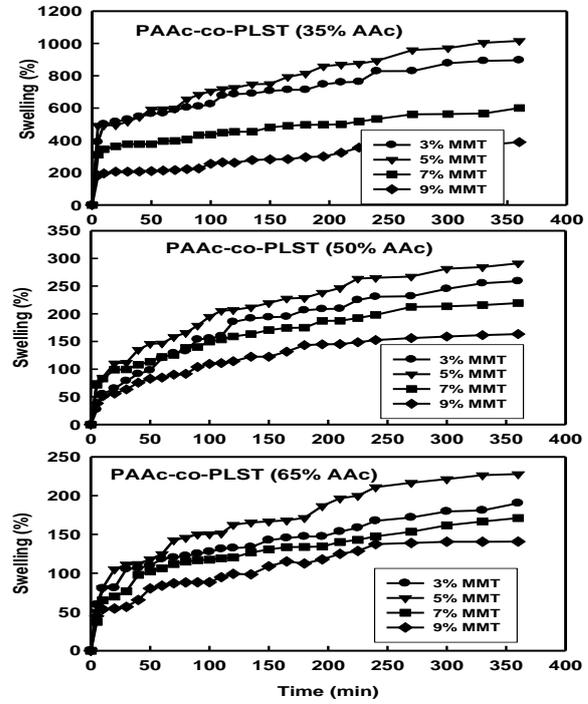
Fig. 7. Swelling (%) in water at room temperature and pH 7 of PAAc-co-PLST nanocomposite hydrogels containing different ratios of nanoparticle montmorillonite clay (MMT) prepared by gamma irradiation at a constant dose of 20 kGy.

FT-IR spectroscopic analysis

FT-IR spectroscopic analysis was used to confirm the formation of PAAc-co-(PLST/ MMT) graft-copolymer hydrogels, **Fig. 8.** It is known that the existence of hydrogen bonding changes the position of the absorption band due to O–H stretching from 3600 cm^{-1} for compounds of less extensive hydrogen bonding to ~3330 cm^{-1} for those with extensive hydrogen bonding. It is clear that both IR spectra for pure MMT clay, pure starch, pure acrylic acid or PAAc-co-(PLST/MMT) graft-copolymer hydrogels showed the existence of extensive hydrogen bonding in the range 3000–3500 cm^{-1}. However, it seems that the PAAc-co-(PLST/ MMT) graft-copolymer hydrogels possess relatively higher extents of hydrogen bonding. The absorption bands due to O–H stretching associated with the PLST and PAAc polymers can be observed as a broad band at about 3400 cm^{-1}. The absorption band arises from C–H stretching of almost all organic compounds can be observed at 2910 cm^{-1}. The band at 1606 cm^{-1} arises from the –COO^{-} stretching vibration of PAAc, whereas the bands at 1428 and 1328 cm^{-1} for CH_2 scissoring and OH-bending vibration, respectively. The bands appeared at ~ 1725 and 1660 cm^{-1} can be attributed to the carbonyl groups
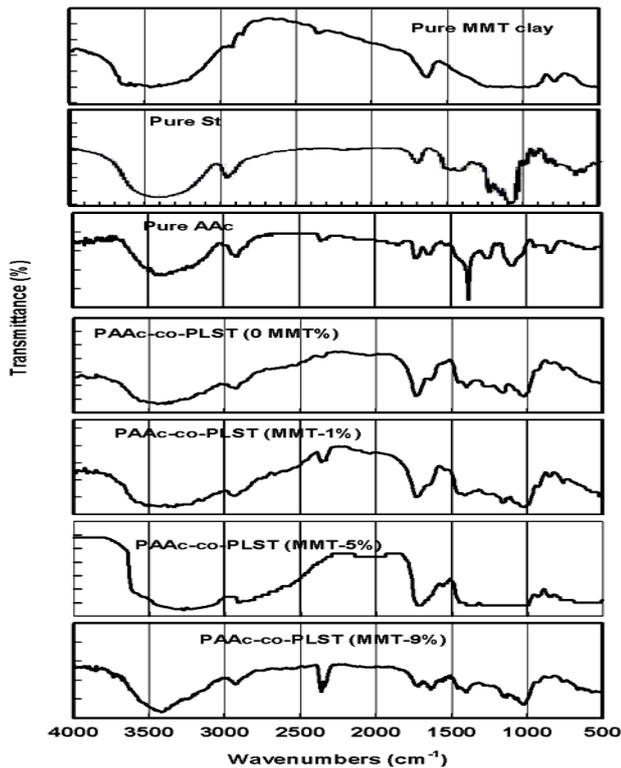
Fig. 8. FT-IR spectra of pure MMT clay, pure St, pure AAcr and PAAc-co-PLST nanocomposite hydrogels containing different ratios of nanoparticle montmorillonite clay (MMT) prepared by gamma irradiation at a constant dose of 20 kGy.

(C=O) of PAAc carboxyl groups for the PAAc-co-(PLST/MMT) graft-copolymer hydrogels [16,17]. Apparently, the characteristic absorption peaks of either pure PAAc-co-(PLST/MMT) graft-copolymer hydrogels or after introduction of MMT nanoparticle clay are clearly noted. However, the intensity of the different peaks was higher in case of hydrogels than MMT nanoparticle clay. These findings suggest the occurrence of graft-copolymerization of AAc onto PLST/MMT blends, which resulte in the formation of a semi-interpenetrating polymer network [18].

Thermogravimetric analysis (TGA)

The thermal stability of polymeric materials is largely dependent on the strength of the covalent bonds between the atoms forming the polymer molecules. Also, intermolecular hydrogen bonds or covalent bonds between the polymer chains are expected to increase the thermal stability in addition to crosslinking. As reported bond dissociation energy values for C-H, C-C, C-O, O-H, C=O and C=C was 414, 347, 351, 464, 741 and 611 kJ/mol, respectively [19]. According to these values, the average dissociation energy for PLST and PAAc as calculated is 385.9 and 578 kJ/ mol, respectively. According to these values, it may be expected that the PAAc-co-(PLST/MMT) graft-copolymer hydrogels will possess higher thermal stability than PLST. TGA was used to investigate experimentally the thermal stability of PAAc-co-(PLST/MMT) graft-copolymer hydrogels.

The TGA thermograms and the corresponding rate of thermal decomposition reaction curves of PAAc-co-(PLST/MMT) nanocomposite copoly-mer hydrogel containing different ratios of nanoparticle MMT clay, prepared by gamma radiation at a dose of 20 kGy isexhibted in **Fig. 9**. Thermal stability may represent an important property in polymer/layered silicate nanocomposites (PLSNs) [20]. It is generally accepted that the improvement in thermal stability is related to barrier properties and the radical-trapping effect of clay platelets. Based on these figures, few points may be concluded:

(1) The thermal decomposition of either PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogel with or without MMT clay passes through three stages upon heating from room temperature to 500°C.

(2) The major decomposition occurs within the temperature range of 300–500°C, in which PVA polymer displayed the lowest thermal stability. Within this range, the thermal stability of PVA/MMT nanocomposites was found to decrease with increasing the MMT content with an increase in percentage weight loss.

(3) The temperatures of the maximum value of the reaction rate of thermal decomposition (T_{max}) indicate these findings. In this contest, the T_{max} was found to inecrease with increasing the MMT ratio up to 9%. However, PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogel possessed higher T_{max} values than PAAc-co-PLST graft-copolymer hydrogel. In this regard, the T_{max} of PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogel before and after introducing 1, 5 and 9% of MMT clay was found to be 317.1, 340.9, 424.5 and 436.1, respectively. The above values for the T_{max} indicate clearly the formation of graft-copolymer hydrogels and that the introduction of MMT nanoparticles enhanced the thermal stability.
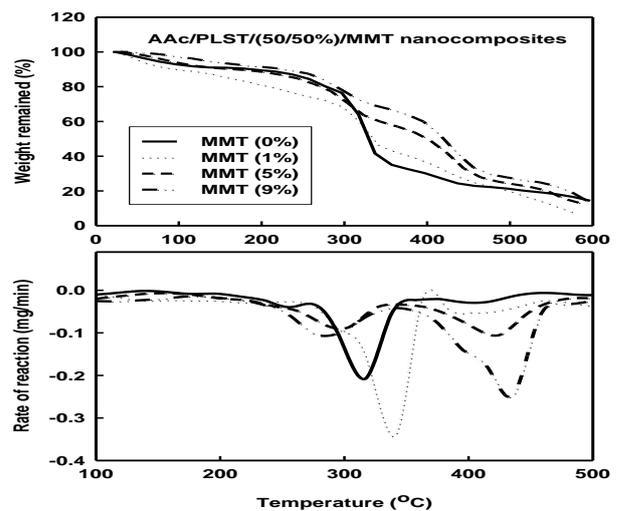
Fig. 9. TGA thermograms and the corresponding rate of thermal decomposition reaction curves of PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogel containing different ratios of nanoparticle MMT clay, prepared by gamma radiation at a dose of 20 kGy.

X-ray diffraction (XRD)

The XRD patterns of pure MMT clay and PAAc-co-(PLST/MMT) nanocomposite co-polymer hydrogels containing different ratios of nanoparticle MMT clay at AAc ratio is 20% and gamma irradiation dose of 20 kGy is shown in **Fig. 10**. XRD reports the spacing between ordered layers of the *d*001 or basal spacing, in which water expanded sodium clay normally exhibits a peak associated with a spacing of 12.5 A° [21]. The absence of this basal peak is commonly taken as evidence for a high dispersion of clay platelets, whereas a peak associated with higher spacing would indicate intercalated nanocomposites. As shown in **Fig. 10**, the diffraction peak corresponding to MMT clay has disappeared completely when dispersed within the PAAc-co-(PLST/MMT) graft-copolymer hydrogels, reflecting the dispersion and the intercalation of MMT. The intensity of this peak decreases as the amount of MMT increases, in agreement with the findings in previous reports [22, 23] This means that the crystal lattice structure of MMT was totally dispersed, the slice layers were exfoliated into the graft -graft-copolymer, and combined with PAAc-co-(PLST/MMT) at the nanometer level, so the exfoliated nanocomposites were formed. The crystalline behavior of graft -graft-copolymer is suppressed by the introduction of sodium clay into polymer matrix in the form of intercalated structure.
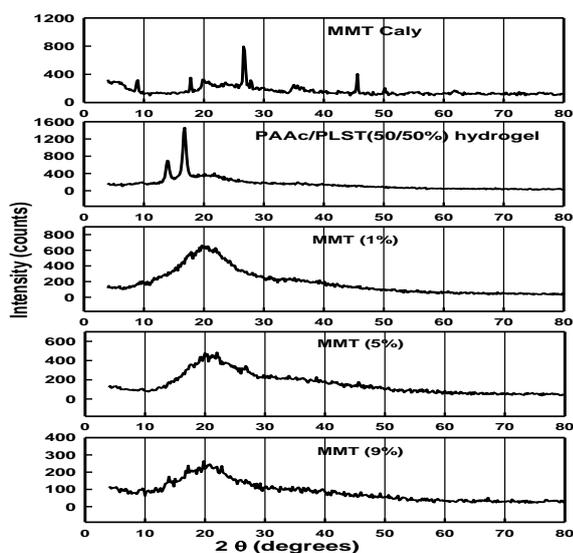
Fig. 10. XRD patterns of pure MMT clay and PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels containing different ratios of nanoparticle MMT clay. AAc ratio is 50% and gamma irradiation at a dose of 20 kGy.

Drug uptake- release properties

Sulphanilamide was selected as drug model to evaluate the PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels for the possible use as drug uptake-release systems. In order to determine the release of Sulphanilamide, a standard calibration curve representing the absorbance of different concentrations of Sulphanilamide was first constructed as shown in **Fig. 11**.

The relation correlating this curve is calculated to be:
Absorbance = 0.04354 (concentration, mg/l) + 0.9995
From this relation, a concentration of unknown sample can be determined.
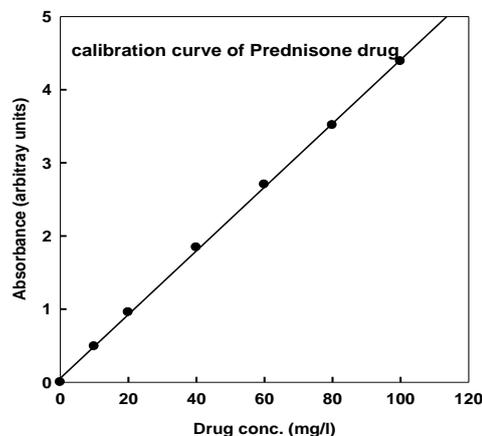
Fig. 11. Calibration curve representing absorbance of different concentrations of the Sulphanilamide drug.

The uptake of Sulphanilamide drug by PAAc-co-(PLST/ MMT) nanocomposite graft-copolymer hydrogels, prepared by gamma radiation at the dose 20 kGy and containing different concentrations of MMT clay nanoparticles IS illustrated in **Fig. 12**. It is clear that the loading of Sulphanilamide depends largely on the MMT content in the PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels; the uptake was found to increase by increasing the MMT content. This finding is understandable since there are many available hydroxyl groups on the structure of Sulphanilamide to form hydrogen bonding and that the MMT nanoparticles with large surface area would facilitate the division of drug.
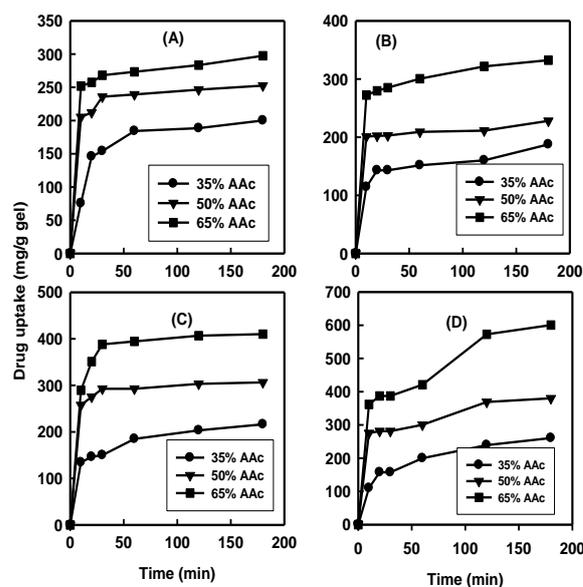
Fig. 12. Uptake of Sulphanilamide drug by AAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogel prepared by gamma irradiation at a dose of 20 kGy and different ratios of AAc monomer containing different contents of MMT clay: (A) (0%), (B) (1%), (C) 5% and (D) 9%.

Release profiles

The release of hydrogels loaded with drug occurs after water penetrates the polymeric networks and this is followed by diffusion along the aqueous medium. Thus, drug release is basically related to the swelling characters of hydrogels. **Fig. 13** shows the release profiles of Sulphanilamide drug by PAAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogels, at different ratios of AAc monomer and containing different ratios of MMT clay nanoparticles. It can be seen that up to 60 minutes nearly no release was observed, regardless of graft-copolymer composition or MMT ratio. Beyond 60 minutes, the amount of released Sulphanilamide was suddenly increased. However, it can be seen that the amount of released drug was found to decrease with increasing the ratio of AAc monomer. This is expected since the increase of AAc ratio is associated with increasing the gel fraction which makes the structure more compact,which retard the release of drug.
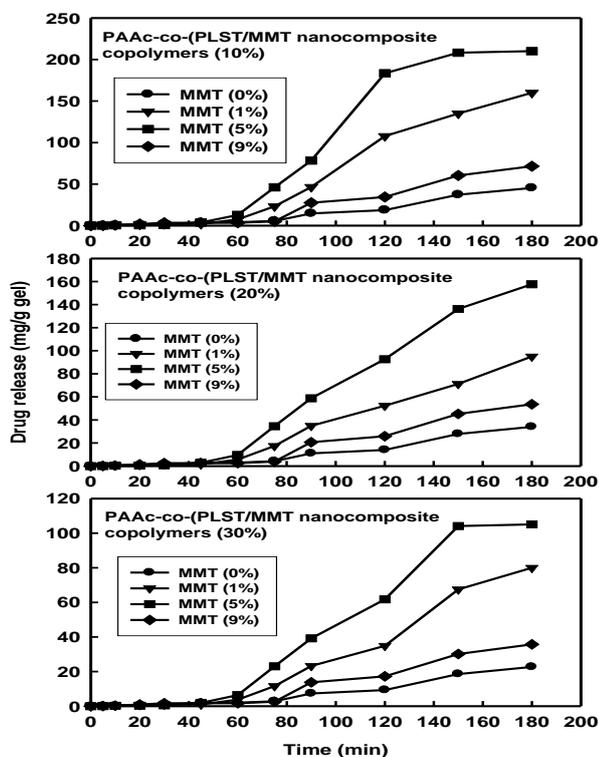
Fig. 13. Uptake of Sulphanilamide drug by AAc-co-(PLST/MMT) nanocomposite graft-copolymer hydrogel prepared by gamma irradiation at a dose of 20 kGy and different ratios of AAc monomer containing different contents of MMT clay: (A) (0%), (B) (1%), (C) 5% and (D) 9%.

Conclusions

In the present work we have synthesized Nanocomposite graft-copolymer hydrogels by gamma-radiation graft-copolymerization of acrylic acid (AAc) onto plasticized starch (PLST)/ montmorillonite clay (MMT) blends, characterized and studied swelling and drug delivery behavior. The Swelling study shows that the water uptake property of the hydrogel is dependent on composition of polymer and irradiation dose. On the

basis of the comparison study carried out between hydrogels terms of swelling; the less AAc content the more swelling we get, while the presence of MMT has little effect on swelling on the other hand MMT affects the uptake and release of Sulphanilamide and the with composition with 5% MMT we get the best uptake and release.

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