Drug Delivery Systems based on Poly(vinyl alcohol)-layered Silicates Hybrid Films

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New systems based on poly(vinyl alcohol), unmodified and modified layered silicates were designed for drug delivery applications. Unmodified and modified montmorillonite with different agents were used as inorganic component in the hybrid structures. The thermogravimetric analysis (TGA), X-Ray Photoelectron Spectroscopy (XPS), X-Ray Diffractions (XRD) and FTIR analysis were useful to characterize the hybrid materials. The modifier agent type used for montmorillonite treatment and the presence of montmorillonite in the polymeric films strongly influence the hybrid materials properties and drug release profile.

Keywords: poly(vinyl alcohol), hybrid materials, montmorillonite, 5-fluorouracil, UV-Vis, X-Ray Photoelectron Spectroscopy

The polymer-clay hybrid materials are a new class of materials characterized by attractive properties like higher mechanical, thermal and barrier properties than for pure polymer matrix. These remarkable properties recommend this class of materials in a wide range of applications like biomedical applications (drug delivery systems), packaging production, coating systems and development of new flame retardant agents with a minimal environmental impact [1-3].

The hybrid materials designed for drug delivery applications represent an interesting alternative to conventional systems because they combine the polymeric advantages with those of layered silicates. This organic-inorganic combination can solve some disadvantages (high drug dissolution rate, low stability in different pH, low drug bioavailability) identified in classical polymeric based drug delivery systems and ensure a better drug loading and encapsulation efficiency, a controlled drug release, mucoadhesive properties with lower hydration properties in acidic environment, an increase of mechanical properties and drug solubility [4-8]. The presence of clay within the polymeric matrix strongly influenced the biopharmaceutical properties of the final products and drug release mechanisms [9].

The properties of polymer-clay hybrid materials depend on the interactions established between the inorganic component (clay) and polymeric matrix. Electrostatic interactions, van der Waals forces and hydrogen bonding are the most common interactions which occurred between clay and polymer [10]. For instance in case of poly(vinyl alcohol)-clay hybrid materials three types of interactions were simultaneous involved: the interactions between the clay with PVA, between the clay nanoparticles with water and between two or more clay nanoparticles [11].

The hydrogel based on polyvinyl alcohol (PVA) is an example of material used in biomedical applications like controlled drug delivery, contact lenses, artificial cartilage, dialysis membrane and tissue engineering [12-16]. The crosslinking of PVA can occur by chemical process which involves the addition of an acid or an aldehyde or by physical processes (freeze-thawing process) [17-19]. The hydrogels obtained by physical crosslinking are recommended as drug delivery systems because they exhibit high swelling degree, high biocompatibility and good mechanical properties [16, 20-22].

The aim of this study was to develop some hybrid hosts based on poly(vinyl alcohol) and montmorillonite modified using different agents designed for 5FU encapsulation. In order to increase the interactions between the polymer, inorganic host and drug, the montmorillonite was modified using a silanization agent and a polyetheramine. The presence of organic fractions grafted on the montmorillonite (MMT) surface or/and intercalated within the clay gallery were pointed out using different methods like FTIR Spectroscopy, thermogravimetric analysis, X-Ray Photoelectron Spectroscopy (XPS). The UV-Vis analysis was useful to study the influence of clay modifier agent on the drug release.

Until now hybrid films based on PVA, drug and unmodified clay were developed [23, 24].

Experimental part

Raw Materials

5-Fluorouracil (5FU), Methanol, 3-(Glycidylpropyl) trimethoxysilane (GOPTMS), poly(vinyl alcohol) (PVA), with 98-99 % hydrolysis degree and a molecular weight 31000-50000 g/mol were purchased from Sigma-Aldrich.

Montmorillonite (Cloisite Na) supplied from Southern Clay Products was used as inorganic host in the hybrid materials structure. The montmorillonite CEC value is about 92.5 meq/100g.

Jeffamine EDR-148 supplied from Huntsman was used as modifier agent for montmorillonite. The chemical structures of the raw materials are presented in figure 1.

Modification of layered silicate

The modification of montmorillonite with GOPTMS was done according to the method used for the halloysite organophilization reported in our previous book chapter [25]. The modification of MMT with GOPTMS consists in the treatment of layered silicate dispersed in toluene with silanization agent (GOPTMS). The reaction mixture was heated at 90°C for 9 h and then the modified clay was centrifuged and washed with anhydrous methanol. In the

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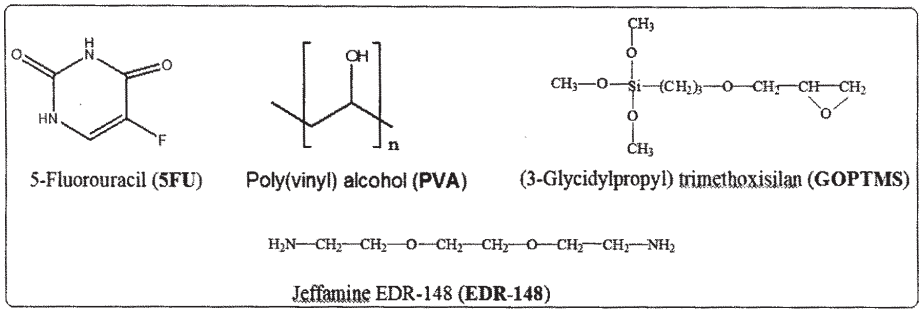


Fig.1. Chemical structure of the raw materials

final step the modified montmorillonite with epoxy groups (MMT-Epoxy) was dried at 90°C for 24 h and finally was grounded until a fine powder was obtained.

For the modified MMT with polyetheramine (EDR 148) the following strategy was used. 10 g of MMT were swelled in 700 mL of deionized water for 1 h at 50°C and then 5g of protonated EDR 148 with HCl 37% were added. The resulted suspension was maintained under stirring for 4 h at 50°C in order to allow the cationic exchange reaction between the sodium cations of the clay and organic cations. In the final step the modified montmorillonite was washed with deionized water until no chloride ions were detected. The modified MMT (MMT-148) was dried at 50°C.

Synthesis of hybrid films

The synthesis of hybrid materials was done according to a modified cyclic freezing-thawing method reported in the literature for synthesis of PVA-montmorillonite hydrogels [26]. A solution of PVA was prepared by dissolving 0.3 g of polymer in 12 mL deionized water for 1 h at 80°C under continue stirring. Then 0.03 g of modified MMT (MMT-Epoxy or MMT-148) was dispersed within the polymeric solution and the obtained suspension was magnetically stirred at 80°C for 1 h. In the next step the suspension was cooled down at room temperature and the drug (5FU) was added. The suspension based on PVA, modified MMT and 5FU was magnetically stirred for 1 h at room temperature and then the solution was transferred in a Petri dish and in the final step the solution was frozen at -20°C for 24 h to induce crystallization. After the freezing step, the sample was maintained at room temperature for 24 h. The freeze-thaw cycles were repeated three times.

Characterization techniques

FTIR spectra were recorded on a Bruker VERTEX 70 spectrometer using 32 scans with a 4 cm^{-1} resolution.

Thermogravimetric analysis (TGA) was done on a Q 500 TA instruments. The samples of 3 mg were heated from 20 to 920 °C at a scanning rate of 10°C/min under a constant nitrogen flow rate (40 mL/min).

UV-VIS spectra were recorded using a UV-3600 Shimadzu equipment provided with a quartz cell having a light path of 10 mm.

X-Ray Diffraction (XRD) analysis was performed on a X'Pert PRO MPD Panalytical equipment.

X-Ray Photoelectron Spectroscopy (XPS) spectra were recorded on Thermo Scientific K-Alpha equipment, fully integrated, with an aluminum anode monochromatic source.

In vitro drug release

The drug release experiments were performed using a 708 DS Agilent Technologies dissolution bath equipped with 40-mesh basket holder. The drug release was performed in 200 mL vessels for 2 h in simulated gastric fluid (*p*H 1.2) and for other 22 h the same sample was released in simulated intestinal fluid (*p*H 7.4). The rotation rate of dissolution bath was 50 rpm, and the temperature was kept constantly at 37 °C. At precise interval times, 3 mL of the dissolution medium were manually taken out and replaced with fresh dissolution medium. The concentration of 5FU was determined by UV adsorption at 266 nm.

Results and discussions

MMT modification with different agents

The special structure of montmorillonite allowed the development of different modification strategies with low molecular weight organic compounds or macromolecular compounds. The most used methods include reactions with coupling agents, cationic exchange reactions with different organic cations or a combination of both reactions [27-29].

The surface modification of montorillonite with GOPTMS involves the reaction of methoxy groups from coupling agent structure with silanol groups from the MMT structure (fig. 2).

The second strategy used for MMT modification consists in the cationic exchange reaction. This method involved the sodium cation exchange reaction with a protonated hydrophilic polyetheramine (EDR 148) (fig. 3).

The MMT surface modification was performed in order to increase the interactions between inorganic (MMT) and organic hosts (PVA).

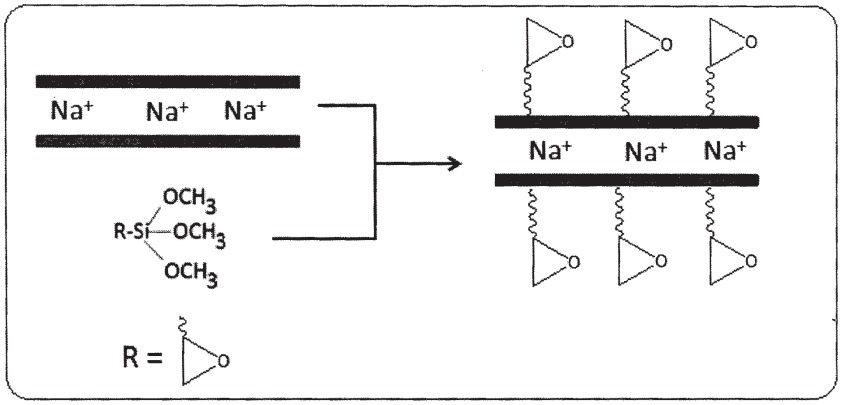


Fig. 2. Reaction of MMT with GOPTMS

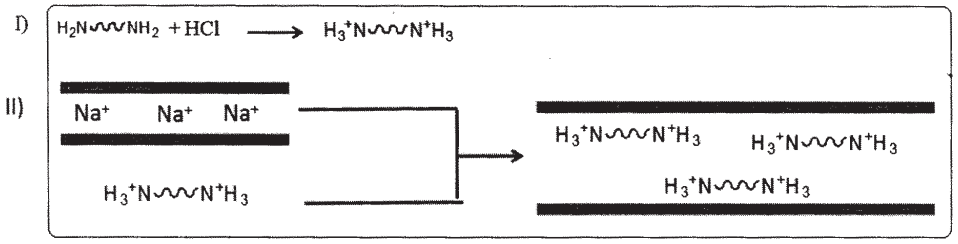


Fig. 3. Cationic exchange reaction of MMT with EDR 148

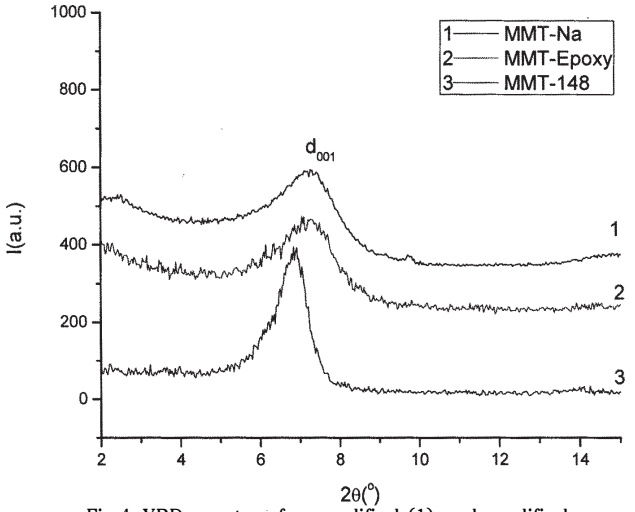


Fig.4. XRD spectra of unmodified (1) and modified MMT : MMT-Epoxy (2), MMT-148 (3)

Characterization of modified layered silicates

The presence of organic fractions within the MMT surface or/and in the gallery was pointed out using different characterization techniques (XRD, XPS, TGA and FTIR).

XRD Analysis

The XRD analysis was performed to check if the modifier agents (GOPTMS, EDR 148) were attached only on the clay surface or were also intercalated within the clay gallery. Figure 4 shows the XRD spectra of unmodified and modified MMT obtained after the treatment with silanization agent and polyetheramine (EDR 148).

In case of MMT-Epoxy the peak assigned to the basal distance (d_{001}) appears at the same position 2θ like in case of unmodified clay. This fact proved that the modifier agent (silanization agent) was attached only on the silicate surface.

The basal distance of MMT-148 has recorded an increase assigned to the polyetheramine intercalation. Because the polyetheramine has not a bulky structure and a long chain the basal distance exhibits only a small increase (12.9 Å).

XPS Analysis

The XPS analysis was useful in order to prove the presence of the organic fraction on the silicate surface after the treatment with the modifier agents (GOPTMS and EDR 148). The presence of organic fraction within the silicates was proven by the appearance of some new signals assigned to C 1s and N 1s in the XPS spectra (table 1).

For the MMT-148 the results of XPS analysis showed that this modified silicate exhibits a lower C1s atomic % in comparison with MMT-Epoxy and a total absence of Na 1s signal. This result leads to the conclusion that only a low quantity of polyetheramine was attached on the clay surface and the sodium exchange reaction with organic cation (protonated amine) successfully occurred.

In case of MMT-Epoxy the XPS results are in good agreement with the XRD analysis. The presence of Na 1s (1.7 %) signal and the high concentration of C 1s (20 %) demonstrated that the silanization agent (GOPTMS) was attached on the clay surface.

Thermogravimetrical characterization

The modification of montmorillonite with GOPTMS and polyetheramine EDR 148 was also studied by thermogravimetric analysis. Figure 5 shows the TG and DTG curves of unmodified and organophilized layered silicates.

The TG and DTG curves of unmodified MMT show that the clay suffers a dehydration at lower temperature and than can be considered thermally stable up to about 600°C when the dehydroxylation reaction starts [30].

In case of modified silicates (MMT-Epoxy, MMT-148) the thermal behaviour was significantly changed. The presence of organic fraction within the clay causes an increase of weight loss (13 % for MMT-Epoxy and 15 % for MMT-148) which was assigned to the degradation of organic fraction. The DTG curves of modified silicates contain some new peaks around 283 and 380 °C assigned to the organic fractions degradation. As one may observe from DTG curve of MMT-Epoxy the dehydroxylation process occured at lower temperature probably due to the catalytic effect of degradation fractions on the mentioned process.

	Atomic % Si 2p	Atomic % Al2p	Atomic % O 1s	Atomic % C1s	Atomic % N1s	Atomic % Na 1s	Atomic % Mg 1s
MMT-Na	25.6	9.6	59.8	-	-	3.3	1.7
MMT-Epoxy	21.3	5.2	49.6	20	-	1.7	2.2
MMT-148	24.9	7.5	54.6	8.4	1.9	-	2.7

Table 1
XPS RESULTS FOR UNMODIFIED AND MODIFIED MMTs

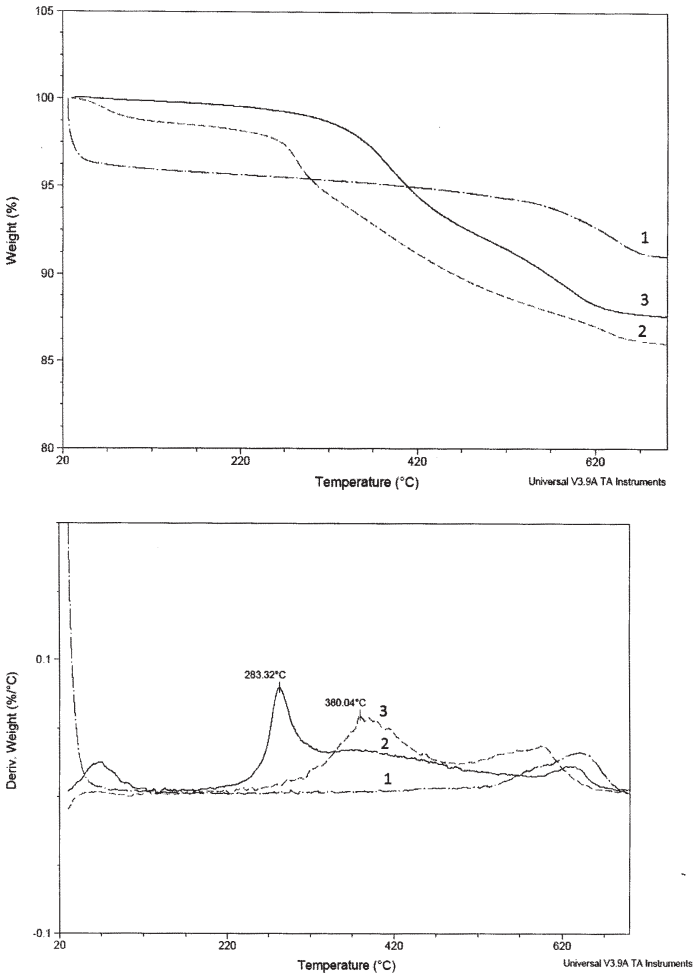


Fig.5. TGA and DTG curves for 1-MMT-Na, 2-MMT-148, 3-MMT-Epoxy

FTIR Analysis

The FTIR analysis results also confirmed the MMT organophilization (fig. 6).

The FTIR spectrum of unmodified MMT shows several characteristics peaks as follows: 3631; 3444 cm^{-1} (assigned to stretching vibration of hydroxyl groups), 1641 cm^{-1} (assigned to interlayer water), 1044 cm^{-1} corresponding to Si-O stretching vibration, 913 cm^{-1} assigned for O-H deformation of inner hydroxyl group; 524 cm^{-1} assigned for Si-O-Al (octahedral) bending vibrations, 466 cm^{-1} assigned for Si-O-Si bending vibrations [31].

The montmorillonite organophilization was demonstrated by the appearance of some new peaks at 2937, 2882, 2876 cm^{-1} assigned to the C-H stretching vibrations. Also a new peak at 1477 cm^{-1} assigned to the C-H bending vibrations was detected.

Synthesis and characterization of hybrid films

The hybrid films based on unmodified/modified montmorillonite and poly(vinyl alcohol) were designed to be used as host for 5FU encapsulation. Due to the presence of inorganic host which exhibits a special structure the drug encapsulation can take place within inorganic host via two routes: by (1) drug adsorption on the MMT surface via non-covalent interactions and (2) drug entrapment within the clay gallery.

FTIR characterization

Figure 7 shows the FTIR-ATR spectra of hybrid films which contains drug molecules (5FU).

The FTIR spectra indicate the presence of some interactions which occurred between the polymer matrix and inorganic host. Both components involved in the hybrid films synthesis contain hydroxyl groups or epoxy groups which can promote the formation of hydrogen bonding or some covalent bonds resulted from epoxy-hydroxyl reaction.

In the hybrid films there are different interactions like polymer-polymer interactions (PVA-PVA), polymer-drug interactions (PVA-5FU), halloysite-halloysite interactions (HNT-HNT), halloysite-drug interactions (HNT-5FU), polymer-halloysite interactions (PVA-HNT). The peak at 3305 cm^{-1} assigned to the hydroxyl groups stretching vibrations involved in the hydrogen bonding formed in the PVA films appears at different wavenumbers (3290 cm^{-1} for PVA-MMT-Epoxy-5FU films, 3294 cm^{-1} for PVA-MMT-5FU and 3293 cm^{-1} for PVA-MMT-148-5FU) in the hybrid films. This fact could be explained by the presence of new interactions established between PVA and unmodified/modified MMT through the hydroxyl/epoxy groups.

Due to the presence of MMT, the number of polymer-polymer interactions decreased in the hybrid films. Similar results were obtained by Y. Turhan and co-workers for the hybrid films based on poly(vinyl alcohol) with modified montmorillonite with 3-aminopropyltriethoxysilane [32].

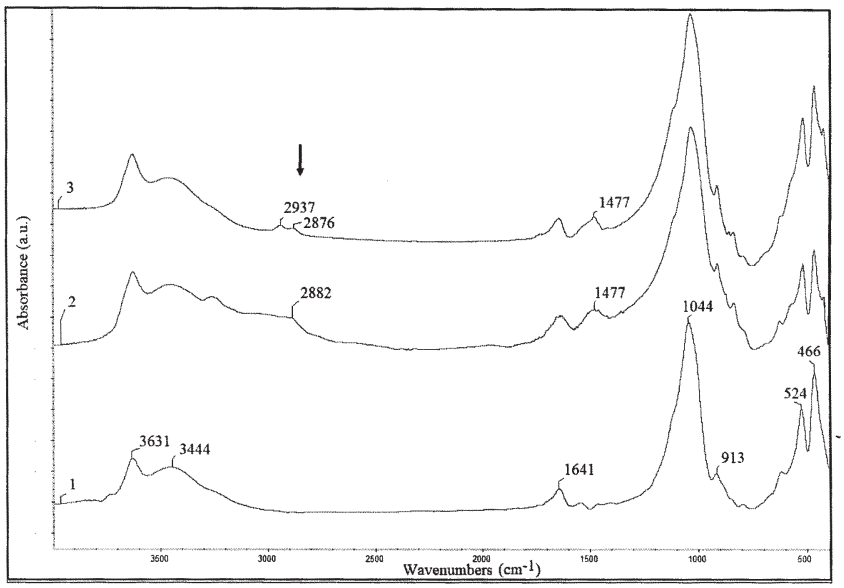


Fig.6. FTIR spectra of unmodified MMT-Na (1), MMT-148 (2), MMT-Epoxy (3)

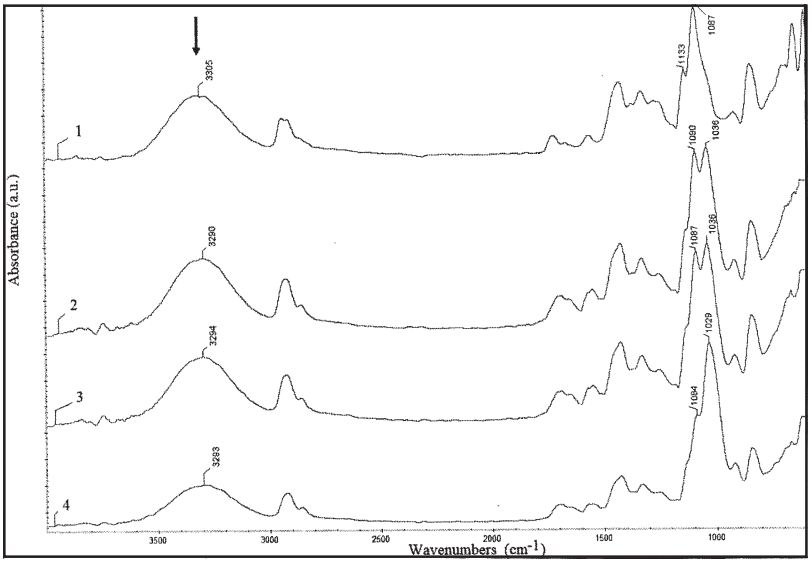
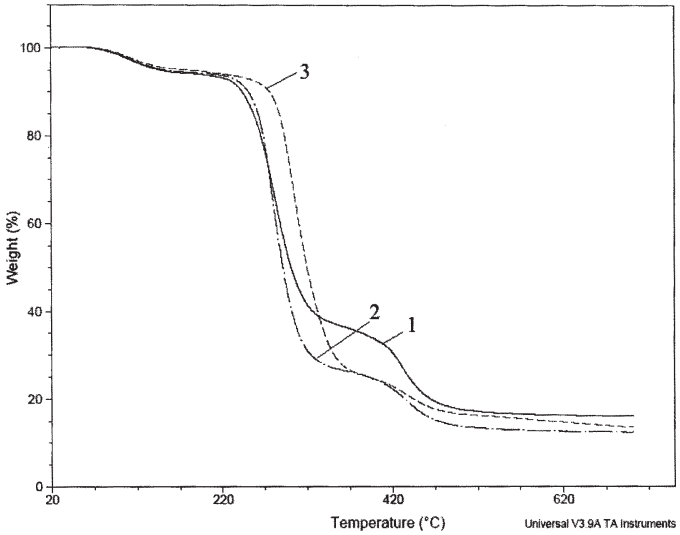
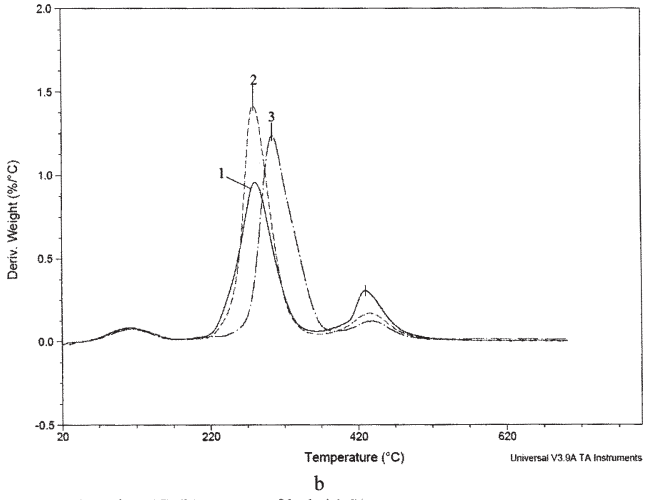


Fig.7. FTIR-ATR spectra of 1-PVA, 2- PVA-MMT-Epoxy-5FU, 3- PVA-MMT-Na-5FU; 4- PVA-MMT-148-5FU films



a



b

Fig.8. TG (a) and DTG (b) curves of hybrid films: 1-PVA-MMT-Na-5FU; 2-PVA-MMT-Epoxy-5FU; 3-PVA-MMT-148-5FU

TGA tests

The thermal stability of hybrid materials was investigated by monitoring the degradation temperature at 10 % weight loss ($T_{onset\ 10\ \%}$) (fig. 8-a,b).

The thermogravimetrical results showed that the presence of modified MMT significantly influences the thermal stability of the polymeric film in comparison with the films which contain unmodified MMT. $T_{onset\ 10\ \%}$ of PVA-MMT-Epoxy-5FU is higher with 8 °C than for PVA-MMT-5FU. The highest thermal stability was recorded for PVA-MMT-148-5FU. $T_{onset\ 10\ \%}$ is higher with 33 °C than for hybrid film which contains unmodified MMT.

UV-Vis analysis

The drug release from the synthesized hybrid materials was studied by UV-Vis analysis. The drug release tests indicate a different behaviour which was influenced by the silicate modifier agent type (fig.9).

In case of modified silicates (MMT-Epoxy, MMT-148) the 5FU release occurred more slowly than for hybrid systems based on unmodified montmorillonite. These results indicate the presence of additional interactions between modified inorganic host with drug and also with the polymeric matrix.

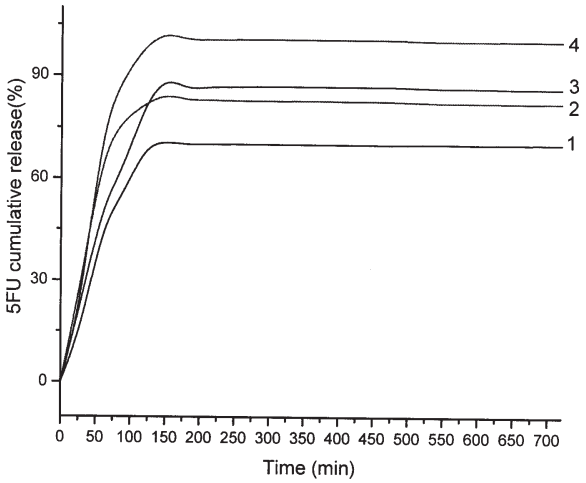


Fig. 9. Drug release curve profile from different hybrid materials: 1-PVA-5FU; 2 - PVA-MMT-148-5FU; 3-PVA-MMT-Epoxy-5FU; 4-PVA-MMT-Na-5FU

The highest drug release rate was observed for hybrid systems based on PVA and unmodified MMT.

Opposite results regarding the drug release were obtained for PVA films. In this case the absence of MMT favours the formation of a compact hydrogel due to the existence of a high number of polymer-polymer bonds.

The presence of MMT within the PVA matrix strongly influences the final structure of hydrogel. Due to the polymer-MMT interactions, the number of polymer-polymer interactions decreased.

Conclusions

Some new PVA-MMT hybrid materials were developed as host for 5FU drug entrapment. The presence of organic fraction grafted on the MMT surface or/and intercalated within clay layers strongly influences the properties of the final materials. The XPS and XRD analyses proved that the silanization agent used as clay modifier agent were grafted on the clay surface, while the protonated polyetheramine was also intercalated in the clay gallery by a cationic exchange reaction.

The drug release tests showed that the presence of MMT within the PVA matrix and the modifier agent type strongly influence the drug release profile.

The subject was also studied in [33,34].

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