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Utilization of MMT Clay and MMT-Chitosan for Platinol Drug Delivery

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ABSTRACT

MMT clay is naturally layered silicates, which is used to delay, and/or target drug release or even to improve drug dissolution. In this study, MMT clay was successfully modified with two types of modifiers, which are platinol drug and chitosan (CS) under different temperatures using different chitosan/MMT ratios in different modification time intervals to produce Platinol-MMT and Cs-MMT-Platinol hybrids. XRD and SEM. characterized the modified clay. The characterization via XRD demonstrate that, Modification of MMT clay with chitosan showed biggest interlayer spacing of 9.23 nm when using CS/MMT ratio of 2:1 at 60ºC for an hour. The loading efficiency of plationl by modified MMT with CS was reached to about 28% using 0.15 g initial drug weight in 1 h under 60ºC. Drug release was studied for both MMT-Platinol and Cs/MMT-Platinol hybrids and it was found that the release was directly proportional with the pH of the medium and reached to 100% after 12 h in case of releasing from Cs/MMT-Platinol hybrids using simulated intestinal fluid (pH 7.4).

Keywords: MMT-Chitosan/Platinol, Drug delivery, Vitro release, XRD, SEM

INTRODUCTION

The MMT clay have a long history to use as in drug formulation both as excipients and as active ingredient, however, some workers have studies of some drugs with clay and observed the reduced absorption of these drugs [1-3]. The main concept in modified the drug delivery technology for delayed, sustained and/or target drug delivery can be using clay minerals [4].

These have been an increased interest in drug delivery systems to involved biopolymer-clay nanocomposites. Nanocomposites are composed of different elements in which the filter material has at least one of its dimensions in the nanoscale. Polymers nanocomposites consist of a polymer or copolymer having nano particles or nano filler dispersed in the polymer matrix. To investigate interactions between process-structure- performance in polymer-clay nanocomposites these have made the systematic effect to investigate and implications for the processing and performances of drug delivery systems [5]. Recently various inorganic hybrid composites have emerged as an imperative class of drug delivery systems. Among them, layer silicate material e.g., Montmorillonate (MMT), have attracted a great deal of attention due to its capability to release rate of procainamide in the gastric region from MMT gallery in controlled manner (Kevadiya) [6]. The drugs of polymers matrix are loading by directly only suffer from low entrapment efficiency and burst release effects. Knowing the drawback of inorganic clay makes it easier through the Kaygusuz and Erim [7] for the entrapment of bovine serum albumin into alginate/montmorillonite nanocomposites. Montmorillonite has been used in medicinally the clay may be an effective treatment properties for many medical uses and it is known to be antibacterial properties [8-10]. The clay are advanced pharmaceutical excipient and active materials. The pharmaceutical clay such as kaolin and talc have less ion-exchange capacity, low cost and hydrophilicity [11-12]. The inorganic cation sodium with alkyl ammonium have been selected as the representative of polymers and hydrophobic matrix system which increase both the interlayer surface between the clay layers and higher drugs retaining ability of surface properties due to their more hydrophobic and water repelling nature [13-15].

Very recent years have studies is (Platinol) (Cisplatin) H6Cl2N2Pt is a chemotherapy agent. It is delivered and performed as a short term in normal saline for treatment of solid malignancies. It is platineem containing anti-cancers drugs; these Pt complexes react in

the body, bindery to DNA and causing the DNA strands to crosslink. Its clinical used to treat different types of cancers, including small cell lung cancer, bladder cells, ovarian cancer, lymphomas, cervical cancer and germ cell tumors [16].

Platinol (Cisplatin) is indicated as therapy to be employed as metastatic testicular cancer; metastatic ovarian tumor and advanced bladder cancer; the cure rate was improved from 10% to 85% and also used in Auger therapy Figure 1 [17].

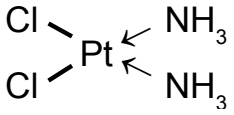

Figure 1: Chemical structure of Platinol (Cisplatin) drug

This work is aimed to using platinol and chitosan for modification of MMT to evaluate the feasibility of loading and release of Platinol drug with applicable efficiency and to elucidate the effect of biopolymer addition and MMT clay addition on the rate of platinol drug release.

EXPERIMENTAL

MATERIALS

The montmorillonite clay (MMT) with cation exchange capacity (CEC) 90 meq per 100 g was supplied by Süd –Chemie-Moosburg-Germany. Chitosan (CS) with medium molecular weight (92.700 g/mol) and deacetylation degree of 82.5 % was obtained from Sigma-Aldrich Company. Platinol ($H_6Cl_2N_2Pt$) was supplied from Chemocare Company-Egypt. Glacial acetic and hydrochloric acid as well as sodium hydroxide, potassium phosphate monobasic and sodium chloride were of pure laboratory grade chemical. All chemicals were used as received without any purification.

METHODS

Modification of MMT clay by platinol drug

MMT (1.0 g) was dispersed into 100 mL deionized water; the mixture was stirred for 1 h and then heated to 60ºC to obtain aqueous suspension of clay. The desired amount of platinol drug (1× and 2× concentrations of the clay based on CEC) and 2 mL of hydrochloric acid in 50 mL deionized water was added into the mixture, the pH value of the solution was adjusted to 6-8 and stirring was continued for 4 h. The reaction mixtures are then filtered and the concentration of drug in the filtrate is determined by UV spectroscopy at λ_{max}=246 nm Figure 2 [18].

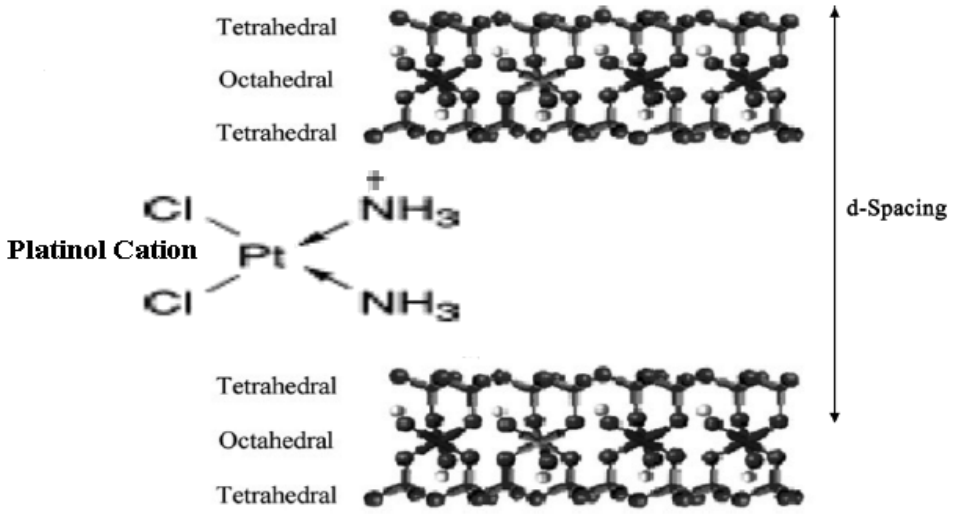

Figure 2: Structural arrangement of Platinol - MMT hybrid

Modification of MMT clay by Chitosan

Dry weight chitosan was dissolved in 2% v/v aqueous glacial acetic acid at a concentration of 2 Wt%. The prepared solution samples were subjected to centrifuging at 2000 rpm to remove the insoluble residual material [19]. In addition, MMT was swelled in 50 ml distilled water by magnetic stirring for 60 min at 30 ± 1ºC. Then added to the prepared chitosan solution with chitosan/MMT Wt ratio of 1/1, 1/2 and 2/1, followed by stirring for 4 h under different temperature (40º, 50º, 60º and 70ºC.) Then, CS/MMT solutions were filtered and dried under vacuum at 70ºC for 48 h.

Preparation of drug-loaded Chitosan modified MMT clay (CS-MMT-Platinol)

Different masses of Platinol (0.05, 0.1, 0.15 and 0.2 g) were dissolved with chitosan modified MMT sample, which was prepared under the optimum conditions of temperature and concentrations [20]. The mixture was subjected to a magnetic stirring at different reaction temperatures (40ºC, 50ºC, 60ºC and 70ºC) for different times (0.5, 1, 2 and 4 h) to affect cross-linking Figure 3.

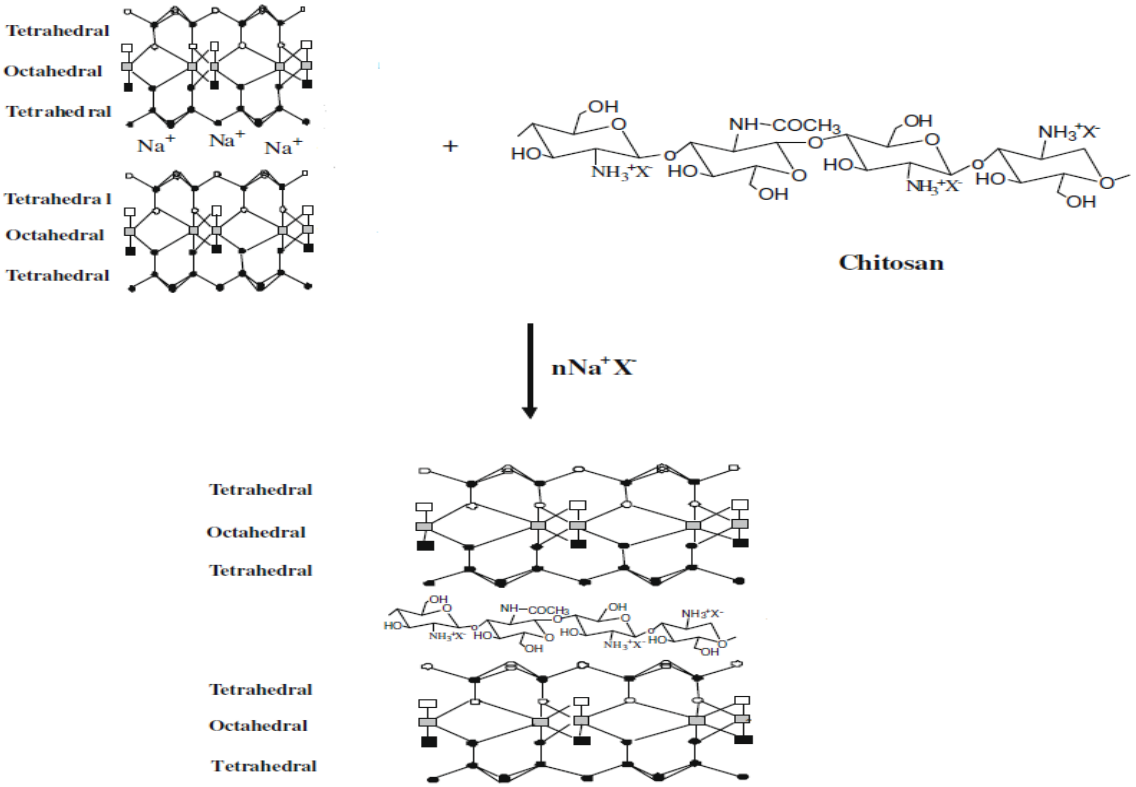

Figure 3: Schematic illustration of intercalation of chitosan in the interlayer space between the MMT clay

***In-vitro* release of Platinol from drug-loaded chitosan modified MMT clay**

In-vitro release of Platinol from MMT-platinol and chitosan-MMT- Platinol hybrids for 24 h were carried in phosphate buffered saline media of pH 7.4 and simulated gastric fluid at pH 1.2 using two different simulated fluid buffer solutions [21]. Simulated gastric fluid with pH 1.2 which was prepared by mixing 250 ml of 0.2 M HCl with 147 ml of 0.2 M KCl and simulated intestinal fluid with pH 7.4 which was prepared by mixing 250 ml of 0.1 M KH_2PO_4 with 195.5 ml of 0.1 M NaOH.

150 mg of MMT-Platinol or Chitosan/MMT- Platinol hybrid in 5 ml of buffer solution was taken in a round flask containing 300 ml dissolution medium, which was incubated in a constant temperature shaker water bath at 37 ± 0.5ºC. The flask was closed to prevent the evaporation losses from the dissolution medium. The shaking frequency was kept at 100 rpm. 5 ml of sample was withdrawn at regular time intervals and the same volume was replaced with a fresh dissolution medium. Samples were analyzed for platinol content by UV spectrophotometer at λ_{max}=246 nm. These studies were performed in triplicate for each sample and the average values were used in data analysis.

CHARACTERIZATION

X-ray diffraction (XRD) measurements were performed using a Philips powder- Diffractogram PW 1050 with ADM software and with Ni-filtered Cu K radiation. The accelerating voltage was 40 KV, and the current was 30 mA. The morphology and fracture surface of the composites were examined by Scanning electron microscope (SEM) analysis using Zeiss, DSM 962 microscope. UV-vis absorbance of Platinol solutions were measured using UV-vis spectrophotometer (Cary 500, Varian) equipped with a quartz cell having a path length of 1 cm at $\lambda_{max=}$246 nm.

RSULTS AND DISCUSIONS

Characterization of modified MMT clay

X-Ray Diffraction (XRD)

Modification of MMT clay by platinol drug

Figure 4 represents X-ray diffraction diagrams of pristine Montmorillonite clay nanoparticles and drug modified Montmorillonite depends on two different platinol drug concentrations based on Montmorillonite clay CEC. The basal spacing (d001) values were determined using Braggs equation and listed in Table 1.

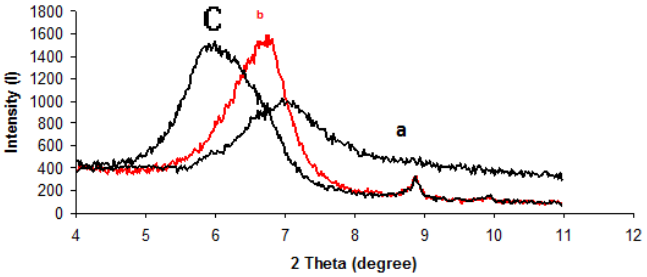

Figure 4: X-ray diffraction patterns for (a) Pristine-MMT, MMT modified by (b) 1x platinol and (c) 2x platinol drug

Table 1: XRD Data Obtained for Pristine MMT, MMT-Platinol and Cs/MMT

Pristine MMT clay		**2 θ**	**d Space (nm)**
		7.0	**5.23**
Effect of Platinol drug concentration on MMT - Platinol (based on CEC of MMT clay)	1× 2×	6.7 5.9	8.02 8.94
Effect of Cs/MMT ratio	1:2 1:1 2:1	6.8° 6.5° 5.8°	8.07 8.50 9.09
Effect of Temperature on CS/MMT	40°C 50°C 60°C 70°C	6.4° 5.8° 5.7° 5.7°	8.64 9.09 9.23 9.23

nλ=2d sinØ

From Figure 4, it is clear that, each sample has a definite peak at 2θ=7.0° for pristine MMT clay and shifted to smaller angles 6.7° and 5.9° for the MMT modified by platinol drug 1× and 2× concentration based on MMT clay CEC respectively.

The results obtained from Figure 4 and listed in Table 1 show that, MMT clay was successfully intercalated with platinol drug and the increasing of the concentration of platinol drug into 2× CEC concentration give increasing in d-spacing more than in the addition of 1× concentration.

Modification of MMT clay by chitosan

Figure 5 delineates the XRD models of MMT and MMT modified chitosan with different Cs/ MMT ratios at 50ºC. From the figure it is clear that, The XRD models of the MMT shows a diffraction peak at 2Ø=7.0°, relating to a d-spacing of 5.23 nm. The data for d-spacing are listed in Table 1. The 2Ø values indicate that the diffraction peaks of all MMT clay samples after modification are moved to smaller 2Ø values compared with the pure Montmorillonite clay. This proves that Montmorillonite clay was effectively intercalated with chitosan [19]. The 2Ø values also indicate that the increasing of chitosan ratio give further enhancement in the d-spacing more than increasing of more MMT clay ratio which is due to CEC of MMT clay and also due to a change in the composite structure of CS/ MMT composites [22].

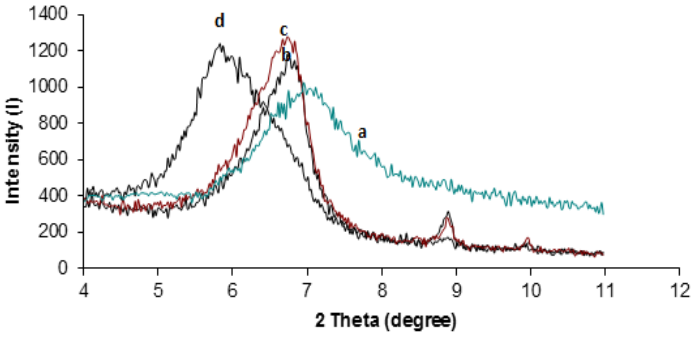

Figure 5: X-ray diffraction patterns for (a) Pristine-MMT, MMT modified by Chitosan at (CS/MMT) ratios of (b) CS/MMT (1:1), (c) CS/ MMT (1:2) and (d)CS/MMT (2:1)

Figure 6 illustrates the XRD patterns MMT modified by chitosan with Cs/MMT ratio 2:1 at different temperatures from 40 to 70ºC. From the figure, it is clear that, the diffraction peaks of all montmorillonite clay samples after modification are moved to smaller 2Ø values, which means an increasing in the d spacing with increasing temperature until 60ºC. Inclusion the presence of a display augmenting and the conversion into a less requested intercalated structure and a less connections in the direction perpendicular to the montmorillonite layers [23]. Where at higher temperatures, more polymer particles or fragments permeate into the galleries to enlarge the gallery, broaden the distribution of the gallery height and possibly exfoliation of individual layers occurs simultaneously. Similar strengthening temperature impact on the structure of polymeric nanocomposites has been explained by Galgali et al. [24],

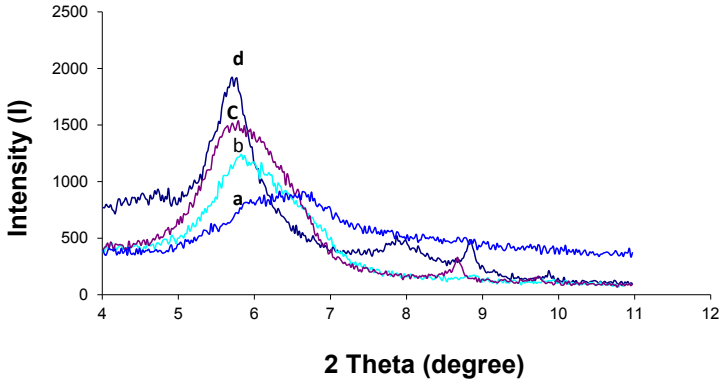

Figure 6: X-ray diffraction patterns for MMT modified by Chitosan at temperatures of (a) 40ºC, (b) 50ºC (c) 60ºC and (d) 70ºC

Vaia and Giannelis [25]. From the Figure and the data recorded in Table 1, it is additionally clear that, after 60ºC, 2Ø and d values are constant with expanding the temperature. This prove that the inter-planar spacing in the hexagonal structures diminishes with raising the heat treatment temperature, recommending that the inter-planar spacing could be temperature controlled [26].

Scanning Electron Microscope (SEM)

The investigation of the surface of prepared specimens by SEM is shown in Figure 7 which displays SEM of unmodified and platinol modified montmorillonite clay modified (2× concentration) in addition of MMT clay modified by chitosan. The SEM prove that platinol drug and chitosan are dispersed with MMT clay to produce MMT-platinol and MMT-chitosan hybrids respectively where the homogeneity of montmorillonite with platinol drug is less the homogeneity of montmorillonite with chitosan.

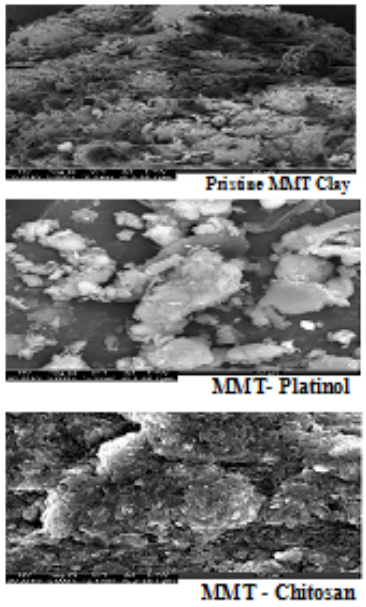

Figure 7: SEM for pristine MMT clay, MMT clay modified by platinol drug and MMT clay modified by chitosan

Preparation of drug-loaded chitosan modified MMT clay (CS-MMT-Platinol)

Effect of initial drug weight

The effect of the initial drug weight on drug loading percentage was studied at optimum CS/MMT ratio (2:1) and optimum temperature (60ºC) for 1 hour was illustrated in Figure 8. From the data illustrated figure, it is clear that, the loaded percentage of platinol drug is effected by the drug initial weight as shown in Figure 8 whereas the initial platinol drug weight increased, the amount of loaded drug was also increased which may be due to the increasing of the active gradients at the initial stage where it reached maximum drug loaded after 0.15 g of platinol drug. From the figure it can be concluded that 28% of platinol was loaded into CS/MMT hybrid.

Effect of drug loading temperature

The effect of drug loading temperature on drug loading percentage was studied at the platinol drug loading performance using optimum CS/MMT ratio (2:1) and optimum initial drug weight (0.15 g) for 1 hour at different loading temperatures (40-70ºC) and illustrated in Figure 9.

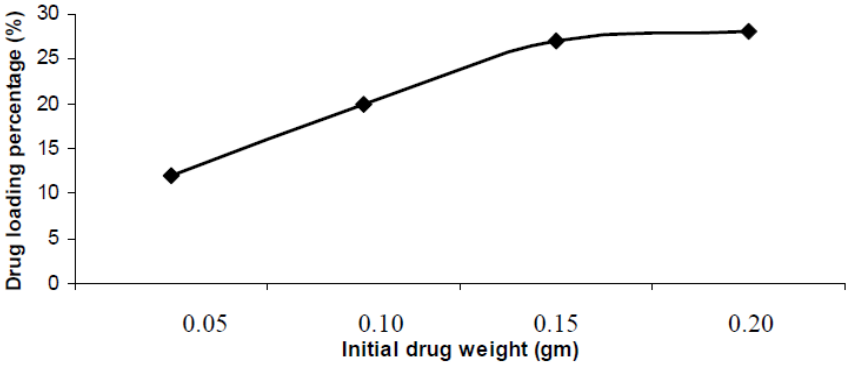

Figure 8: Effect of the initial drug weight on the drug loading percentage on CS/MMT hybrids

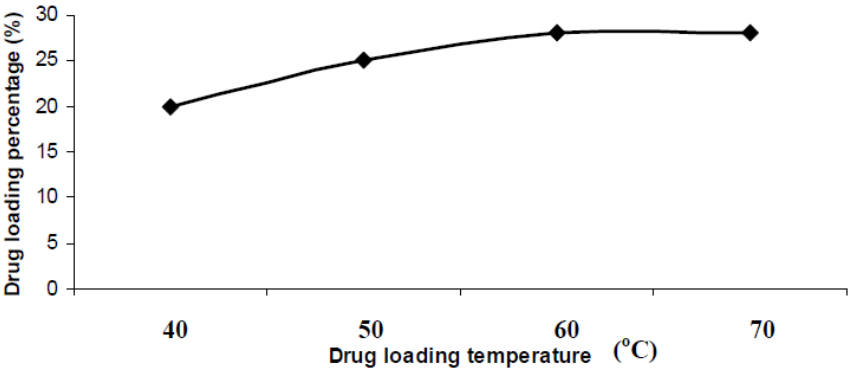

Figure 9: Effect of the drug loading temperature on the drug loading percentage on CS/MMT hybrids

From the figure, it is clear that, the platinol drug loading percentage increased as the loading temperature increased and reached maximum (28%) at 60ºC.

The increasing of the drug loading percentage with increasing loading temperature may be due to at high temperature, the efficiency of the drug penetration into Cs/MMT hybrids also increased.

Effect of drug loading time

The platinol drug loading into CS/MMT hybrid was studied at different time (0.5 – 4 h), constant loading temperature (60ºC), constant initial drug weight (0.15 g) and optimum CS/MMT ratio (2:1).

Figure 10 shows the relation between the drug loading time and drug loading percentage. From this figure, it can be seen that, the drug loading is very rapidly at first interval and reached maximum value (28%) after an hour then it remains constant up to 4 h.

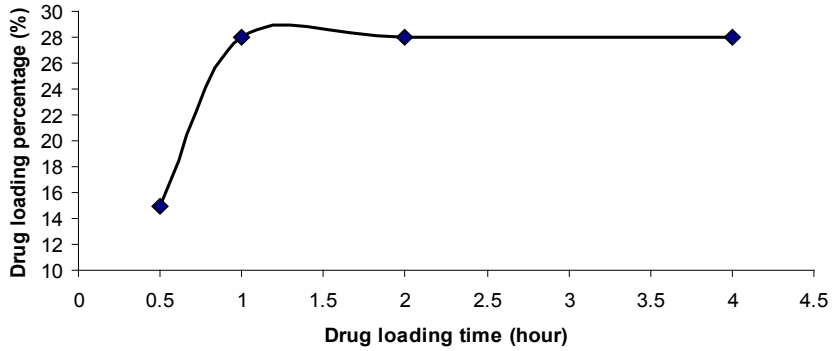

Figure 10: Effect of the drug loading time on the drug loading percentage on CS/MMT hybrids

The loading time 1 hour was taken as a best condition to avoid the partial drug intercalation in the subsequent experiments [27].

The data illustrated in the Figures 8-10 shows that, the optimum conditions for achieving maximum drug loading percentage on CS-MMT hybrid to obtain CS-MMT-Platinol are loading of 0.15 g platinol for an hour under temperature 60ºC.

***In-vitro* Release Profile**

The drug release rate was examined under two different pH values of the medium by suspending MMT-Platinol and CS-MMT-platinol separately in (pH 1.2) and (pH 7.4) under continuous shaking at 37 ± 0.5ºC for 24 h.

platinol drug release from MMT-Platinol andCS-MMT-platinol was measured by measuring the absorbance at ƛ –max=246 nm. The resulted date was illustrated in Figures 11 and 12.

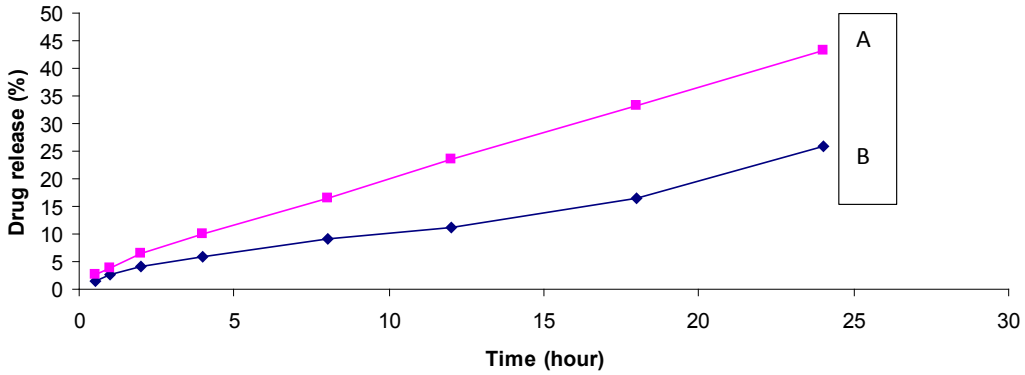

Figure 11: Release profile of Platinol drug from Cs/MMT hybrid in simulated gastric fluid (pH 1.2) from A) MMT-Platinol and B) CS-MMT-platinol at 37ºC.

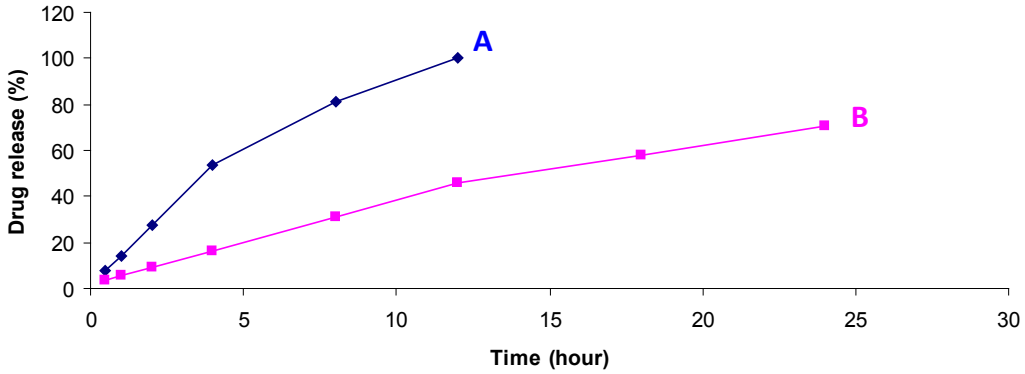

Figure 12: Release profile of Platinol drug from Cs/MMT hybrid in simulated intestinal fluid (pH 7.4) from A) MMT-Platinol and B) CS-MMT-platinol at 37ºC.

From the figures, it is clear that, for the two prepared hybrids MMT-Platinol andCS-MMT-platinol, the drug release rate depends on the pH value. The drug release values increased at higher pH where the release process may be interpreted based on the ion exchange process between the loaded drug and the alkali metal ions of the buffer [28].

From the figures, it is also concluded that the amount of platinol drug release from CS-MMT-platinol is higher and faster than amount of platinol drug release from MMT-platinol hybrid where about 43% of the loaded drug was released from CS-MMT-platinol and only 24% of the loaded drug was released from MMT-platinol within the 24 h using simulated gastric fluid (pH 1.2) while the release using intestinal fluid (pH 7.4) the drug release reaches 100% in case of CS-MMT-platinol and reached to about 70.7% from the loaded platinol drug in case of release from MMT-Platinol hybrid.

From the figure, it is also clear that, the platinol drug release reach 100% only from CS-MMT-platinol in pH 7.4 this is due to an equilibrium process and the interlayer cations cannot be exchanged completely [29].

CONCLUSION

MMT clay with interlayer spacing 5.23 nm and CEC 90 mg/100 g was successfully modified with two types of modifiers, which are platinol drug and chitosan (CS) for different temperatures using different chitosan/MMT ratios in different modification time intervals to produce Platinol-MMT and Cs-MMT-Platinol hybrids. MMT-Platinol hybrid shows biggest interlayer spacing 8.94 nm using 2× platinol concentration (based on CEC of MMT clay) where Cs/MMT hybrid displays the biggest interlayer spacing of 9.23 nm when using CS/MMT ratio of 2:1 at 60ºC for an hour. Platinol drug was successfully loaded into CS/MMT hybrid under several conditions as initial drug weight, loading temperature and different loading time intervals where the drug loading percentage reached to about 28 % using 0.15 g initial drug weight in 1 hour under 60ºC. The platinol drug release from both MMT-Platinol and Cs/MMT-Platinol hybrids was studied and the results showed that the release was directly proportional with the pH of the medium and reached to 100% after 12 h in case of releasing from Cs/MMT-Platinol hybrids using simulated intestinal fluid (pH 7.4).

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