Carvedilol drug-organo montmorillonite nanocomposites: Preparation, characterization and drug release studies

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Abstract

In this study the Carvedilol drug-organo modified montmorillonite (CV/OMMT) nanocomposites were prepared using different organo modified MMT (Nanomer 1.31PS, Nanomer 1.34TCN, Nanomer 1.44P) through solution intercalation method. The degree of intercalation, microstructure and morphology of the nanocomposites were characterized by FTIR spectroscopy, thermo gravimetric analysis and transmission electron microscopic analysis. The purpose of this study is to elaborate the drug loading capacities and drug release behaviours of different organo modified MMT (OMMT) on enhancing their swelling in aqueous medium. The *in vitro* drug release profiles from the CV/OMMT nanocomposites at pH 1.2 and pH 7.4 were also assessed. Simultaneously, the drug release kinetic parameters for all the CV/OMMT nanocomposites at both gastric and intestinal pH have also been discussed with established mathematical models.

Keywords: Carvedilol, montmorillonite, intercalation, nanocomposites, drug release**.**

Introduction

The concept of controlled drug delivery systems is of growing interest and improvements are being made on developing carriers that are harmless to the human body. Among the various organic and inorganic carriers, nanoclays are inorganic minerals, which have a high aspect ratio with at least one dimension of the particle in the nanometer range [**1**]. They are naturally occurring cation exchangers and have the ability to adsorb and desorb organic molecules, thus can act as efficient drug carriers [**2**]. Montmorillonite (MMT) is the most widely studied nanoclay mineral for sustained drug release due to its high cation exchange capacity and high sorption capacity [**3,4**]. The structure of MMT is a framework of layers, each layer consists of two silica tetrahedral sheets having opposite polarity and are connected by one alumina octahedral sheet in the middle [**5**]. The interlayers consist of hydrated monovalent and divalent cations (Na^+, Ca^{2+} or K^+) , which are adsorbed to balance the net negative charge induced by the imperfect crystal lattice on replacing the Al^{3+} ions in the octahedral layer by Mg^{2+} or Fe^{2+} [**6**] .

These days MMT nanocomposites are a promising class of materials due to the different properties of the intercalated materials into the interlayer of the layered silicates [**7**]. Various materials can be intercalated into the MMT through different reactions and the materials will be adsorbed by hydrogen bonds, ion-dipole interaction and Vander-Waal's forces. The materials can be intercalated in the solid, liquid or gas phase directly into the dried nanoclay mineral or may displace the hydrated molecules in the interlayers of the MMT [**10**]. The basal spacing of MMT is found to be 1.18 nm (2θ = 7.4) and the peak shifts from higher diffraction angle to lower diffraction angle indicating the presence of intercalated material in the interlayers of the MMT [**8**]. Recently, Wang et al. reported quaternized chitosan organic MMT nanocomposites for antimicrobial activity by solution mixing method [**9**]. MMT composites with alginate intercalated with diclofenac sodium drug by gelation method were reported and drug encapsulation efficiency increased with increase in MMT content [**8**]. Captopril intercalated MMT have been prepared using three intercalation methods and characteristic release of the drug has been studied [**10**]. Soy protein/MMT nanocomposite films were prepared for controlled release studies of the drug ofloxacin [**11**]. OMMTs have been fundamentally studied in the area of nanocomposites. They have been formed by the exchange of interlayer hydrated cations for organic molecules or cations called surfactants, therefore in OMMT the surface energy decreases and interlayer spacing increases [**12,13**]. The basal spacing of resulting organo nanoclays

depends on the chemical structure of the surfactant, the extent of cation exchange and the thickness of silicate layer [**14**].

Intercalation of carvedilol drug into MMT and drug release at different pH levels was reported recently. The amount of drug adsorbed on unmodified MMT as a function of pH was investigated in order to determine the optimum pH required for the adsorption of carvedilol [**15**]. The drug adsorption capacity is dependent on the pH of the solution and it seems to be higher in lower pH values (acidic pH). Since carvedilol is a basic drug, it readily ionizes in the acidic media and the anions of the drug interact with the cations in the interlayers of the MMT. This research work is an attempt to study the intercalation of carvedilol drug into different OMMT (Nanomer 1.31PS, Nanomer 1.34TCN and Nanomer 1.44P) through solution intercalation process.

The characterization results of the CV/OMMT nanocomposites have been reported and it may be concluded that the maximum drug loading capacity was achieved by Nanomer 1.44P. Furthermore, the drug release profile and release kinetics for the CV/OMMT nanocomposites taking four different theoretical models (Zero-order, First order, Higuchi and Korsemeyer-Peppas) at two different pH levels (pH 1.2 and pH 7.4) have been discussed.

Experimental

Materials and methods

Different OMMTs such as Nanomer 1.31PS, Nanomer 1.34TCN and Nanomer 1.44P were supplied by Sigma Aldrich in collaboration with Nanocor®. All the OMMTs are MMT nanoclay. Surface modified with different organic cations. Nanomer 1.31PS is MMT nanoclay surface modified with 0.5-5 wt.% aminopropyltriethoxysilane and 15-35 wt.% octadecylamine. Nanomer 1.34TCN is MMT nanoclay surface modified with 25-30 wt.% methyl dihydroxyethyl octadecyl ammonium. Nanomer 1.44P is surface modified MMT nanoclay with 35-45 wt.% dimethyl dialkyl (C14-C18) amine. All other chemicals used were of analytical grade. Industrial samples of carvedilol drug (melting point: 113-115 °C) were kindly supplied by Medreich pharmaceuticals Pvt. Ltd. and used without any further purification.

Preparation of CV/OMMT nanocomposites

There are number of methods for the synthesis of drug/MMT nanocomposites out of which solution intercalation, melt intercalation and grinding intercalation methods are prominently used. In this work, solution intercalation method for different CV/OMMT nanocomposites has been discussed since the highest drug loading capacity is achieved in a shorter period of time through solution intercalation when compared to the other two processes [**10,15**].

Solution intercalation method

Optimization of nanoclay colloidal dispersion

Different OMMT nanoclay solutions (Nanomer 1.31PS, Nanomer 1.34TCN, Nanomer 1.44P) of 1% were prepared in aqueous medium and kept for swelling at 28 °C for 15 h and ultra-sonicated for 2 h. The mixture was gently agitated with a magnetic stirrer for 24 h to achieve good dispersion. The solutions were then allowed to settle for 6 h. The volumetric change shows that among the three OMMT nanoclay solutions, Nanomer 1.44P had shown the maximum swelling **(Fig. 1).**

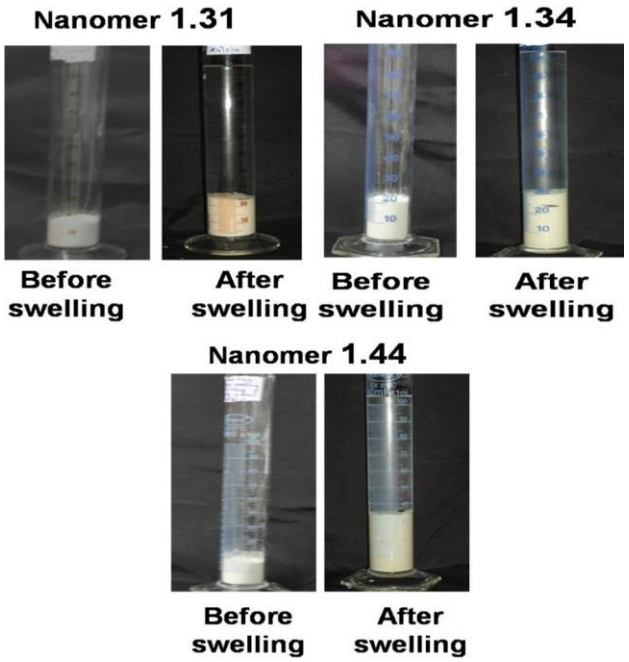


Fig. 1. Colloidal dispersions of OMMT and CV/OMMT systems prepared by solution intercalation

The swelling of OMMT resulted in the increase of interlayer spacing, which is necessary for drug loading. The nanoclay particles were suspended in a colloidal state in the mid portion of the solution. The mid portion was collected and used for further study. The pH of the nanoclay suspensions were adjusted to 4 using 0.1 N HCl solutions. Thus, the three different nanoclay solutions with pH 4 were stirred and heated gradually from 28 to 70 °C.

Intercalation of carvedilol into OMMT

The solution mixtures were dispersed with 100 mg carvedilol each and the temperature was maintained at 70 °C. The intercalation was carried out for 1, 2, 3 and 4 h. The dispersion was centrifuged at 3500 rpm for about 15 min. The supernatant liquids were collected separately and washed thrice with acetone, water and mixture of acetone and water (1:1 v/v) respectively to remove the free drug molecules. The OMMT residues were then dried at 28 °C and taken for further analysis.

CV/OMMT in vitro release studies

The *in vitro* drug release study was performed in a constant temperature (37 ± 3 °C) bath fitted with a round bottom flask with 850 ml buffer media. A buffer solution of pH 1.2, a simulated gastric fluid was prepared by mixing 250 ml of 0.2 M HCl and 147 ml of 0.2 M KCl. A buffer solution of pH 7.4, a simulated intestinal fluid was prepared by mixing 250 ml of 0.1 M KH_2PO_4 and 195.5 ml of 0.1 M NaOH. A dialysis membrane bag with 20 ml of CV/OMMT dispersions was suspended in the dissolution media. The rotation speed was set at 100 rpm and temperature was maintained at 37 ºC. At predetermined time intervals, 5 ml of the dissolution medium was taken, and was replaced with fresh buffer solution of same quantity. The released carvedilol concentration was determined by UV absorption at 217 nm and 210 nm for acidic and basic buffers respectively.

Drug release kinetics

The *in vitro* drug release data was fitted into the established mathematical models to assess the carvedilol release at two different pH levels: gastric pH 1.2 and intestinal pH 7.4. For zero order kinetics, the relationship between the rate of drug release and its concentration was examined from a plot of percentage drug release vs. time:

$$Qt = Q_0 + Kt \quad (1)$$

Where, Q_0 = initial amount of drug, Qt = cumulative amount of drug release at time t, K_0= zero-order rate constant and t = time in h.

The first order kinetics was assessed through a plot of log percentage of drug remaining vs. time:

$$\log Qt = \log Q_0 + K_1 t/2.303 \quad (2)$$

Where, K1 = first-order rate constant

Higuchi model was used to assess the diffusion mechanism of the drug through a plot of percentage of drug vs. square root of time:

$$Qt = KH\ t^{1/2} \quad (3)$$

Where, Q = cumulative drug release at time t, KH = constant reflective of the design variables of the system.

The Korsmeyer–Peppas model is used to identify the release mechanism of a drug/ drug carrier system and was employed to assess data collected during the first 210 min of the *in vitro* experiment.

$$Mt / M\infty = Ktn \quad (4)$$

Where, $Mt/M\infty$ = fraction of drug released at time t, K = rate constant and n = release exponent.

Characterization

The concentration of Carvedilol was measured by recording the UV spectra from UV-Vis absorbance spectrophotometer (SHIMADZU UV-240) equipped with a quartz cell having a path length of 1 cm in the medium of acetone (99.0 %).Infrared spectra (KBr disks) were recorded using a PERKIN-ELMER Spectrum RX1, FTIR V.2.00 spectrophotometer. The thermo gravimetric determinations (37–800 °C, 10 °C min-1; TA instruments TGA Q50) were carried out under nitrogen. The transmission electron micrographs (TEM) and high resolution transmission electron micrographs (HRTEM) were taken for morphological analysis with JEOL 3010 field emission electron microscope with an accelerating voltage of 300 kV.

Results and discussion

CV/OMMT intercalation by spectroscopic analysis

The drug loading capacities of the three different OMMTs (Nanomer 1.31PS, Nanomer 1.34TCN and Nanomer 1.44P) are presented in the Figure 7 as analyzed using the UV-Vis spectrophotometer. The drug loading capacities of Nanomer 1.31PS and Nanomer 1.34TCN were 479.59 mg g-1 and 436.25 mg g-1 respectively. The drug loading capacity achieved by Nanomer 1.44P was 542.26 mg g-1 in solution method. Nanomer 1.44P showed the highest dug loading capacity among the three OMMTs.

The interlayer spacing values of MMT and three different OMMTs have been compared **(Table 1, Fig.2).** The interlayer distance of MMT is 1.18 nm and is lower than the three OMMTs. The interlayer spacing of Nanomer 1.31PS and Nanomer 1.34TCN is 2.19 nm and 1.85 nm respectively [**16,17**].The drug loading capacities of Nanomer 1.31PS and 1.34TCN is 1.17 mmol g^{-1} and 1.07 mmol g^{-1} respectively. Nanomer 1.44P has the interlayer spacing of 2.58 nm [**18**], thus may have the higher drug loading capacity of 1.33 mmol g^{-1} among the three nanomers. The intercalation process was successful due to the interaction of anions of the drug with the organic cations in the interlayer spacing of the different OMMT. Therefore, it is evident that interlayer spacing is an important factor for maximum drug loading in MMT and different OMMTs.

Table 1. Basal spacing of MMT and OMMT's (Nanomer 1.31PS, Nanomer 1.34TCN and Nanomer 1.44P).

Type of nanoclay	Drug loaded amount (mmol/g)	Interlayer distance before drug loading (nm)
MMT	—	1.18
Nanomer 1.31PS	1.17	2.19
Nanomer 1.34TCN	1.07	1.85
Nanomer 1.44P	1.33	2.58

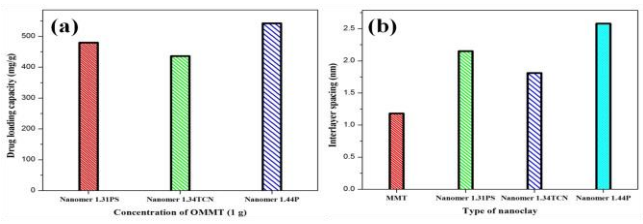


Fig. 2. Drug loading capacity of different CV/OMMT nanocomposites prepared by solution intercalation (a) and Interlaying spacing of MMT, Nanomer 1.31 PS, Nanomer 1.34 TCN and Nanomer 1.44 P.

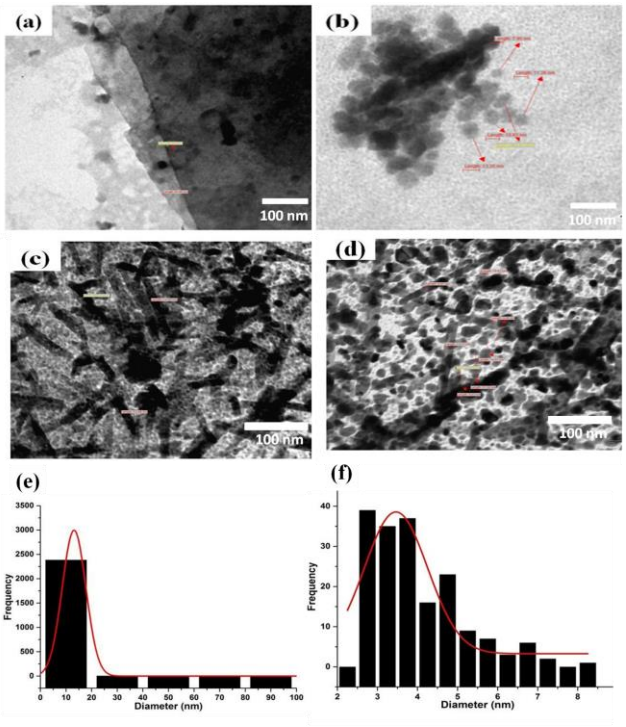


Fig. 3. TEM micrographs of (a) Interlayers of OMMT (b) OMMT particles (c) Exfoliated OMMT layers (d) Exfoliated OMMT layers with carvedilol drug particles

Transmission electron microscope analysis

The transmission electron micrographs **(Fig.3)** of (a) interlayers of OMMT (b) organo modified MMT (c) Exfoliated OMMT with drug particles and (d) Exfoliated OMMT layers have been demonstrated. The micrograph **Fig. 3 (a)** shows the interlayers of OMMT, which provides the possibility for the intercalation of drug by interaction of cations between the layers with the anions of the drug molecules. The **Fig.3 (b)** shows the aggregated spherical particles of OMMT along with the layer of the nanoclay. The exfoliated OMMT layers showed in **Fig.3 (c)** gives a particle size distribution of around 15 nm and the individual layers lose their geometry. The **Fig.3 (d)** shows exfoliated OMMT layers with the drug particles dispersed with the layers, and showed a size distribution of around 3 to 5 nm. Thus, the layers of nanoclay should not lose their geometry for the intercalation of drugs in the OMMT layers.

FTIR analysis

The FTIR spectra **(Fig. 4 a, b)** of all the CV/OMMT nanocomposites show broad band around 1,200-1,300cm^{-1} assigned to Si-O-Si and Si-O stretching vibrations present in the OMMT. A band around 1,600 cm^{-1} was observed for -OH bending vibrations due to the adsorbed water in the OMMT. OMMT's have been formed by modifying MMT with certain surfactants. The spectrum of CV/Nanomer 1.31PS shows two peaks of medium intensity at 3,416 cm^{-1} and 3,523 cm^{-1} indicating the presence of a primary amine. In the spectra of both CV/Nanomer 1.34TCN and CV/Nanomer 1.44P, a band corresponding to N-H stretching at around 3,415 cm^{-1} was observed thus confirming the presence of primary amine. All the three spectra also have a small range peak around 2,960-2,850 cm^{-1} showing the presence of long chain alkyl group attached with the amine group. The peak corresponding to the alkyl groups is sharper and intense for CV/Nanomer 1.44P, which characterizes the presence of more number of alkyl groups in the nanoclay making it suitable to intercalate the hydrophobic drug carvedilol into the hydrophobic nanoclay [**10**].

This could be a possibility for Nanomer 1.44P to show higher drug loading capacity compared to Nanomer 1.31PS and Nanomer 1.34TCN. The spectral studies of Carvedilol drug **(Fig. 4 c, d)** shows a band of -OH stretching at around 3,620 cm^{-1}. A broad peak around 1,450-1,650 cm^{-1} was observed due to the aromatic C-H band stretching. The peaks around 400-450 cm^{-1} and 600-800 cm^{-1} correspond to C-N-C bending and aromatic ring deformation.

In the three CV/OMMT nanocomposite spectra, all the peaks similar to the CV drug were found indicating the intercalation of the drug. The intensity of respective functional groups in the carvedilol and OMMT has changed due to the adsorption of the drug. The drug has been adsorbed in the interlayers through electrostatic attraction, hydrogen bonding and Vander Waal's forces of attraction. The adsorption of carvedilol in the OMMT was further evidenced with the reduction in N-H wave numbers or the intensity of the N-H peaks [**15**].

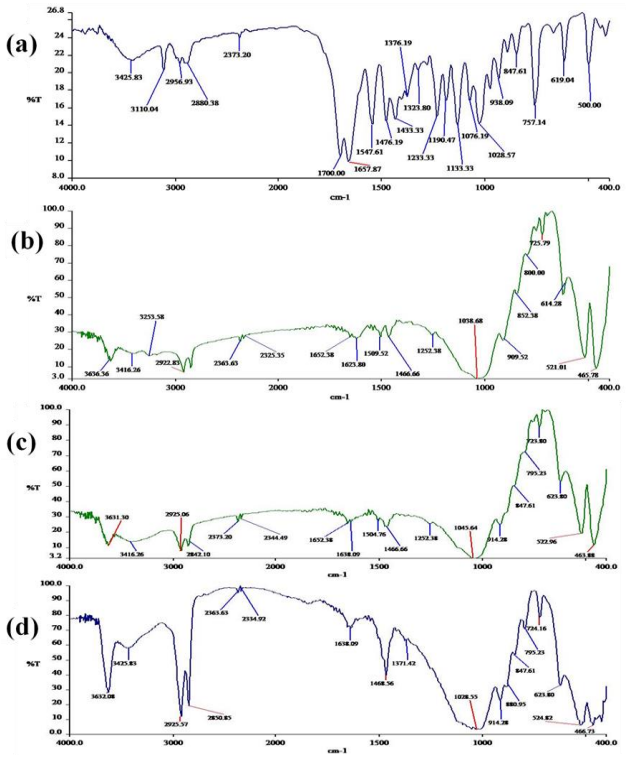


Fig. 4. FTIR curve of (a) Carvedilol drug, (b) CV/Nanomer 1.31PS nanocomposite, (c) CV/Nanomer 1.34TCN nanocomposite and (d) CV/Nanomer 1.44P nanocomposite

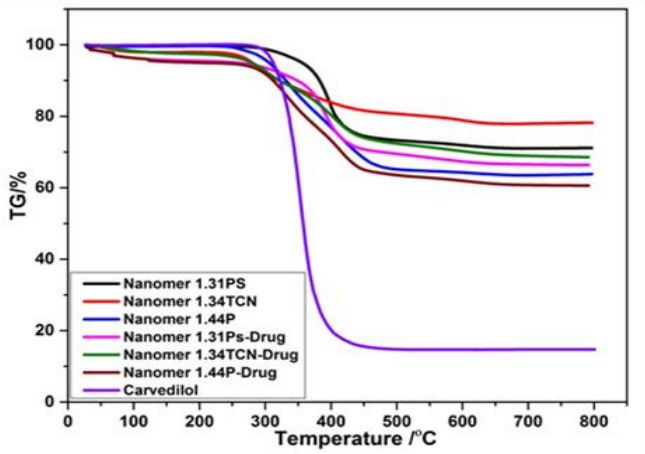


Fig.5. Thermograms of pure OMMT's and CV/OMMT nanocomposites.

Thermogravimetric analysis

The TGA curves **(Fig. 5)** of the different OMMT, CV/OMMT nanocomposites and carvedilol show three steps of thermal degradation in the temperature range of 100-800°C. The thermal degradation between 100-150°C corresponds to desorption of water from the OMMT. The second step of thermal degradation between 250-400°C indicates the decomposition of organic molecules and drug molecule present in the interlayers of the OMMT. The third step of thermal degradation is in the temperature range of 450-600°C might be due to the oxidation of partially decomposed organic molecules under airflow. The actual drug loading **(Table 2)** is determined by the thermo gravimetric analysis. Interestingly, the highest mass loss shown by CV/Nanomer 1.44P nanocomposite indicated the maximum intercalation of carvedilol in Nanomer 1.44P as analysed in UV spectroscopy studies.

Table 2. Thermo gravimetric analysis values of carvedilol, OMMT and CV/OMMT nanocomposites.

Drug carrier biomaterial	Residual mass (%)	Mass decomposed (%)	Drug loaded (%)	Actual drug loading capacity (mg/g)	Drug loading capacity (mg/g)
CV/Nanomer 1.31PS	66.37	33.63	11.30	113.0	479.59
CV/Nanomer 1.34TCN	68.56	31.42	9.82	98.2	436.25
CV/Nanomer 1.44 P	60.63	38.37	15.06	150.6	542.26
Nanomer 1.31 PS	77.67	21.33	—	—	—
Nanomer 1.34 TCN	78.38	21.62	—	—	—
Nanomer 1.44P	75.69	24.31	—	—	—
Carvedilol	0	100	—	—	—

Carvedilol in vitro release profile

The *in vitro* drug release pattern is plotted between cumulative % drug release (CDR %) and time (hours) for three CV/OMMT nanocomposites in **Fig. 6.** Nanomer 1.31PS and Nanomer 1.34TCN with drug loading capacities of 1.17 mmol g^{-1} and 1.07 mmol g^{-1} have released 79.6% and 53.2% CV respectively in the simulated gastric pH 1.2 and 76.5 % and 94.5 % respectively in simulated intestinal pH 7.4. The drug loading capacity of 1.33 mmol g^{-1} in CV/Nanomer 1.44P has showed a drug release of 61.5% CV in acidic medium and 38.7% CV in alkaline medium during 24 h. The CV/OMMT nanocomposite with higher drug loading capacity had a slower release rate in the intestinal pH thus showing a sustained release and affording an intestine selective drug delivery system. A diagrammatic representation of CV/OMMT nanocomposites have been shown in **Fig.7**.

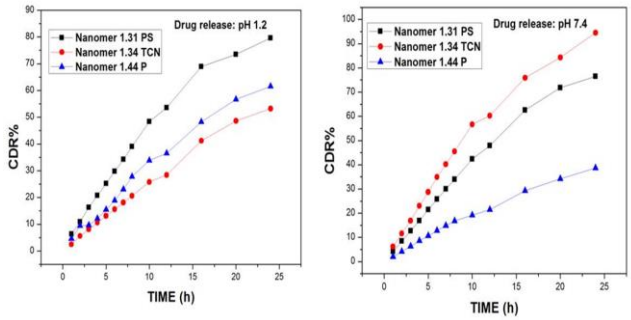


Fig. 6. Drug release patterns of CV/OMMT nanocomposites at gastric pH 1.2 and intestinal pH 7.4.

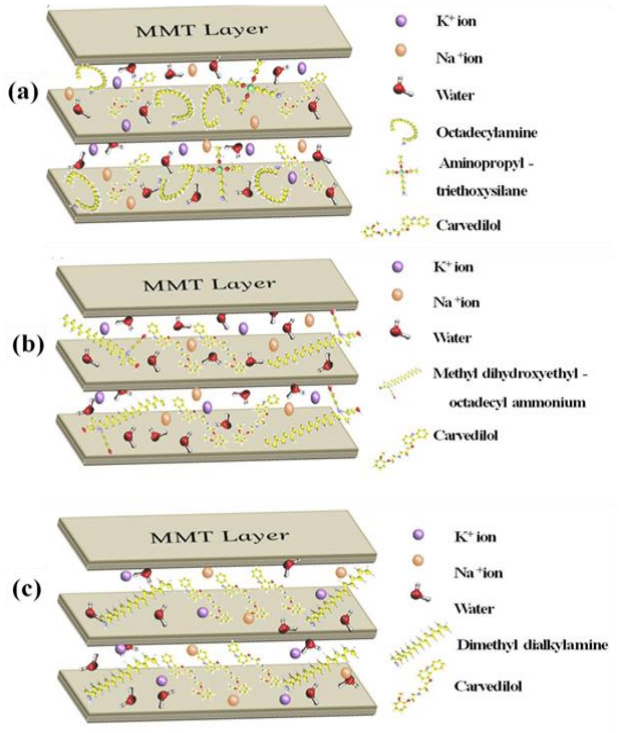
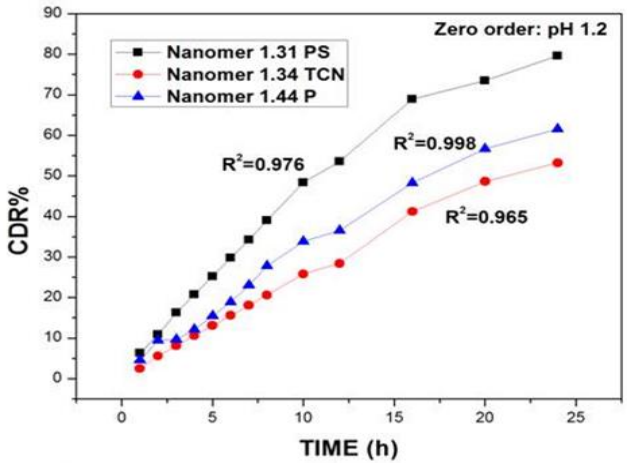


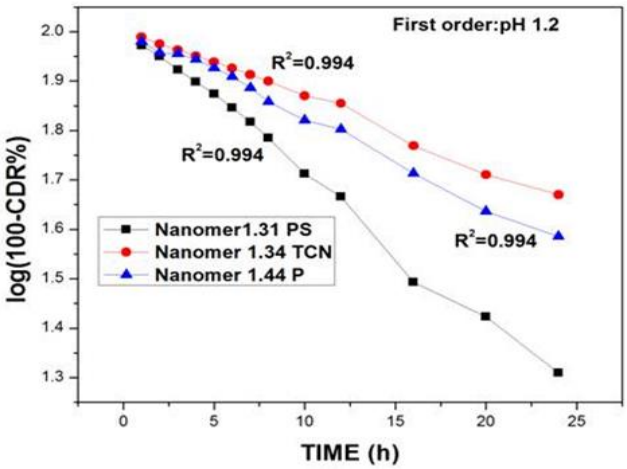
Fig. 7. Schematic representation of CV/OMMT nanocomposites as obtained by solution intercalation process: (a) CV/Nanomer 1.31PS (b) CV/Nanomer 1.34TCN and (c) CV/Nanomer 1.44P.

Drug release kinetic analysis of CV/OMMT nanocomposites

The *in vitro* release **(Fig. 8 and 9)** of CV from CV/OMMT has been fitted into theoretical models at both acidic and intestinal pH. On comparing the regression coefficient values (r^2) in **Table 3** and **Table 4,** CV/Nanomer 1.31PS and CV/Nanomer 1.44 P followed first order kinetic release at both acidic and alkaline pH. Thus, the release of drug is proportional to the amount of drug remaining in the OMMT nanoclay. Hence, the amount of drug released will diminish with unit time. CV/Nanomer 1.34 TCN fits into Korsemeyer-Peppas model at acidic pH while in alkaline pH it fits into Higuchi model.

The diffusion coefficient (n) in **Table 3** and **Table 4**, describes the mechanism of the drug release. The values $0.45 < n < 0.89$ indicates non-Fickian transport or anomalous transport of drug which is due to drug diffusion in the matrix and relaxation of the clay layers [**19**]. Such type of transport has been shown by CV/Nanomer 1.31 PS and CV/Nanomer 1.44 P at acidic pH whereas CV/Nanomer 1.34 TCN shows it in alkaline pH. The diffusion coefficient $n > 0.89$ indicates Super Case II transport mechanism, which occurs only due to the relaxation of the clay layers [**20,21**]. CV/ Nanomer 1.31 PS and CV/Nanomer 1.44 P shows Super Case II transport in alkaline pH while CV/Nanomer 1.34 TCN shows such mechanism at acidic pH.





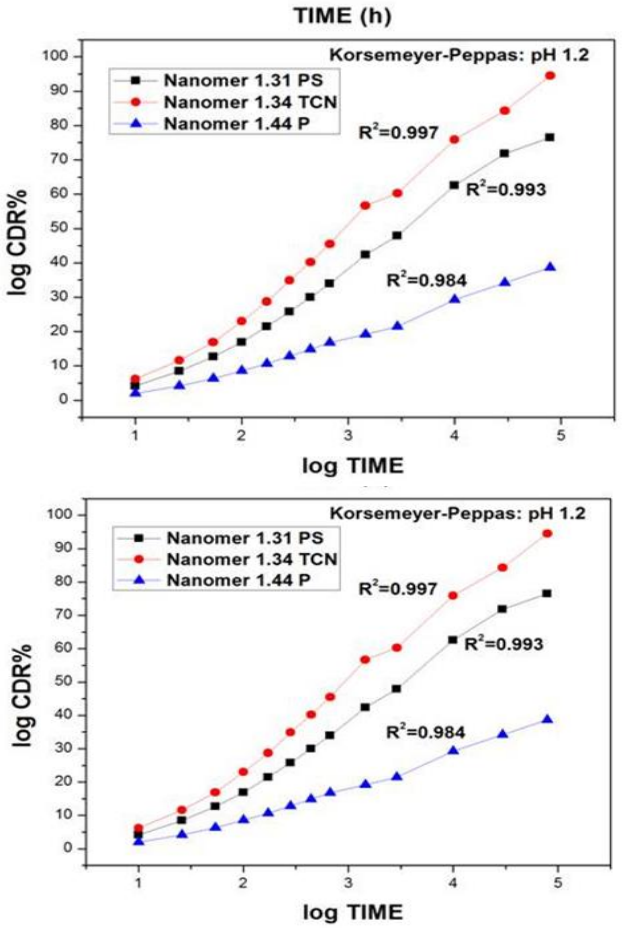


Fig. 8. Zero order, first order, Higuchi and Korsemeyer-Peppas kinetic models at pH 1.2

Table 3. Release kinetic parameters of carvedilol release at pH 1.2.

CV/OMMT nanocomposite	Zero order	First order	Higuchi	Korsemeyer-Peppas	
	r^2	r^2	r^2	r^2	n
CV/Nanomer 1.31PS	0.960	0.994	0.989	0.993	0.830
CV/Nanomer 1.34TCN	0.991	0.994	0.976	0.997	0.959
CV/Nanomer 1.44P	0.982	0.994	0.978	0.984	0.845

Table 4. Release kinetic parameters of carvedilol release at pH 7.4

CV/OMMT nanocomposites	Zero order	First order	Higuchi	Korsemeyer-Peppas	
	r^2	r^2	r^2	r^2	n
CV/Nanomer 1.31PS	0.976	0.995	0.989	0.994	0.935
CV/Nanomer 1.34TCN	0.965	0.958	0.993	0.990	0.878
CV/Nanomer 1.44P	0.988	0.997	0.988	0.993	0.928

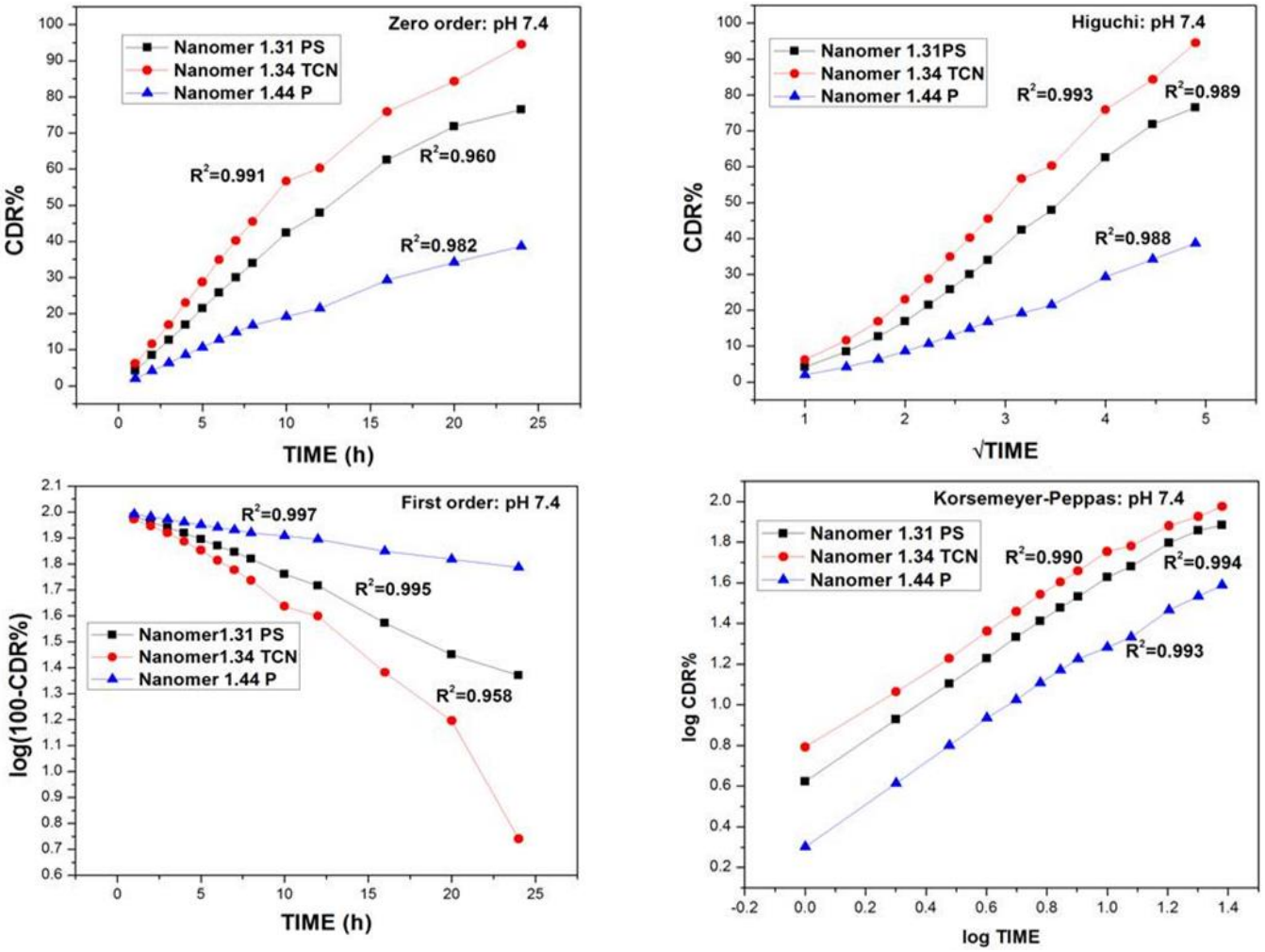


Fig. 9. Zero order, first order, Higuchi and Korsemeyer-Peppas kinetic models at pH 7.4.

Conclusion

Nano drug delivery systems that combined the benefit of organic drug molecules with the excellence of organically modified nanoclay materials were prepared via solution intercalation method. The nanocomposite systems prepared using three different organo modified MMT with carvedilol drug were characterized. The maximum drug loading capacity of 1.33 mmol g-1 was achieved by CV/Nanomer 1.44P nanocomposite as compared to other two CV/OMMT nanocomposites. The interlayer spacing in the OMMT gave the possibility of intercalation of the drug by the observation of TEM analysis. CV/Nanomer 1.44P had the highest mass loss among the three CV/OMMT nanocomposites, indicating higher drug loading capacity. It shows a sustained release pattern with a slower release rate in the intestinal pH. The carvedilol release rate in simulated intestinal fluid (pH 7.4) is highest for CV/Nanomer 1.31PS while in simulated gastric fluid (pH 1.2) the release rate is highest for CV/Nanomer 1.34TCN. This finding of internal flexibility of the clay by organo modification would open a new opportunity to develop drug delivery systems with additional significance like higher drug loading capacity and sustained release pattern compared to CV/MMT nanocomposite.

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Author's contributions

Conceived the plan: xx, xy, yz; Performed the expeirments: xx, xy; Data analysis: xx yz; Wrote the paper: xx, xy, yz (xx, xy, yz are the initials of authors). Authors have no competing financial interests.

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