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Open Access Research Article

Synthesis, Characterization and Drug delivery of Verapamil Hydrochloride loaded Montmorillonite Nanocomposite Beads

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ABSTRACT

In the present research programme, Verapamil Hydrochloride loaded Sodium Alginate/Polyethylene oxide/Montmorillonite nanocomposite beads were prepared by using gelation method. Sodium alginate (SA) and Poly ethylene oxide (PEO) with different ratios were blended with different weight ratios of MMT solution. The nanocomposite beads were characterized Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscope (SEM), X-ray diffraction (X-RD). FTIR was used to understand the hydrogen bonding between SA, PEO, MMT and drug. The X-RD studies were performed to understand the crystalline nature of drug after encapsulation into the beads. SEM was used to study the surface morphology of nanocomposite beads. In vitro studies were carried out in buffer media by using UV-vis spectroscopy(λ_{max}-263nm) at pH 7.4. The Controlled drug release studies were observed upto 12hrs.

Keywords: Sodium Alginate (SA), Poly ethylene oxide (PEO), Montmorillonite (MMT), Verapamil Hydrochloride (VPHCl), Nanocomposite beads and Drug Delivery

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INTRODUCTION

In recent years, researcher's shows much interest in the preparation of Nanocomposite materials for biomedical applications. Nanocomposites are composite materials in which at least one phase shows dimensions in the nanometer range. These nano-materials exhibit unique properties for which they are considered as the materials of the 21st century. The nanocomposite materials are of great importance for many industries because major improvements in functional and structural properties in material applications. The growing demand for nanocomposite material shows a promising future. The application of such material is strongly influencing the industry of medicine and pharmacy [1].

The site specific drug delivery provides an opportunity for optimum pharmacological activity of drug. Recently special attentions have been paid to find novel approaches to control the rate of drug release by means of carrier systems, where the drug should be dispersed in an inert matrix. Polymer based nanocomposites are of great importance as controlled drug delivery vehicles due to their unique structures and properties. These nanocomposites are prepared using inorganic materials including Montmorillonite (MMT), Hydroxyapatite (HA), calcium deficient hydroxyapatite[2,3], mineral clays[4-8], and silica[9]. They possess improved mechanical properties, swelling properties, drug loading efficiency and controlled release behaviour as compared to bulk counterparts. Clay minerals (layered silicates) have been proposed as fundamental constituents of several MDDS, with different purposes and acting through various mechanisms[3]. The intercalation of organic species into layered inorganic materials provides a useful and convenient route to prepare organic-inorganic hybrids that combine the properties of both inorganic host and organic guest [4,5]. A very interesting possibility is to use clay mineral polymer composites to modify drug release. Although clay minerals and polymers are frequently used as single drug carriers, this type of drug delivery system (DDS) often does not meet all

requirements. Preparation of polymer layered silicate composite offers the possibility of improving the single components properties: those of the clay mineral particles (stability of the clay mineral dispersions and changes in its ion exchange behavior) and, more frequently, those of the polymer (mechanical properties, swelling capacity, film forming abilities, rheological properties, bioadhesion or cellular uptake)[6].

Montmorillonite clay (MMT) belongs to the smectite group, composed of silica tetrahedral sheets layered between alumina octahedral sheets at a ratio of 2:1, respectively[10]. It has large specific surface area, exhibits good adsorbance ability, high cation exchange capacity, standout adhesiveness, and drug-carrying capability. Thus, MMT is a common ingredient in pharmaceutical products, both as excipient and as active support. It was reported [11] that drug incorporation into clays takes place by adsorption, both by intercalation into the clay structure within the interlayer spacing (by replacing the water molecules), and also on the surface. The most important interactions taking place between the two components of the hybrid system are ionic[12]. The ionic exchange process may take place by mixing ion exchangers with ionic drugs in solution. In biological fluids, "counterions" can displace the drug from the substrate and deliver it into the body, while the exchanger is eliminated. The positively charged edges on the layers of MMT can interact with anionic polymer like alginate (sodium salt of alginic acid) to form unique polymer silicate materials, having superior capability to incorporate drug molecules. Involvement of MMT to alginate composites decreases the drug release rate by increasing drug/matrix adsorbtion capacity/entrapment efficiency

Sodium alginate contains pendant carboxylate and is known as polyanionic copolymer of 1,4 linked-α-L-guluronic acid and β-D-mannuronic acid residues found in brown seaweeds[13]. Physical cross-linking of sodium alginate could be done through electrostatic interactions between polyvalent cations especially Ca^{2+} and aligned guluronic blocks of alginate chains.[13] Biocompatible polymers such as polyvinyl alcohol,[14] chitosan,[15] hdroxypropyl methylcellulose,[16] and starch[17] have been incorporated in the synthesis of alginate beads with improved properties and evaluated in the drug delivery and biomedical systems. In addition to biopolymers, inorganic and organic nanoparticles including silica,[18] clay,[19] carbon nanotubes,[20] magnetic Fe_3O_4,[21] and hydroxyapatite [22] have been used for the synthesis of alginate composite beads with unique structure and properties.

Polyethylene oxide (PEO) is a nontoxic and water-soluble polymer, widely used in chemical, cosmetic, and pharmaceutical industries. PEO gels produced in water can be dehydrated and the material produced is extremely hydrophilic and possesses a good bioadhesive property[23] . Due to its properties Polyethylene oxide (PEO) is used in various drug delivery systems. Christine *et.al.,*[24] have reported PEO blend copolymer micelles as a delivery vehicle for dihydrotestosterone. Zeng *et.al.,*[25] have also reported PEO blend nanoparticles with crosslinked cores as drug carrier. Polyethylene oxide (PEO) is a good drug delivery vehicle in pharmaceutical industries [26-27].

In this research work the drug was used Verapamil Hydrochloride. Verapamil hydrochloride is a calcium channel blocker (acts on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thus reducing heart rate and blood pressure). Approximately about 90% of verapamil is absorbed from GIT, but is subjected to very considerable first-pass metabolism in the liver and the bioavailability is only about 20%. Verapamil exhibits bi-or-tri-phasic[6] elimination kinetics and is reported to have a terminal plasma half-life of 2 to 8 hrs following a single oral dose or after intravenous administration. After repeated oral doses this increases to 4.5 to12 hrs. It acts within 5 mins of intravenous administration and in 1 to 2 hrs after an oral dose. The short biological half-life and poor availability of drug favor development of drug favor development of controlled release formulations [28-30].

Recently some of the groups are working on clay loaded polymeric matrices for controlled release of drug delivery. Earlier Babul Reddy et.al.,[31] have been prepared 5-flurouracil loaded chitosan-PVA/Na^+MMT nanocomposite film for drug delivery and antibacterial studies. Rehab Abdeen et. al.,[32] have prepared modified chitosan-clay nanocomposite as a drug delivery system intercalation and in vitro release of ibuprofen. Ilescu et. al.,[21] have been prepared montmorillonite nanocomposite as a drug delivery system-incorporation and in vitro release of irinotecan.

The scope of the present study was to synthesize, evaluation and drug delivery of sodium alginate/PEO/MMT nanocomposite beads using verapamil hydrochloride as a model drug. However, no report is available in the literature. The nanocomposite materials were characterized by Fourier infrared spectroscopy (FTIR), X-ray diffraction (X-RD), scanning electron microscopy (SEM). The invitro release studies were carried out in buffer media at pH 7.4 by using UV-vis spectroscopy (λ_{max}=263nm) and the results are presented here. The schematic representation as shown in Figure 1.

MATERIALS AND METHODS

Materials

SA (viscosity [2 W/V%], 1100–1900 cps) was purchased from Merck, Mumbai, India, PEO (MW _70,000) of analar grade purchased from Sd.Fine, Mumbai, India. Verapamil Hydrochloride (VPHCl) drug was purchased from Sigma-Aldrich (St. Louise, USA). Montmorillonite clay (MMT) was supplied as powder by Southern Clay products, Inc. (Texas, USA) and $CaCl_2$ from Fischer Scientific. All the chemicals and reagents were used without further purification. Double distilled water was used for preparation of all solutions.

Procedure

The nanocomposite beads of sodium alginate/polyethylene oxide/montmorillonite were prepared by gelation method. The sodium alginate and polyehylene oxide stock solutions were prepared 2 %(W/V).The solutions are mixed in different ratios as per given in the Table-1. To these solution different concentrations of VPHCl drug and Montmorillonite clay (MMT) are added at 70^{o}C for 30mins to get homogenous solution. Afterwards the prepared slurry was put into 10 ml disposable syringe with the nozzle diameter of 3mm and added dropwise in 5 % of $CaCl_2$ solution with continuous stirring at 300rpm. The obtained beads were left in the $CaCl_2$ $_{solution}$ overnight with constant stirring followed by wash with distilled water. The prepared SA/PEO/MMT nanocomposites beads were then dried in an oven at 50^{o}C and stored in clean vials for further use.

Table 1: Formulation of nanocomposites

Code	SA (% W/W)	PEO (% W/W)	Mmt (mg)	Drug (mg)	% of EE
SPM1	100	00	00	50	64.23
SPM 2	70	30	00	50	62.81
SPM 3	70	30	40	50	69.42
SPM 4	70	30	40	70	73.35
SPM 5	70	30	40	90	76.17
SPM 6	70	30	60	50	71.53
SPM 7	70	30	80	50	74.82
SPM 8	60	40	40	50	59.61
SPM 9	50	50	40	50	57.25

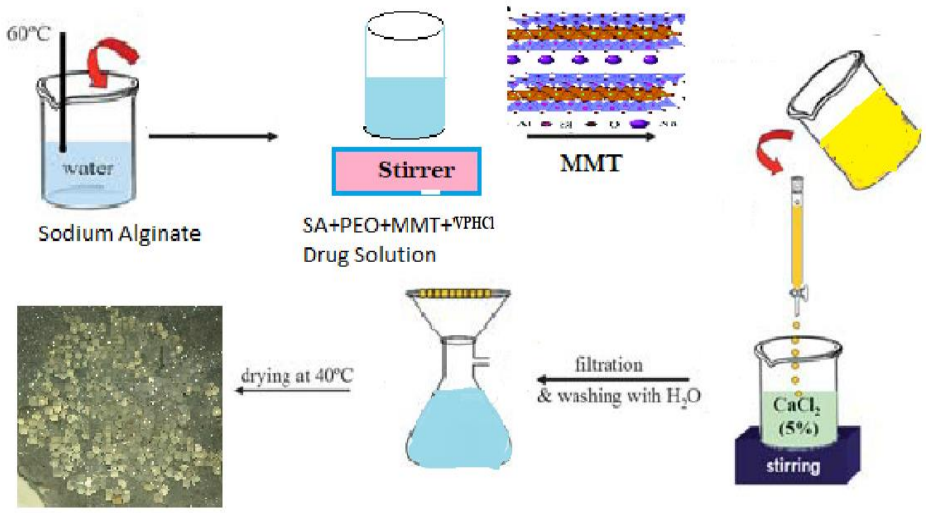

Figure 1: A simple scheme for synthesis of Nanocomposite beads

Encapsulation Efficiency:

The % of encapsulation efficiency was estimated was calculated by using the following formula. 10 mg of nanocomposites beads were soaked and shaken occasionally in 100 ml of phosphate buffer solution pH.7.4 for 24h and then crushed the beads to ensure the complete extraction of VPHCl from beads. The VPHCl content was determined using a UV-Vis spectrophotometer (LabIndia, Mumbai, India) at the λ_{max} of 263 nm with pH 7.4 PB solution as a blank. The average of three determinations was considered. The % encapsulation efficiency was calculated by the following equation (1)& (2):

$$\text{Drug loading (\%)} = \frac{\text{Weight of drug in nanocomposite beads}}{\text{weight of nanocomposite beads}} \text{ X } 100$$

$$\text{Encapsulation Efficiency EE (\%)} = \frac{\text{Actual drug loading}}{\text{Theortical drug loading}} \text{ X } 100$$

In vitro drug release studies

In vitro drug release studies of different formulations were performed at 37°C using a dissolution tester (Lab India, Mumbai, India) capable of eight baskets. Accurate quantity of nanocomposite beads (100mg) was immersed into 600mL of phosphate buffer solution pH7.4 at a rotation speed of 50 rpm. At regular intervals of time, aliquot samples were withdrawn, and analyzed using UV spectrophotometer at fixed λ-max value of 263nm for verapamil hydrochloride, and the released drug amount was calculated by using concentration versus absorbance calibration curve.

Characterization Methods

Fourier Transform Infrared (FTIR) Spectral Analysis

Brucker, Model: ALPHA II (Make: Jarmany) Fourier Transform Infrared (FTIR) spectrometer and analyzed with OPUS FTIR software was used to record the spectrum of pure SA nanocomposite beads, pure VPHCl drug, placebo and drug loaded nanocomposite beads to find out the possible chemical interactions between polymer and drug. Spectra were taken in the wavelength range 400-4000 cm^{-1}.

X-Ray Diffraction (XRD) Analysis

Bruker D8 advanced refractometer X-ray diffraction (XRD) was used to determine pure VPHCl drug, drug loaded SA/PEO nanocomposite beads and MMT loaded SA/PEO/drug nanocomposite beads were performed by a wide angle X-ray scattering diffractometer with CuKα radiation (λ= 1.54060) at a scanning rate of 5 °/min to determine the crystallinity.

Field Emission Scanning Electron Microscopy (FESEM) Analysis

The morphological characterization of the pure composite and drug, clay MMTloaded nanocomposite was observed by using Merlin Field Emission Scanning electron microscopy from Carl Zeiss (MODEL 1610-1217) with an accelerating voltage of 20 kV equipped with an EDAX detector.

RESULTS AND DISCUSSIONS

Fourier Transform Infrared (FTIR) Spectral Analysis

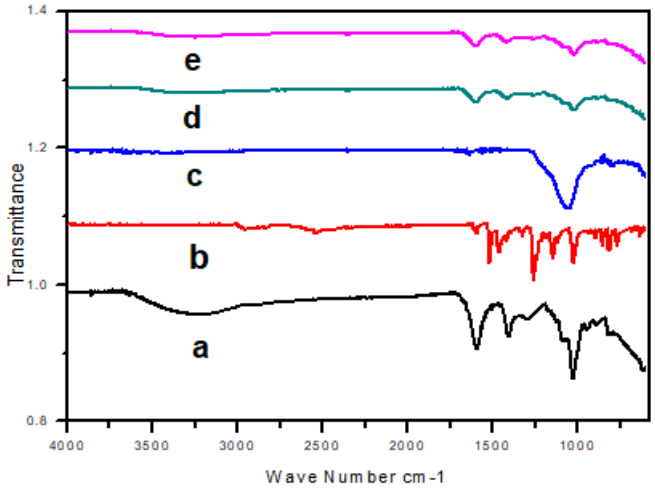

Figure 2. FTIR spectra of pure sodium alginate (a), pure drug (b), pure clay MMT (c), drug loaded SA/PEO beads(d) and drug loaded SA/PEO/MMT nanocomposites beads

The FTIR spectra of pure sodium alginate, VPHCl drug, MMT, drug loaded SA-PEO beads and drug loaded SA/PEO/MMT nanocomposite beads are shown in Figure 2. In the spectra of pure sodium alginate (a) the band at 3451 cm^{-1} corresponds to –OH stretching vibration. The peaks at 1627 and 1415 cm^{-1} showed asymmetric and symmetric stretching vibrations of carboxyl anion and the band at 1045cm^{-1} is ether linkage C-O in cyclic bridge. The FTIR spectra of VPHCl (b), the absorption band at 2947cm^{-1}showed the C-H stretching vibration of methoxy group, the peaks at 2785cm^{-1} is due to N-H stretching of the protonated amine group and a strong absorption band at 1260 cm^{-1} is C-O of aromatic ester group. In the FTIR spectrum of MMT (c) the peaks at 3450 and 3631 cm^{-1} correspond to OH stretching mode in molecular water and in Si-OH, Al-OH bonds, respectively. The band at 1640 cm^{-1} corresponds to the bending vibration of water; 1044, 623 and 523 cm^{-1} are attributed to Si-O stretching in $[SiO4]^{4-}$ tetrahedral; 916 cm^{-1} is for Al-Al-OH bending vibration; 798 cm^{-1} corresponds to Si-O vibration in SiO_2 and 467 cm^{-1} to Si-O-Si and Na-Al-OH vibrations.

FTIR spectrum of verapamil hydrochloride loaded SA-PEO nanocomposite bead (d) resembled to the superimposition of the spectra corresponding to the drug and sodium alginate. This indicates that the interaction between the polymer matrix and drug is weak. The FTIR spectrum of MMT present SA/PEO/VPHCl nanocomposite revealed that the bands of the nanocomposite beads was similar to alginate, which was major composition in the composite. The carboxyl and C-O (1685 and 1067 cm^{-1}) stretching peaks of alginate decreased in intensity and shifted to a higher wave number. The negative charge of the carboxyl groups might have an electrostatic interaction with the positively charged sites which are present in the MMT[33]. The OH stretching peaks of alginate was shifted to a lower wave number (3401cm^{-1}) in the MMT present nanocomposite. This indicates that the existence of intermolecular hydrogen bonding and electrostatic forces between drug, MMT and SA/PEO.

X-ray Diffraction Analysis

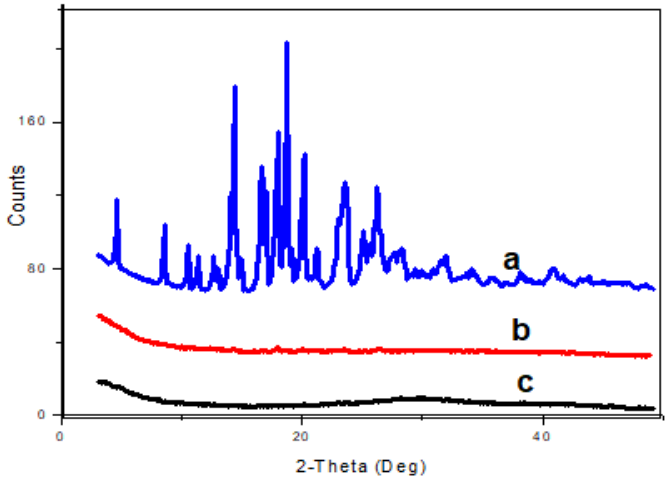

Figure 3. X-ray diffractograms of pure drug (a), drug loaded SA/PEO beads (d) and MMT loaded SA/PEO/drug nanocomposites beads

X-RD patterns of pure drug (a), drug loaded SA/PEO beads (b) and MMT loaded SA/PEO/drug nanocomposites beads are shown in Figure 3. The X-RD of plain drug has shown characteristic intense peaks at the 2theta in the range of 10-25^0 which are characteristic of its crystalline nature. Whereas, in the case of drug loaded and MMT loaded nanocomposite beads, no intense peaks related to drug was observed. This indicates the molecular dispersion of the drug after incorporation into the nanocomposite beads.

FESEM and EDS Analysis

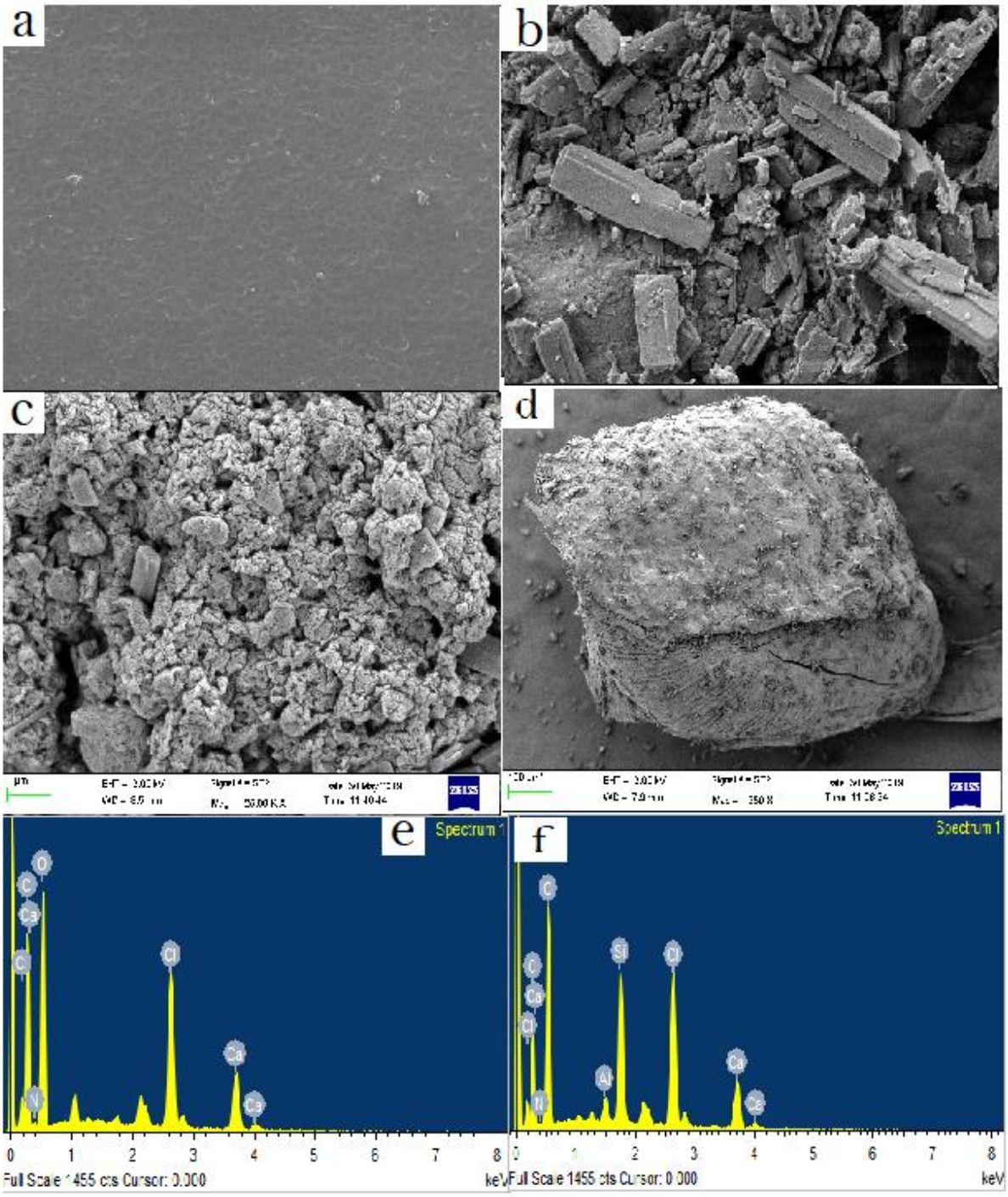

Figure 4. FESEM images of plain sodium alginate (a), drug loaded SA/PEO beads(b), MMT loaded SA/PEO/drug beads(c,d) and EDS analysis of drug loaded SA/PEO beads (e), MMT loaded SA/PEO/drug beads (f)

FESEM and EDS images of the nanocomposite beads are shown in figure 4. As seen in the figure, the pure sodium alginate and drug loaded nanocomosite beads (a,b) shows smooth surface with detectable pores. Where as in the MMT loaded nanocomposite beads a rough surface was observed, it indicates that the polycation ability of the matrix was attracted to the negative ability of clay and resulted in a physical bond (hydrogen bond) form between them and it was also observed by Rhim et al.[34]

The presence of MMT in nanocomposite beads was confirmed by using EDS. The energy dispersive X-ray spectra of drug loaded SA/PEO(e) beads shows the presence of C, N, O, Ca, Cl elements. These elements are present in the drug and in the polymers. Where as EDS shows the presence of C, N, O, Ca, Cl, Al, Si elements in the MMT loaded SA/PEO/drug beads which confirms the presence of MMT in the nanocomposite beads.

Encapsulation Efficiency

The percentage of encapsulation efficiency values (%EE) of verapamil hydrochloride loaded nanocomposite beads are shown in Table.1. The values are lies between 57.25 to 76.17, this indicates that, the % of encapsulation efficiency depends on the percentage of blend composition, drug variation and amount of clay (MMT). The % of EE increases with increase of drug concentration of drug increases; this is due to as the concentration of drug increase, the amount of drug loaded in the matrix increases. The % of EE increases with increase the concentration of clay (MMT). This is due to the clay provides large area and good absorption capacity.

In vitro drug release

Drug-release kinetics was analyzed by plotting the cumulative release data versus time by fitting the data to a simple exponential equation [35]

$$(M_t/M_\infty) = kt^n \qquad (3)$$

Where M_t and M_∞ represent the fractional drug release at time t, k is a constant characteristic of the drug-polymer system and n is an empirical parameter characterizing the release mechanism. Using the least square procedure, we have calculated the values of n and k for all the formulations and these values are given in Table-2. If n= 0.5, the drug diffuses and release from the polymer matrix following a Fickian diffusion. For n > 0.5, anomalous or non-Fickian drug diffusion occurs. If n = 1, a completely non-Fickian or case-II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to an anomalous type diffusive transport [35].

In the present study, the values of k and n showed a dependence on the extent of PEO, drug loading and clay (MMT) content in nanocomposite beads. The values of n for beads prepared by using various amounts of VPHCl drug (50, 70, 90 mg) while keeping blend composition and clay constant, ranged from 0.596 to 0.640 indicates Non-Fickian type. The clay (MMT) –loaded nanocomposite beads exhibited n values ranging from 0.596 to 0.721, indicating the Non- Fickian type mechanism. This may be due to the reduction in the regions of low microviscosity and closure of microcavities in the swollen state of the polymer. Similar findings have been observed elsewhere, where in the effect of different polymer ratios on dissolution kinetics was studied[36]. Correlation coefficients, r^2 obtained while fitting the release data are in the range from of 0.898 to 0.964.

Table.2. Drug release rate constant and correlation coefficient of all formulations after fitting drug release data into mathematical model at pH-7.4.

Formulation codes	*k*	*n*	Correlation coefficient, r^2	Transport mechanism
SPM-1	0.207	0.666	0.907	Non-Fickian
SPM-2	0.298	0.608	0.898	Non-Fickian
SPM-3	0.251	0.596	0.920	Non-Fickian
SPM-4	0.225	0.626	0.937	Non-Fickian
SPM-5	0.218	0.640	0.938	Non-Fickian
SPM-6	0.208	0.721	0.928	Non-FIckian
SPM-7	0.233	0.713	0.923	Non-Fickian
SPM-8	0.082	0.707	0.902	Non-Fickian
SPM-9	0.062	0.655	0.964	Non-Fickian

Effect of drug variation

Fig.5. shows the release profile of VPHCl loaded nanocomposite beads SPM-3, SPM-4 and SPM-5 at different amounts of drug loading (50, 70 and 90mg, respectively) in phosphate buffer solution pH-7.4(PBS) at 37°C. The release data shows that the nanocomposite beads containing higher amount of VPHCl drug (SPM-5) displayed faster and higher release rates than those formulations containing lower amount of VPHCl drug (SPM-3). A prolonged release was observed in the SPM-3 nanocomposite beads because it containing lower amount of drug. Notice that the release rate becomes quite slower at the lower amount of drug in the beads, due to the availability of more free void spaces through which a lesser no of drug molecules will transport

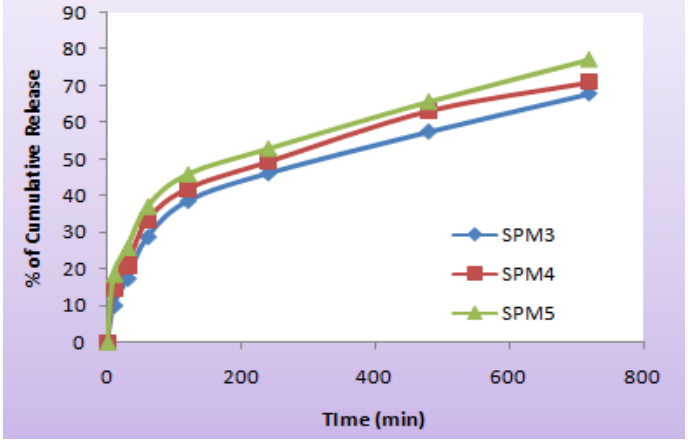

Fig.5. % cumulative release of VPHCl drug through the nanocomposite beads containing different amounts of drug 50mg (SPM-3), 70mg (SPM-4) and 90mg (SPM-5) at pH- 7.4.

Effect of MMT

Figure 6. shows the effect of MMT on in vitro release studies was studied by plotting cumulative releases vs time at pH 7.4. From 6. It is observed that the formulation (SPM-3,40mg) which contain lower amount of MMT shows higher cumulative release and the formulation (SPM-7, 80mg) which contain higher amount MMT shows lower cumulative release. This is due to electrostatic and intermolecular hydrogen bonds formed between MMT, SA, PEO and drug. It clearly explains that the MMT clay loaded formulations shows slower release rates of drug than compare with pure sodium alginate polymer.

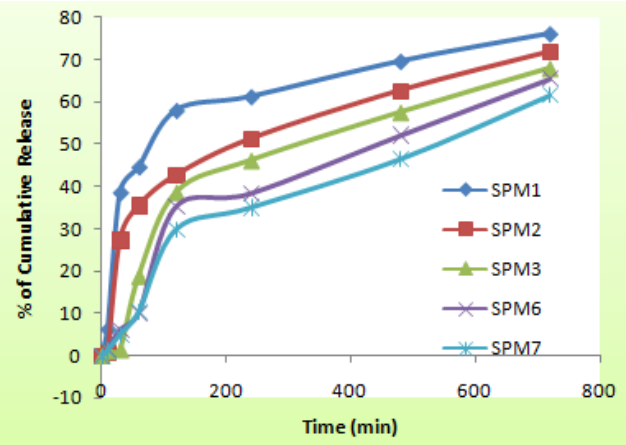

Fig.6. % cumulative release of VPHCl drug through the nanocomposite beads containing different amounts of MMT 40mg (SPM-3), 60mg (SPM-6) and 80mg (SPM-7) at pH- 7.4.

Effect of PEO

To understand the release profiles of VPHCl from the nanocomposite beads SPM-3, SPM-8 and SPM-9 with different PEO concentrations (30, 40 and 50wt %) were studied in pH-7.4 at 37°C. From Fig.7; it was observed that the highest cumulative release is obtained in SPM-3 formulation, which has lowest amount 30wt% of PEO. On the other hand, the least cumulative release was observed, the formulation containing higher amount (50wt %) of PEO. When the amount of PEO increased in the nanocomposites beads, the drug release was decreased and a lower cumulative release was observed for the formulation containing higher amount of PEO. It may be due to developing of hydrogen bonding between –OH group of sodium alginate and oxygen atom of PEO.

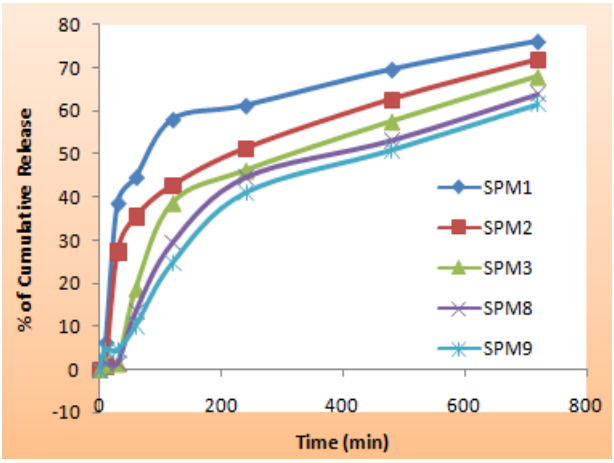

Fig.7. % cumulative release of VPHCl drug through the nanocomposite beads containing different amounts of PEO 30wt% (SPM-3), 40wt% (SPM-8) and 50wt% (SPM-9) at pH-7.4.

CONCLUSIONS

VPHCl drug incorporated nanocomposite beads based on Sodium Alginate/Polyethylene oxide/Montmorillonite were prepared by ionotropic gelation technique. The FTIR spectroscopy revealed the existence of intermolecular hydrogen bonding between MMT,drug-polymer. The X-RD data indicates the molecular dispersion of drug into nanocomposite. EDS confirms the presence of MMT into nanocomposite beads. The in vitro drug release studies clearly suggested pure sodium alginate is hydrophilic in nature it shows burst relase, whereas MMT nanoclay loaded polymeric matrice provides new insight into inter layer structure, the drug molecules present in the interlayer structure and comes out slowly from the beads. The results of controlled release tests showed that the amount of VPHCl release decreased with an increase of PEO and increase of MMT, the amount of drug release increased with increase of drug amount. By observing all the results the MMT loaded nanocomposite beads was a quite promising for controlled release of VPHCl drug. The prolonged release rates of VPHCl were observed upto 12h.

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