Short Communication

Montmorillonite/Poly (L-Lactide) microcomposite spheres as reservoirs of antidepressant drugs and their controlled release property

Shalini Rajkumar a,*, Bhavesh D. Kevadiya a,b, Hari C. Bajaj b,**

a Institute of Science, Nirma University, Ahmedabad 382481, Gujarat, India
b Discipline of Inorganic Materials and Catalysis, Central Salt and Marine Chemicals Research Institute, Council of Scientific and Industrial Research (CSIR), Gijubhai Badheka Marg, Bhavnagar 364 021, Gujarat, India

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ABSTRACT

This work evaluates intercalation of Nortriptyline (NT) and Venlafaxine (VFX) in an interlayer gallery of Na+-MMT (Montmorillonite), which was further compounded with Poly (L-Lactide) (PLLA) to form microcomposite spheres (MPS) for oral controlled drug delivery. The XRD patterns, thermal and spectroscopic analyses indicated intercalation of drugs into the MMT interlayer that was stabilized by electrostatic interaction. No significant changes in structural and functional properties of drugs were found in the MMT layers. In vitro drug release studies showed controlled release pattern.

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1. Introduction

Nortriptyline (NT) and Venlafaxine (VFX) are most commonly prescribed antidepressants that inhibit reuptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Clinical studies have demonstrated that controlled release drug treatment is clinically more valuable to commence and preserve the anticholinergic properties compared to instantaneous release or conventional therapy [1–7].

* Corresponding author. Institute of Science, Nirma University, Ahmedabad 382481, Gujarat, India. Tel.: +91 2717 241900 to 04, +91 2717 241911 to 15; fax: +91 2717 241916 17.
E-mail address: shalini.rjk@nirmauni.ac.in (S. Rajkumar).

** Corresponding author. Discipline of Inorganic Materials and Catalysis, Central Salt and Marine Chemicals Research Institute, Council of Scientific and Industrial Research (CSIR), Gijubhai Badheka Marg, Bhavnagar 364 021, Gujarat, India. Tel.: +91 278 2471793; fax: +91 278 2567562.
E-mail address: hcbajaj@csmcri.org (H.C. Bajaj).

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Therefore, there is a need to prepare formulations for the controlled and safe release of drugs, which may be done by using clay-based materials.

The design of effective, controlled drug delivery systems to circumvent the problem of high drug clearance rates is an ongoing challenge. One strategy is the use of layered silicate material-based delivery systems, consisting of layered structure constructed from tetrahedrally coordinated silica atoms fused into an edge-shared octahedral plane of aluminum-based nanosheets like assemblies, such as Montmorillonite (MMT), for intercalation of a wide range of toxic drugs. Montmorillonite (MMT) is one of the most commonly used medical clay that consists of a lamellar stack of crystalline, 1 nm thick aluminosilicate sheets. Naturally occurring cations (i.e., Na⁺) reside between the sheets to balance the overall negative surface charge of the MMT. In water, the lamellar stack swells, producing an electrostatically stabilized dispersion of nanoscale sheets. The ion exchange capacity of MMT enables the replacement of Na⁺ with other organic and inorganic cations to add functionality, spurring research into the use of MMT. Overall, the ion exchange nature and biocompatibility of clays make them versatile carrier for many vital drugs [8–14].

Here we report a method for preparation and characterization of NT and VFX loaded layered silicates, Montmorillonite (MMT) (drug–clay hybrids) and further compounding in PLLA to form microcomposite spheres (MPs), XRD, TGA, FT-IR and SEM characterizations and their potential applications in drug delivery. The in vitro release characteristics and release kinetics models are also presented.

2. Materials and methods

2.1. Materials

For the present study, sodium MMT (Cloisite Na⁺) was given by Southern Clay Products Incorporation, USA. Poly (L-Lactide) (PLLA) with MW of 152,000 (inherent viscosity: 2.0 d/g), cellulose acetate dialysis tube (MW: 07014), nortriptyline hydrochloride were from Sigma–Aldrich, USA, and Venlafaxine (VFX) was obtained as a gift sample from Lupin Pharmaceuticals Ltd (India). PVA, Mw. 1, 25,000 were purchased from S.D. Fine Chemicals Pvt. Ltd. All the other HPLC reagents were used as received. Millipore water was prepared by a Milli-Q plus system (Millipore Corporation, USA).

2.2. Drug–clay hybrids preparation

For preparing the drug–clay hybrids, 2 g MMT was vigorously stirred in 100 ml of Milli-Q water for 1 h. Two grams of NT solution (2 wt. % in Milli-Q water) was added drop wise (2 ml/min) into the suspension of MMT within 1 h at room temperature using peristaltic pump (Master flex L/S 7518-00, Cole–Parmer, USA). The mixed solution was further stirred (800 rpm) for 24 h, filtered, washed several times with water to remove the non-intercalated NT, dried at 60 °C, and ground with mortar and pestle to obtain fine powder. This sample was designated as NT–MMT hybrid. The same method was followed for VFX–MMT preparation. The remaining concentrations of drugs in the filtrates were measured by UV absorbance at λ_max = 236 nm for NT and λ_max = 224 nm for VFX using UV-visible spectrophotometer UV 2550 (Shimadzu, Japan), equipped with a quartz cell having a path length of 1 cm. All the intercalation studies were performed in triplicates, and the values were averaged for data analysis.

2.3. Preparation of micro composite spheres

The micro composite spheres (MPs) were prepared with the oil in water (o/w) solvent evaporation method. Two grams of PLLA was dissolved in 100 ml dichloromethane and sonicated for 20 min, to which NT–MMT hybrid (PLLA:NT–MMT = 1:0.5% w/w) was added and further sonicated for 10 min followed by stirring for 1 h. The organic phase was added drop wise (0.5 ml/min) into the external aqueous phase containing 0.5% w/v of polyvinyl alcohol (500 ml) with stirring until dichloromethane evaporated. The microcomposite particles were collected using filter paper, washed 5 times with Milli-Q water and resuspended in 25 ml Milli-Q water, frozen in liquid nitrogen and lyophilized. The samples were designated as NMPs, and the same methods of preparation followed for VFX with samples were designated as VMPs.

2.4. Characterization

X-ray diffraction (XRD) analysis was carried out on Phillips powder diffractometer X’ Pert MPD using PW3123/00 curved Ni-filtered Cu-Kα radiation with a scanning of 0.3°/min in 2θ range of 2–10°. Fourier transform infrared spectra (FT-IR) were recorded on Perkin-Elmer, GX-FTIR as KBr pellet in 4000–400 cm⁻¹ range. Thermo gravimetric analysis (TGA) was carried out within 30–800 °C at the heating rate 10 °C/min under nitrogen flow (20 ml/min) using TGA/SDTA 851e (Mettler-Toledo, Switzerland). The particle size distributions were measured with the Zeta sizer-Nano ZS90, Nano Series (Malvern Instruments Ltd., Malvern, UK). The morphology of pristine MMT, NT/VFX intercalated MMT and microcomposite particles (MPs) was observed by scanning electron microscope (SEM), LEO-1430VP, UK. The UV-visible absorbance of drug solutions was measured using UV-visible spectrophotometer UV2550 (Shimadzu, Japan), equipped with a quartz cell having a path length of 1 cm.

2.5. In vitro release behavior of drugs

In vitro release of drug was carried out in Julabo shaking water bath (SW23) using a buffer solution of pH 7.4 (simulated intestinal fluid) as release medium. In brief, precise amounts of pristine NT/VFX, NT/VFX–MMT hybrid and MPs were immersed in cellulose acetate dialysis tube and set in flasks containing 150 ml release medium. The temperature was maintained at 37 ± 0.5 °C with the shaking frequency at 100 rpm. One milliliter aliquots were withdrawn at regular time interval, and the same volume was restored with fresh release medium. Samples were analyzed by HPLC in triplicates, and the average values were used in data analysis. The release behavior of the drug from the NT–MMT and MPs was fitted in Higuchi, Korsmeyer–Peppas, Elovich equation, parabolic
diffusion, Bhaskara equation, and modified-Freundlich kinetic models [12–14].

2.6. Drugs quantification by HPLC

The quantification of drug from release media was determined by using a validated HPLC method. Briefly, subsequent to the preparation of samples, analysis by high-performance liquid chromatography (HPLC) system consisting of photodiode array detector (Waters Alliance model: 2695 separation module with Waters 2996 Photo Diode Array Detector, Waters Corporation, Milford, MA, USA) and a reverse-phase C18 column (for NT: Waters X'Bridge™ C18 HPLC column with length = 100 mm, ID = 2.1 mm, particle size = 5.0 μm, Waters Corporation, Milford, MA, USA; and for VFX: Phenomenex® make Luna C18 (2) HPLC column with length = 25 cm, ID = 4.6 mm, particle size = 5.0 μm, Phenomenex Inc, Torrance, CA, USA) was carried out. Drug-containing samples were transferred to autosampler vials, capped and placed in cassettes of the HPLC autosampler. The mobile phase employed for NT analysis was the mixture of 0.05 M KH₂PO₄ buffer (pH 3.0 ± 0.05) and acetonitrile (50:50% w/v). The injection volume was 10 μl with flow 0.1 ml/min, and detection wavelength (λ<sub>max</sub>) was set at 240 nm, while the mobile phase employed for VFX analysis was the mixture of 0.025 M potassium dihydrogen phosphate (pH: 3.3,)–acetonitrile (60:40 v/v). The injection volume was 10 μl with flow 1 ml/min, and detection wavelength (λ<sub>max</sub>) for VFX was at 225 nm. The drug concentration in samples was determined using the standard curve obtained for known concentrations of NT and VFX in release medium processed similarly (r² = 0.9996–0.9999).

3. Results and discussion

3.1. The chemistry of NT intercalation in interlayer gallery of Na⁺-MMT

The ionic exchange reaction between the amine groups (-NH₂) and sodium ions (≡Si—O—Na⁺) in the layered MMT is the main driving force for the cationic drugs intercalation. The NT and VFX intercalation course was mainly controlled by cationic exchange mechanism due to the Coulombic interaction between the positive amine groups of both the drugs and the positively charged sodium ions present in the interlayer gallery of MMT layers.

3.2. The drugs intercalation in MMT confirmation

3.2.1. X-ray diffraction

The XRD was used for the investigation of structural change of MMT lattice. Fig. 1[A] shows the XRD patterns of pristine MMT, NT–MMT and MPs. The XRD of MMT exhibited broadened peak at 2θ = 8.0°. The broadened peak reflected the fine particle size of MMT. After intercalation of drugs, the peak shifted from 8.0° to 5.8°–5.9°. The XRD results confirmed successful intercalation of drug into the interlayer space of MMT and increased basal spacing of silicate interlayer. The d-spacing of basal planes of NT/VFX–MMT with 1.5 to 1.45 nm significantly increased from the initial value of 1.1 nm in MMT. However, the intensity of the XRD characteristic peak increased in drug-loaded MMT, which indicated an impervious ordering of sheet structure caused by cation exchange and higher restoration of charge density during drug loading. The chemical structures of NT and VFX are shown in Fig. 1[B], and 2–80° scanning XRD data are presented in supplementary material as Fig. S1.

3.2.2. FT-IR spectroscopy

The FT-IR spectra of the drugs-loaded clay hybrid NT/VFX–MMT and MPs were compared with that of the pristine MMT and NT/VFX (Fig. 2). The spectrum of MMT revealed the characteristic absorption bands [12–14]. Pristine NT displayed characteristic absorption bands of aromatic C=C (1592 cm⁻¹) and aromatic C—H (2945 cm⁻¹) stretch vibrations; peaks at 3400 cm⁻¹ and 608 cm⁻¹ were indicative of a secondary amine moiety and the C—N—C scissors vibrations, respectively. Pristine VFX had absorption band at 3347 cm⁻¹, which corresponded to the stretching vibrations of hydroxyl group and

![Fig. 1 – [A] XRD patterns of pristine MMT and drugs loaded MMT and [B] chemical structures of the drugs.](image-url)
bands at 2940 cm\(^{-1}\), 1515–1475 cm\(^{-1}\), and 1250 cm\(^{-1}\) corresponded to the stretching vibrations of aromatic \(-\text{CH}\), benzene ring, and methoxy group present in the VFX framework [15]. Moreover, compared with pristine MMT spectrum and pristine both drugs, the NT–MMT/MPs showed bands at 3415 cm\(^{-1}\), 3630 cm\(^{-1}\) and 3660 cm\(^{-1}\) due to \(-\text{OH}\) stretching for interlayer water of MMT [12–14]. The overlaid absorption peak at 1610–1632 cm\(^{-1}\) was attributed to \(-\text{OH}\) bending mode of adsorbed water of MMT and absorption bands of aromatic \(-\text{C} = \text{C}\) stretching vibrations of NT. The peak at 1036–1080 cm\(^{-1}\) was due to Si–O stretching (in-plane) vibration of MMT. The peak shifted from 1592 cm\(^{-1}\) to 1480 cm\(^{-1}\) due to \(-\text{C} = \text{C}\) aromatic stretching vibrations of NT and shifted 2940 cm\(^{-1}\) to 2965 cm\(^{-1}\) due to \(-\text{CH}\), benzene ring aromatic stretching vibrations of VFX, which confirmed that NT/VFX was intercalated and stipulated in the MMT/MPs.

**3.2.3. Thermal analysis and SEM study**

Fig. 2 illustrates the thermal analysis (TGA and DTA patterns) of dried MMT and drug-loaded MMT. The TGA profile of pristine MMT showed weight loss in three steps at the temperatures around 100 °C, 270 °C and 430 °C. We could trace one strong and two weak endothermic peaks on the DTA pattern of pristine MMT in the same temperature range. The first weight loss and endothermic peak at ~100 °C in MMT corresponded to the loss of adsorbed water. The weight loss at 430 °C was due to the dehydroxylation of the MMT. The TGA curve of NT–MMT hybrid had four steps for weight loss at the temperatures around 150 °C, 230 °C, 330 °C, and 600 °C. One strong and three weak endothermic peaks were observed in DTA patterns, while the VFX–MMT hybrid had three steps for weight loss at the temperature around 240 °C, 350 °C, and 600 °C. The first weight loss and the weak endothermic peak at the temperature around 150 °C were due to the free water evaporation from NT–MMT. The second and third weight losses at the temperature around 230–350 °C were due to the elimination of the drugs from drug-intercalated MMT, corresponding to the complete degradation of drugs from drug–MMT hybrids. The third endothermic peak was due to weight loss at the temperature around 600 °C, consequent to complete disintegration of MMT from drug–MMT hybrids.

The SEM images of the pristine MMT, NT/VFX–MMT and MPs are shown in Fig. 3. It is clearly seen that MMT (Fig. 3A) has layered structure with platelet morphology consisting of silicate sheets that are approximately 1 nm thick and 200 nm long. Fig. 3B–F shows the surface morphology of NT/VFX–MMT hybrid and revealed a slight swelling of the layered matrix structure due to drug intercalation in the interlayer galleries of MMT. The SEM images of the MPs are presented (Fig. 3Ci and Cii where MPs are seen as solid spheres). This demonstrated the advantage of using MMT over PLLA matrices, which are fragile and exhibit uncontrollable solidity. The particle size of MMT increased after intercalation of AT (Fig. 4). However, the intensity of the size distribution peak increased in drug-loaded MMT, which indicated higher restoration of charge density during drug loading.

**3.3. In vitro release study**

The drug release patterns of drug from NT/VFX–MMT hybrid and MPs in buffer solutions with pH = 7.4 were studied at the physiological temperature (37 ± 0.5 °C) by dialysis bag technique (Fig. 5). The formulations exhibited controlled release profiles for over 72 h. The NT released from MPs showed the controlled release pattern with ~8% of drug released in 10 h followed by sustained release >72 h (~14%). No initial burst release was obtained from the MPs as compared to NT–MMT and pristine NT. The initial release of the drug from NT–MMT hybrid was somewhat quicker compared to that from MPs, where ~30% of the intercalated drug was released in 10 h and ~42% the drug was released in 72 h, while the VFX released from VFX–MMT and MPs showed the controlled release patterns with ~32–37% and ~5–6% of drug released in 10 h, respectively, followed by sustained release up to 48 h (~38–42% and ~8–9%) correspondingly. The prolonged delay from MPs can be explained on the basis of the differences in the distribution of NT/VFX–MMT hybrid plates by PLLA matrix and wrapping of the NT/VFX–MMT hybrid plates by PLLA. This was probably due to low permeability of the water in the interior of MPs due to PLLA. The burst effect must not be measured as negative in all cases. At the later stage, the NT/VFX release from NT/VFX–MMT hybrid was more controlled and sustained, whose rate was determined by the de-intercalation of drug from the clay plates.

To understand the release mechanism of drug molecules from the NT/VFX–MMT and MPs carriers better, the Hiriguchi, Korsmeyer–Peppas, Elovich equation, parabolic diffusion, Bhaskara equation, and modified-Freundlich kinetic models were used (Figs. S3 and S4 (a–f) and Table 1). The best linearity was obtained in the Korsmeyer–Peppas, Bhaskara equation, Elovich equation and modified-Freundlich model ($r^2 = 0.9384–0.9970$). Thus, the kinetics of drug release was governed by diffusion-controlled exchange and partial diffusion through swollen matrix of the MMT. The Elovich equation has been used to explain drug adsorption and desorption in clay and release from MPs. Therefore, the excellent fit of the experimental data in the Elovich model and modified-Freundlich suggested that
Fig. 3 – SEM images of [A] pristine MMT, [Bi] NT–MMT hybrid, [Bii] NT–MMT hybrid, [Ci] NMPs and [Cii] VMPs.

Fig. 4 – Particle size distribution.

Fig. 5 – In vitro release profiles of drugs in simulated intestinal fluid (pH 7.4) at 37 ± 0.5 °C; data represent mean of n = 3.
drug release from the drug–MMT was from flat surface with heterogeneous sites for ion exchange diffusion process [16–21].

4. Conclusion

We have successfully intercalated antidepressant agents (NT and VFX) into MMT galleries, and incorporation of PLLA with NT/VFX–MMT hybrids achieved controlled drug release property. In vitro studies showed release of NT/VFX from MMT/MPs by partial diffusion through a swollen matrix/del-intercalation of layers of carriers to its individual components or nanostructures of different compositions. This simple entrapment technology will be valuable in aiding to overcome burst release of the NT/VFX, and this clay showed great potential to become a new dosage form of NT/VFX, and the methodology can also be applied to other drugs.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.ajps.2015.06.002.

REFERENCES


