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ORIGINAL ARTICLE

Controlled release formulation of ranitidine-containing montmorillonite and Eudragit® E-100

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Abstract

Aim: The objective of this work was to illustrate the suitability of montmorillonite (MMT) as a drug delivery carrier, by developing a new clay–drug composite of ranitidine hydrochloride (RT) intercalated in MMT. *Methods*: The MMT–RT composite was prepared by ion-exchange process. X-ray diffraction and Fourier transform infrared spectra were employed to confirm the intercalation of RT in the MMT interlayers. The prepared MMT–RT hybrid was coated with cationic polymer Eudragit® E-100 by oil-in-water solvent evaporation method. The release processes of RT from MMT–RT and MMT–RT/Eudragit® E-100 were monitored under in vitro condition in the gastric fluid. *Results*: X-ray diffraction and Fourier transform infrared spectra analysis indicated the intercalation of RT molecules within the clay lattice. The in vitro release studies showed that MMT–RT released RT in a controlled manner. In the case of MMT–RT/Eudragit® E-100, both the release rate and the release percentages noticeably increased in the presence of Eudragit® E-100, because of its effective exchange with intercalated RT molecules. The release kinetics followed parabolic diffusion mechanism. *Conclusion*: MMT has great potential as a drug delivery carrier with various scenarios. The dosage of the MMT–RT/Eudragit® E-100 can be in the tablet form. The hybrid material and polymer-coated hybrids are microparticles.

Key words: *Controlled release; Eudragit®E-100; intercalation; kinetics; montmorillonite; ranitidine*

Introduction

The main concept in a modified drug delivery system is to provide therapeutic levels of drug to the site of action and maintain it during the treatment. The continuous development of new drug delivery systems is driven by the need to maximize therapeutic activity while minimizing negative side effects. Special attention has been paid to control the rate of drug release by means of a carrier wherein the drug is dispersed or integrated in an inert matrix. Organic–inorganic composites have been recognized as one of the most promising material for such purpose. Recently, attempts have been made for the use of clay minerals, such as smectites, palygorskite, kaolinite, and talc for pharmaceutical application[1–5]. Among them, smectite clay has attracted more attention because of its high specific surface area, adsorptive capacity, rheological properties, chemical inertness, and most importantly cation exchange capacity[6,7]. Montmorillonite (MMT), a bioinert clay mineral, has large interlayer–planar spacing with a superior capability to intercalate cationic drug molecules and to release it in a controlled way in the simulated fluids[8,9]. MMT can be regarded as medical clay, because of enhanced gel strength, and can absorb bacterial and metabolic toxins[10].

In recent years, many drug molecules have been adsorbed in the MMT layers to achieve controlled drug release. Various drug molecules such as donepezil, timolol maleate, ibuprofen, sertraline, vitamin B_1, promethazine chloride, buformin hydrochloride, and vitamin B_6[8,11–16] have been studied to execute controlled drug delivery using smectite clay. There are a few reports suggesting combination of biopolymer with MMT as drug delivery carrier. A novel bioadhesive drug delivery system containing poly(D,L-lactide-co-glycolide)/MMT nanoparticles

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was proposed. However, MMT was included as matrix material component[17]. Combination of biopolymer with clay as drug delivery system was also suggested by preparing quaternized chitosan/MMT nanocomposites[18]. Depan et al. developed a novel hybrid of chitosan-g-lactic acid and sodium MMT for controlled drug delivery and tissue engineering applications[10]. Lee et al. prepared a series of nanocomposite hydrogels from acrylic acid, poly(ethylene glycol) methyl ether acrylate, and intercalated bentonite clay by photopolymerization[19].

Ranitidine hydrochloride (RT, Figure 1a) reversibly inhibits the action of histamine at histamine H2–receptors, also inhibits receptors on gastric cells[20]. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger–Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis[21,22]. RT is a highly water-soluble drug, readily dissolves, and gets absorbed in the system as soon as it is administered. Therefore, the concentration of drug in the system reaches toxic level and then falls rapidly[23]. Moreover, the suggested oral dosages of ranitidine are too high (150 mg twice daily or 300 mg once daily). Thus a sustained release dosage form of RT is advantageous. The short biological half-life ~2.5–3 hours also favors development of a sustained release formulation[21,22,24]. MMT can also act as active antacid, as it contains magnesium and aluminum.

This work describes the preparation of MMT–RT hybrid via ion exchange reaction and the systematic characterization of the prepared hybrid. The synthesized hybrid was further coated with Eudragit® E-100, a basic dimethylaminoethyl methacrylate copolymer (Figure 1b)

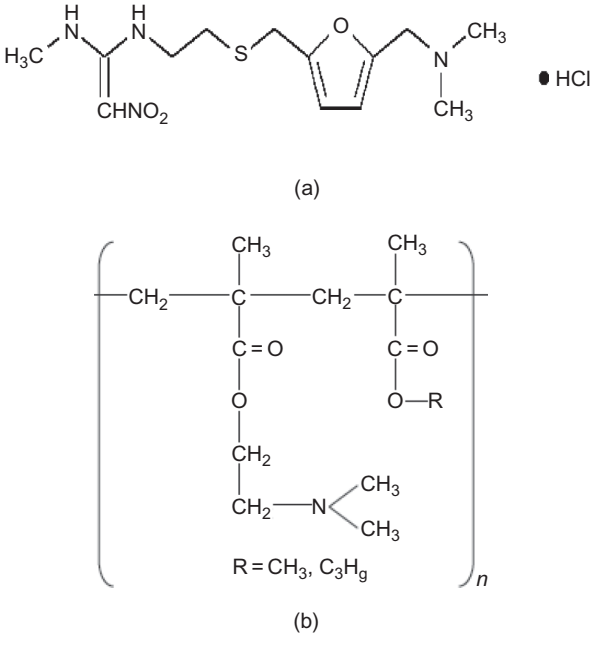


Figure 1. Molecular structure of (a) RT (b) Eudragit® E-100.

using oil-in-water solvent evaporation method to facilitate the drug release. The RT release profiles from MMT–RT hybrid and coated hybrids were monitored in the gastric environments at 37 ± 0.5°C. In addition, the possible release kinetic mechanism involved is also investigated using different mathematical models.

Materials and methods

Materials

$C_{13}H_{22}N_4O_3S{\cdot}HCl$ (RT) was purchased from Sigma–Aldrich (St. Louis, MO, USA). Eudragit® E-100 (Drug-coat E-100) was gifted by Vikram Thermo Ltd. (Ahmedabad, India). Hydrochloric acid, sodium chloride, and sodium hydroxide were purchased from S.D. Fine Chemicals (Mumbai, India) and were used as received. MMT-rich bentonite was collected from Akli mines, Barmer district, Rajasthan, India. The collected bentonite was purified as reported earlier[11,25,26]. Milli-Q deionized water was used.

Intercalation at different pH

The experiments were performed to optimize the pH for intercalation of RT in the MMT interlayer. For this purpose 20 mL aqueous solution of RT containing 63 mg of RT was mixed with 100 mg of MMT powder at pH 2–12 for 3 hours, at 50°C in a 100-mL conical flask with continuous shaking (Julabo shaking water bath, SW 23, Seelbach, Germany). The reaction mixtures were filtered and analyzed for RT by ultraviolet (UV)–Visible spectroscopy at $\lambda_{max} = 314$ nm.

Preparation of hybrid

The RT solution (1 wt%, pH 6) was added drop wise into the clay dispersion (1 wt% MMT, dispersing 7 g MMT in 700 mL deionized water with vigorous stirring for 3 hours) within 1 hour at 30°C, 50°C, and 80°C using peristaltic pump (Master flex L/S 7518–00, Cole–Parmer, Vernon Hills, IL, USA). The resulting solutions were further stirred for 3 hours. The intercalated products were separated by filtration, washed several times with water to remove the nonintercalated RT, dried, and ground to obtain fine powder. The samples were designated as N1, N2, and N3. In the further experiments (polymer coating and drug release) N2 was used as MMT–RT hybrid. To check the interaction of Eudragit® E-100 with MMT, 1 g of Eudragit® E-100 was dissolved in dichloromethylene. To this, 1 g of MMT was added and the reaction mixture was stirred for 3 hours. Finally, it was filtered and dried. The product was analyzed using X-ray diffraction (XRD).

Preparation of polymer-coated hybrids

MMT–RT coated with Eudragit® E-100 was prepared by oil-in-water solvent evaporation method[27]. The hybrid:polymer ratios for the studies were 1:0.5, 1:1, and 1:5. An amount of 0.4 g of MMT–RT (N2) was added into 20 mL solution containing 0.2, 0.4, and 2 g Eudragit® E-100 dissolved in dichloromethylene and stirred for 5 hours to obtain homogeneous suspension. Then, the suspension was poured into vigorously stirred water (500 mL). The solvent was evaporated at room temperature. Finally, the coated hybrids were obtained by filtration and dried at room temperature for 24 hours. The samples were designated as N4, N5, and N6. The collected filtrates were utilized to calculate the encapsulation efficiency (EE) of the coated hybrids.

Encapsulation efficiency and drug content

To measure the EE% and drug content DC%, the filtrates collected subsequent to the coating process were analyzed by measuring its absorbance at 314 nm. The EE% and the DC% in the coated hybrids were calculated as follows:

$$\mathrm{EE}(\%) = \frac{\text{weight of RT fed} - \text{weight of RT in the supernatant}}{\text{weight of RT fed}} \times 100,$$

$$\mathrm{DC}(\%) = \frac{\text{weight of RT in coated hybrids}}{\text{weight of coated hybrids}} \times 100.$$

Characterization

XRD analysis was carried out with a Phillips powder diffractometer X' Pert MPD (Almaelo, The Netherlands) using PW3123/00 curved Ni-filtered Cu K alpha radiation with a scanning of 0.3 deg/s in 2θ range of 2–80°. Fourier transform infrared spectra (FT-IR) of KBr pellets were measured with Perkin–Elmer, GX-FTIR (Waltham, MA, USA). The particle size analysis was done using Malvern Master sizer (Hydro 2000S, Worcestershire, UK). The samples were prepared by suspending the materials in distilled water (0.5 wt%). The analyses were carried out five times. UV-visible absorbances of RT solutions were measured at λ_{max} = 314 nm using UV-visible spectrophotometer UV 2550 (Shimadzu, Kyoto, Japan), equipped with a quartz cell having a path length of 1 cm.

Drug release

Drug release profiles of RT from the MMT–RT hybrid (N2) and coated hybrids were measured using the United States Pharmacopeia (USP) digital tablet dissolution test apparatus (VEEGO Instruments, Mumbai, India) by suspending a dialysis membrane bag containing MMT–RT hybrid and coated hybrids in 500 mL of dissolution media (gastric fluid of pH 1.2). Rotation speed was 100 rpm, and the bowls were kept in a thermostatically controlled circulation water bath at 37 ± 0.5°C. To improve the drug release, 135 mg of Eudragit® E-100 was added to the dissolution media for the noncoated hybrid sample. Aliquots of dissolution media were withdrawn at schedule time intervals for 720 minutes. The content of RT was measured by UV absorption. The dissolution media was immediately supplemented to maintain a volume of 500 mL. The tests were carried out in triplicates and the average values are reported.

To determine the drug release kinetics, parabolic diffusion model and Elovich equation were employed to explain diffusion-controlled exchange phenomenon[7,8].

$$\text{Parabolic diffusion:} \quad \frac{C_t}{C_\infty} = K_P t^{\frac{1}{2}}, \tag{1}$$

where C_t/C_∞ is fraction of drug released at time t and K_P is the constant.

$$\text{Elovich equation:} \quad C_t = K_E \log t, \tag{2}$$

where K_E is the rate constant.

Results and discussion

Intercalation at different pH

Effect of the pH on RT adsorption onto MMT (Figure 2) showed that between pH 4 and 8, the adsorption of RT on MMT remained almost same; and below pH 4

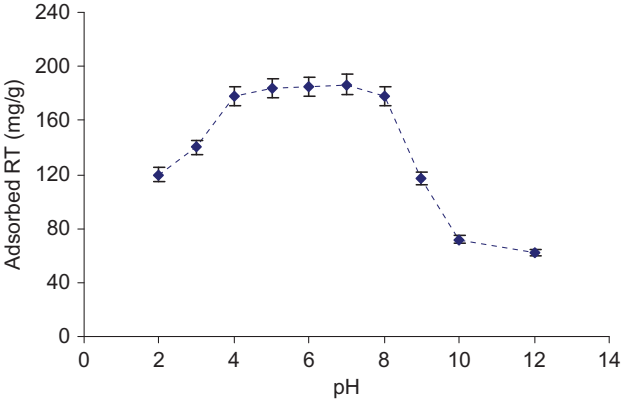


Figure 2. Effect of pH on adsorption of RT on MMT (MMT concentration = 100 mg/20 mL, RT = 63 mg, 50°C, 3 hours).

and above 8, a sharp decrease in the adsorption of RT in MMT was observed. As the pK_a of RT is ~8.3[28,29] there exists an equilibrium between ionized and unionized RT molecules at each pH with 50% ionized and unionized RT at pH 8.3. In acidic conditions, the protonated form of the RT is strongly adsorbed onto the negatively charged MMT by cation exchange process. The adsorption under basic conditions decreased significantly, because the negatively charged surface site on the clay did not favor the adsorption of the RT molecules. There was a decrease in adsorption of RT in the clay lattice below pH 4 because of competition between the cationic drug and the H^+ ions as the silanol groups on the clay surface get protonated[11,30].

Characterization

The XRD patterns of MMT, MMT–RT (N2), and MMT–Eudragit® E-100 showed broad basal reflections (Figure 3). MMT showed the reflection at 2θ=7.46, MMT–RT hybrid showed peak at 2θ=5.26, whereas MMT–Eudragit® E-100 showed the reflection at 2θ=7.25. The reflections indicated a basal spacing of MMT of about 11.8Å, MMT–RT of about 16.8Å, and MMT–Eudragit® E-100 of 12.2Å. According to the Bragg's law, the peak shifting from higher diffraction angle to lower diffraction angle is due to increase in the d spacing, which indicates that RT and Eudragit® E-100 have been effectively intercalated into the interlayer of MMT. The vertical dimension of the RT molecule is ~4.15Å (Accelreys MS Modelling 3.2, San Diego, CA, USA). Taking into consideration a silicate layer thickness of 9.6Å, RT expanded the interlayer space by 7.2Å, which corresponds to a vertical orientation of the RT cations in a bilayer[8,31] (Schematic 1).

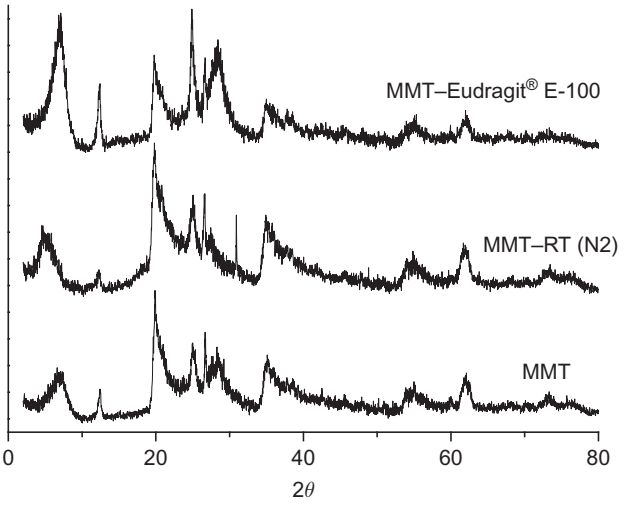


Figure 3. XRD pattern of MMT, MMT–RT (N2), and MMT–Eudragit® E-100.

The FT–IR spectra of MMT (Figure 4) showed a broad band centered at 3400 cm^{-1} because of –OH stretching band for interlayer water. The bands at 3620 and 3698 cm^{-1} were due to the –OH stretching band for Al–OH and Si–OH. The shoulders and broadness of the structural –OH band were mainly because of contributions of several structural –OH groups occurring in the clay mineral. The overlapping absorption bands in the region of 640 cm^{-1} attributed to the –OH bending mode of the adsorbed water and the peak at 1115 cm^{-1} was due to Si–O stretching (out-of-plane) band. The peak at 1035 cm^{-1} attributed to the Si–O stretching (in-plane) vibration for layered silicates. The bands at 915, 875, and 836 cm^{-1} were due to AlAlOH, AlFeOH, and AlMgOH bending vibrations, respectively[32]. In the IR spectra of MMT–RT hybrid (N2), the absorption band at 1359 cm^{-1} was due to C–H vibrations. Bands at 1404 and 1456 cm^{-1} were attributed to C=C stretching vibrations. Characteristic bands of RT at 2400 cm^{-1} (C=NH) and 1610 cm^{-1} (C–N) were shifted to 2357 and 1627 cm^{-1}, respectively, in the hybrid material[33–35], signifying the strong interaction of RT into the MMT layers.

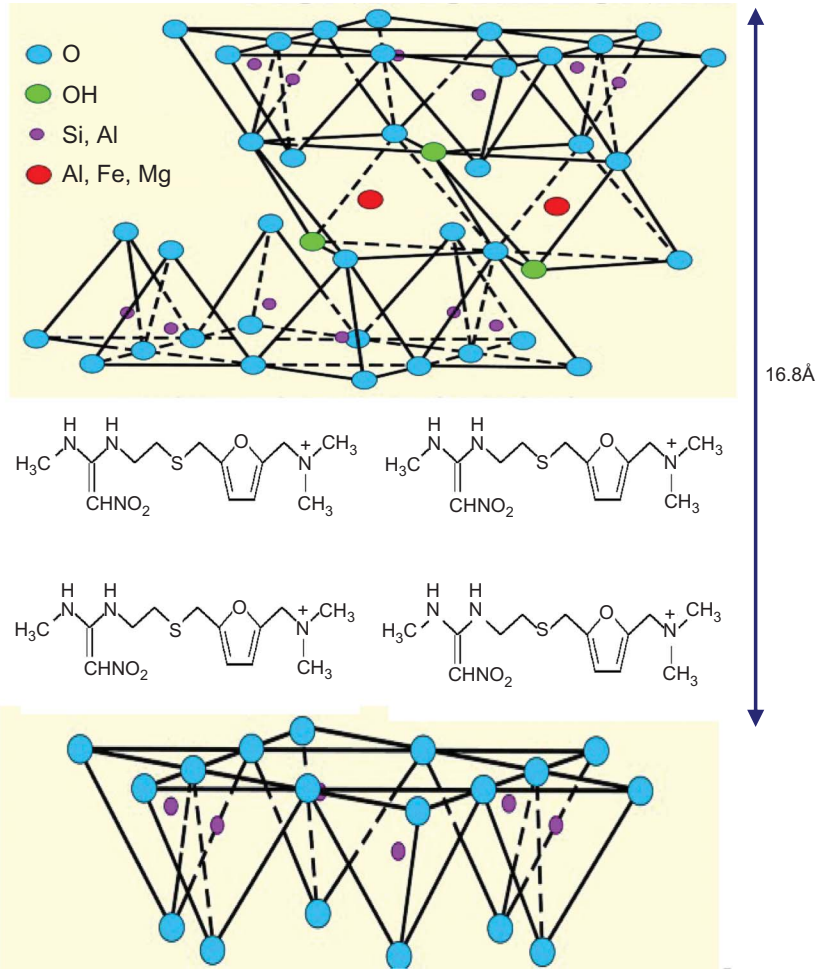
The average particle size of MMT was 1.1 ± 0.2 μm, which upon intercalation with drug molecules increased to 14.1 ± 1.0, 13.6 ± 2.1, and 11.4 ± 2.7 μm for N1, N2, and N3, respectively. Coating of the hybrid with Eudragit® E-100 resulted in further increase of the particle size. For N4 (hybrid:polymer, 1:0.5) the particle size was 40.0 ± 2.8; for N5 (hybrid:polymer, 1:1) 56.3 ± 3.5 and for N6 (hybrid:polymer, 1:5) it was 79.9 ± 3.3 μm.

Encapsulation efficiency

The EE% of the coated hybrids decreased significantly because of the cationic nature of Eudragit® E-100. The filtrate obtained after coating process contained RT, may be due to the ion exchange between Eudragit® E-100 and RT molecules, which resulted in lowering the EE of the coated hybrids (Table 1). EE of MMT–RT/Eudragit® E-100 decreased with increasing polymer content in the formulations. It is noticeable here that the EE of N6 decreased to a great extent compared with the other two formulation as with an increase in Eudragit® E-100, it will exchanged with the drug molecules from hybrid, consequently, decreasing the EE.

Drug release

The release profile of RT was performed in gastric fluid as it is targeted in the stomach. To facilitate the drug release from MMT–RT hybrid, Eudragit® E-100 (cationic



Schematic 1. Possible arrangement of RT molecules within the interlayer space of MMT.

polymer) was added to the dissolution media. The release of RT from MMT–RT (N2) was in a controlled manner, 51% of RT was released in 720 minutes (Figure 5a). However, MMT–RT was not able to deliver the total amount of drug adsorbed. This may be due to the strong interaction between the drug molecules and the surfaces of the MMT. The total release amount increased from 51% to 58% for MMT–RT when Eudragit® E-100 (135 mg) was added in the dissolution media. This clearly suggested that Eudragit® E-100 was able to enhance the drug release percentage and the rate.

The release profiles of Eudragit® E-100-coated hybrids (Figure 5b) showed that the total amount of drug release during 720 minutes greatly increased because of coating with Eudragit® E-100. The amount of release was enhanced to 64%, 85%, and 90% for N4, N5, and N6 as compared with 51% from N2. However during the first 120 minutes the release amount for all the formulations was almost similar, but afterward the amount of drug release was greatly enhanced for coated hybrids. Eudragit® E-100 may open the layered edges of MMT, subsequently increasing the drug release. Additionally, Eudragit® E-100 is surrounded by several hydrophilic groups like NH_4^+, which improve the hydration of the hybrid in the dissolution media[7,8,36]. The release patterns of the N5 and N6 was almost same, suggesting that 1:1 coating was sufficient enough to achieve controlled delivery of RT.

Two mathematical models were used to determine the drug release kinetics from the hybrids. Correlation coefficient and regression equations obtained from different kinetic models (Table 2) suggested that the parabolic diffusion explain the release profile better. Thus, the kinetics of RT release is governed by diffusion-controlled exchange phenomenon. By taking into account the different slope values according to the parabolic diffusion for N2, N4, N5, and N6 (0.0605, 0.0431, 0.0343, and 0.0361, respectively), it is concluded that Eudragit® E-100 did not alter the kinetic mechanism but it influenced the rate of drug release[37].

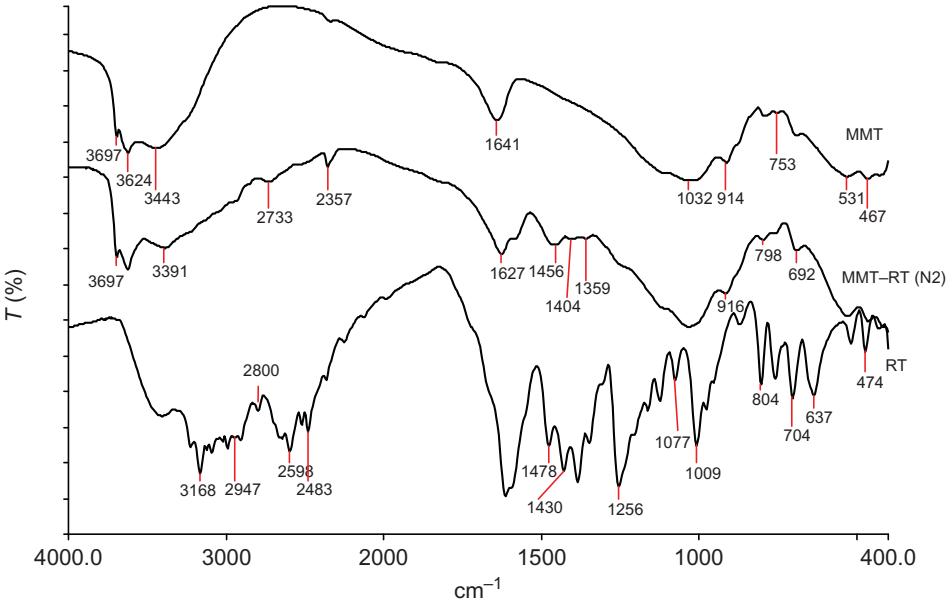


Figure 4. FT-IR spectra of MMT, MMT-RT (N2), and RT.

Table 1. Encapsulation efficiency and drug content (DC).

MMT–RT/Eudragit® E-100	EE (%)	DC (%)
N4[a]	85.8 ± 2.4	9.1
N5[b]	81.1 ± 2.7	6.8
N6[c]	60.3 ± 2.3	1.7

[a]Hybrid:polymer, 1:0.5.
[b]Hybrid:polymer, 1:1.
[c]Hybrid:polymer, 1:5.

Conclusion

Ranitidine was successfully intercalated into MMT via ion exchange process. The interlayer spacing of 16.8Å for MMT–RT determined by XRD, suggested a vertical orientation of the RT cations in a bilayer arrangement. Coating of MMT–RT was achieved to obtain a new composite system for drug delivery. In vitro release showed that 51% of RT was released from MMT–RT hybrid in gastric fluid of pH 1.2, which was greatly enhanced to 64%, 85%, and 90%, utilizing the cationic polymer Eudragit® E-100. The release of RT from hybrids followed the parabolic diffusion mechanism.

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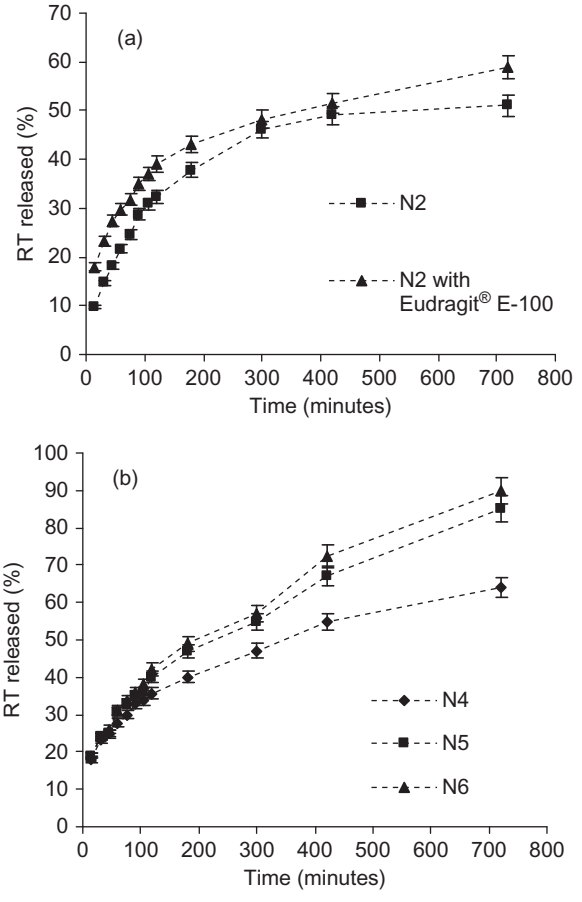

Figure 5. Release profiles of RT from (a) N2 and N2 with Eudragit® E-100 (135 mg) in the dissolution medium; (b) N4, N5, and N6 in gastric fluid at 37 ± 0.5°C.

Table 2. Correlation coefficient and regression equations for kinetic models.

Formulation	Kinetic model	Regression equation	R^2
N2	Parabolic diffusion	$y = 0.0605x - 0.0382$	0.9895
	Elovich	$y = 4.0484x - 3.6751$	0.9709
N2 with Eudragit® E-100 in dissolution media	Parabolic diffusion	$y = 0.0457x + 0.148$	0.9863
	Elovich	$y = 3.5583x - 1.6979$	0.9848
N4	Parabolic diffusion	$y = 0.0431x + 0.2009$	0.9922
	Elovich	$y = 2.668x - 0.7891$	0.9647
N5	Parabolic diffusion	$y = 0.0343x + 0.0882$	0.9917
	Elovich	$y = 3.3951x - 1.7785$	0.9464
N6	Parabolic diffusion	$y = 0.0361x + 0.0603$	0.9945
	Elovich	$y = 2.8163x - 1.781$	0.9551

Parabolic diffusion: $y = C_t/C_\infty$, $x = t^{1/2}$. Elovich equation: $y = C_t$, $x = \log t$.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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