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Original Article

Formulation and evaluation of taste-masked oral disintegrating tablet containing tolterodine-loaded montmorillonite

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Abstract

Background and purpose: The present study aimed to obtain a taste-masked oral disintegrating tablet (ODT) containing tolterodine tartrate (TT) intercalated into montmorillonite (MMT)
Experimental approach: The TT-MMT hybrid was prepared by ion exchange reaction. The effect of the initial concentration of TT, MMT, temperature, and pH on the encapsulation efficiency (EE) % of the drug in MMT was evaluated. The selected TT-MMT hybrid was characterized by X-ray diffraction (XRD), Fourier transforms infrared (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). Then, the optimized TT-MMT hybrid was incorporated in the ODT prepared by direct compression method and taste-masking assessment performed by a human test panel.
Findings/Results: The EE% of TT was in the range of 22.67 to 71.06% in different formulations. It was found that increases in MMT concentration significantly increased EE%. DSC and XRD studies indicated that the TT was intercalated in the MMT interlayer space in an amorphous or molecular state. *In-vitro* release studies at pH 6.8 showed that the amount of the drug released from the TT-MMT hybrid was negligible for the first 3 min. The post-compression of ODT also showed satisfactory results in terms of friability, hardness, disintegration time, and taste.
Conclusion and implications: MMT-ODT could be a suitable vehicle for the taste masking of TT, with the potential for use in patients with swallowing problems.

Keywords: *In vitro* release; Montmorillonite k10; Orally disintegrating tablet; Tolterodine tartrate; Taste masking.

INTRODUCTION

Overactive bladder is a condition characterized by frequent urination, urinary incontinence and urgency, and nocturia. It affects up to 20% of the world's population. Although the overall prevalence of bladder overactivity is the same in the two sexes, with aging, it may become predominant in men. The coexistence of benign prostatic hyperplasia and obstruction with bladder overactivity in men can further complicate the treatment and have a substantial effect on the quality of life (1,2). Tolterodine tartrate (TT) is an anti-muscarinic agent with more specificity for the M_2 receptor. It is a drug choice for the treatment of bladder overactivity due to its direct effects on the bladder's smooth muscle (3). TT in the form of immediate-release tablets and extended-release capsules is available in the market. However, swallowing difficulties (dysphagia) are common in older people, which can affect their ability to take oral medicines (4).

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Oral disintegrating tablets (ODT) can be regarded as a novel solid dosage form that may rapidly disintegrate upon contact with saliva without the need for water. While they have benefits, tablet formulation can be easily taken by both pediatric and elderly patients with swallowing difficulty (5). Despite such distinctive properties, taste masking of bitter active substances such as TT is an obstacle hindering the development of ODT. There are different approaches to mask the unpleasant taste of drug substances including (1) adding flavors, amino acids, and sweeteners in the formulation, (2) applying conventional granulation, (3) coating with polymeric materials, (4) spray congealing with lipids, (5) using complexation with ion-exchange resins, and (6) intercalating within montmorillonite (MMT) (6). Some previous studies have used MMT as an encapsulant to achieve taste masking (7-9). MMT is a main component of bentonite that has been studied extensively as a carrier in drug delivery systems in the past decades due to its large specific surface area, biocompatibility, high capacity for ion exchange, the ability to control the drug release, and mucoadhesiveness (10). MMT material is made up of two silica tetrahedral sheets sandwiching an edge-shared octahedral sheet of aluminum, known as T-O-T sheets. Depending on the type of MMT, variable amounts of sodium and calcium along with water reside between the sheets that can be exchanged by different organic molecules. MMT is extensively used in pharmaceutical applications as an excipient and as an active support. Drug adsorption on clay can happen within the interlayer space by the exchange with the interlayer cations, and on the outer surface and edges (10,11). The study conducted by Oh *et al.* demonstrated that aripiprazole could be intercalated within the layered space of MMT, which considerably decreased the drug release and masked the taste (9).

Considering the aforementioned factors, in the present study, we developed ODT containing the TT-MMT hybrid with taste-masking ability. The effect of the initial concentration of TT, MMT, temperature, and pH on the potential of these carriers to encapsulate TT was then evaluated. The optimized TT-MMT hybrid was then incorporated in ODT and the prepared ODT was investigated in terms of hardness, friability, disintegration time, drug release, and taste-masking capability.

MATERIALS AND METHODS

Materials

TT was obtained as a gift sample from Tehran Darou Co. MMT K10 was purchased from Sigma Aldrich (US), and Avicel® PH 102 was purchased from Sigma Aldrich (US). Croscarmellose sodium (CS), mannitol, Talc, magnesium stearate, and saccharin were obtained from Merck (Germany).

Preparation of hybrid of MMT-TT and encapsulation efficiency assay

To achieve maximum intercalation of TT within the interlayer region of MMT, the effects of various parameters such as the initial concentration of TT and MMT, temperature, and pH were investigated. To prepare TT-MMT, according to Table 1, accurately weighed MMT (50-100 mg) was dispersed in 20 mL deionized water containing TT (12.5-50 mg) and then stirred for 6 h.

Table 1. Different prepared TT-MMT hybrid formulations and their encapsulation efficiency % (mean ± SD, n = 3).

Formulations	MMT amount (mg)	pH	Temperature (℃)	TT amount (mg)	Encapsulation efficiency (%)
1	50	4	25	12.5	32.30 ± 2.01
2	100	4	25	12.5	71.06 ± 3.00
3	100	4	25	25	41.06 ± 0.43
4	100	4	25	50	22.67 ±0.29
5	100	2	25	12.5	57.63 ± 1.19
6	100	6	25	12.5	45.92 ± 0.44
7	100	4	50	12.5	68.87 ± 1.29
8	100	4	75	12.5	61.45 ± 0.72

TT, Tolterodine tartrate; MMT, montmorillonite.

To determine the optimum pH for the intercalation of TT into the interlayer of MMT, the pH of each mixture was set at 2, 4, and 6. To optimize the temperature for the preparation of the TT-MMT hybrid, the reaction was carried out at 25, 50, and 70 ℃. After that, the reaction mixture was centrifuged (Microcentrifuge Sigma 30 k, UK) at 7500 rpm for 15 min. The precipitated TT-MMT was rinsed with water and then frozen at -20 °C in a freezer for 24 h. The frozen sample was lyophilized for 48 h in a freeze-dryer (Christ Alpha2-4 LD plus, Germany) at the temperature of -70 °C and a pressure of 0.001 mbar and then maintained inside the desiccator for further investigation. After filtering the obtained supernatant through a 0.45 µn filter, the concentration of free TT in the filtered supernatant was determined by using UV spectrophotometry (Shimadzu®, Japan) at 282 nm. Encapsulation efficiency (EE) % was determined using the following equation:

$$\text{EE}\ (\%) = \left(\frac{\text{Total amount of added drug} - \text{free drug}}{\text{Total amount of added drug}}\right) \times 100 \quad (1)$$

Drug release assay

The release of TT from the formulation with the highest EE% was assessed using a dialysis bag. To simulate the buccal condition and evaluate the taste-masking ability of the hybrids, the release test was performed in phosphate buffer solution (PBS) at pH 6.8 for 3 min; also, to simulate the gastric conditions, the release test was performed at pH 1.2 for 2 h (7). For this purpose, the freeze-dried precipitate was dispersed in deionized water and then poured into a dialysis bag. After sealing, the dialysis bag was placed in 25 mL of PBS (pH 6.8 and 1.2) at 37 °C and stirred at 500 rpm using a magnetic stirrer. At the predetermined time, the amount of released drug was calculated by using UV spectrophotometry at 282 nm.

Particle size, polydispersity index, and zeta potential determination

The particle size, polydispersity index (PdI), and zeta potential were measured by using a Malvern zetasizer (PCS, Zetasizer 3000, Malvern, UK) after 1:10 dilution with deionized water.

Differential scanning calorimetry study

For the differential scanning calorimetry (DSC) study, 8 mg of TT, MMT, and TT-MMT was heated in the range of 30-400 ℃, using a hermetically sealed platinum pan at the heating rate of 10 ℃/min under nitrogen flow using DSC 200 F3 (Maia, Germany).

Powder X-ray diffraction analysis

Powder X-ray diffraction (PXRD) analysis of TT, MMT, and TT-MMT was investigated by using an X-ray diffractometer in the 2θ range of 3°-60°, by applying a Ni filter with Cu Kα radiation. The d interplanar spacings of MMT and TT-MMT were calculated with the X'Pert HighScore Plus software.

Fourier-transform infrared spectroscopy

Fourier-transform infrared (FTIR) spectrometer (Rayleigh, WQF-510/ 520, China) was used for the FTIR analysis of TT, MMT, and TT-MMT in a region from 500 to 4000 cm^{-1}. The sample was mixed with KBr and molded into a disc.

Morphology

The morphology of the drug-free MMT and optimized TT-MMT hybrid was visualized by scanning electron microscopy (SEM, Philips XI30, US). The freeze-dried specimens were placed on a metal stub, coated with a film of gold under a vacuum, and then observed using the SEM.

Design of experiment

D-optimal design with 2 factors and 3 levels was used for the optimization study using Design-Expert software (version 11, USA). The Avicel® and CS amount were selected as independent variables. The independent variables and their levels, as shown in Table 2, were selected based on a preliminary study. The disintegration time, hardness, and friability were chosen as the responses. The components of 9 formulations generated by the Design Expert software are shown in Table 3. For the statistical data analysis and plotting of the graphs, Design Expert software was used. Analysis of variance (ANOVA) was performed to conclude the significance of the factor and their interaction.

Table 2. Variables and their levels in D-optimal design for development of oral-disintegrating tablet containing tolterodine tartrate-montmorillonite complex.

Independent variables	Symbol	Levels		
		I	II	III
Amount of Avicel® (mg)	A	20	60	100
Amount of croscarmellose (mg)	B	2.5	5	7.5
Disintegration time (s)	Y1	Minimize		
Hardness	Y2	Maximize		
Friability (%)	Y3	Minimize		

Table 3. The composition of different oral-disintegrating tablets containing TT-MMT.

Formulations	TT-MMT (mg)	CS (mg)	Avicel® (mg)	Saccharin sodium (mg)	Talc (mg)	Mg stearate (mg)	Mannitol (mg)
F1	24.8	2.5	20	2	4	4	144
F2	24.8	5	20	2	4	4	141.5
F3	24.8	7.5	20	2	4	4	139
F4	24.8	2.5	60	2	4	4	104
F5	24.8	5	60	2	4	4	101.5
F6	24.8	7.5	60	2	4	4	99
F7	24.8	2.5	100	2	4	4	64
F8	24.8	5	100	2	4	4	61.5
F9	24.8	7.5	100	2	4	4	59

TT-MMT, Tolterodine tartrate-montmorillonite complex; CS, croscarmellose sodium.

Preparation of ODT containing TT-MMT (TT-MMT-ODT)

Tablets containing 2 mg of TT were prepared by direct compression method. The composition of different formulations is shown in Table 3. The diluents and superdisintegrants at different levels, mannitol and fixed level of TT-MMT (equivalent to 2 mg TT) were passed through a 25-mesh sieve and then mixed for 10 min. After that, the mixtures were blended with talc and magnesium stearate as glidant and lubricant, respectively. Various characteristics of blends, including the angle of repose, bulk density (ρb), tapped density (ρt), Carr's index (%), and Hausner ratio, were evaluated according to United States Pharmacopeia (USP) (12). The angle of repose (θ) was evaluated by funnel method (13) and calculated by determining the height (h) and radius (r) of the formed powder heap and putting the values into the following equation:

$$\text{Tan } \theta = (h/r) \quad (2)$$

Carr's index and Hausner's ratio were calculated to employ the predetermined bulk ρb and ρt using the following equations:

$$\text{Carr's index (\%)} = \frac{\rho t - \rho b}{\rho t} \times 100 \quad (3)$$

$$\text{Hausner's ratio} = {}^{\rho t}/_{\rho b} \quad (4)$$

At last, all the powder blends were compressed into tablets by using a single punch machine (Kilian & Co., Inc., Germany). The total weight of the tablets was kept at 200 mg.

Evaluation of tablets

Hardness and thickness

Erweka hardness tester (Erweka, TPA, Germany) was used to determine the hardness of TT-MMT-ODT. Ten tablets from each formulation batch were randomly tested, then the average hardness was recorded. Moreover, the thickness of 10 tablets from each formulation was determined with Vernier calipers.

Friability

Twenty pre-weighed tablets (W1) of each formulation were put in the Erweka friability tester (Erweka TAP, Germany). After the friability tester turned in a drum for 4 min and 25 rpm, tablets were weighed again (W2) and friability% was calculated using equation 5.

According to the literature, weight loss should not be more than 1% (12,14).

$$\text{Friability (\%)} = \left(\frac{W1-W2}{W1}\right) \times 100 \quad (5)$$

Drug content

Ten tablets randomly were chosen, individually powdered and then dispersed in 20 mL of water and stirred at 400 rpm for 24 h, then the mixture was centrifuged at 7500 rpm for 15 min and the concentration of TT in filtered supernatant was determined by using UV spectrophotometry at 282 nm. The acceptance value was calculated by the formula from USP <905> content uniformity of dosage units (12).

In vitro disintegration study

In-vitro disintegration time for ODTs was evaluated using a Digital Tablet Disintegration Test Apparatus (Erweka ZT- Germany). Briefly, 6 tablets were placed in each of the six tubes, immersed in 900 mL distilled water, maintained at 37 °C and the basket shook at the rate of 30 cycles/min (15). According to European pharmacopeia (16), ODT should disintegrate within 3 min.

Human taste panel

For the evaluation of taste masking, 30 healthy adult volunteers took part in the experiment (15 males and 15 females, with a mean age of 27 years), from whom informed consent was obtained. The ethical approval was received from the ethics committee of Isfahan University of Medical Sciences (Ethics No. IR.MUI.RESEARCH.REC.1399.449). The volunteers were trained before the experiment precisely about the purpose of the experiment and the possible side effects of TT. Finally, the flavor was assigned a numerical value based on the following scale: (1) extreme bitterness, (2) medium bitterness, (3) low bitterness, (4) very little bitterness, and (5) no bitterness.

Statistical analysis

One-way analysis of variance (ANOVA) followed by the LSD post-hoc test was employed to test the difference between groups and the *P*-values < 0.05 were considered statistically significant. The results related to the particle size and zeta potential were analyzed using a t-test.

RESULTS

Preparation and physicochemical characterization of TT-MMT

The effect of the MMT concentration, drug amount, pH, and temperature on the drug intercalation capacity of MMT was evaluated. The results of EE% are shown in Fig. 1. The EE% of TT was in the range of 22.67 to 71.06% in different formulations.

According to the obtained data, the formulation prepared using 100 mg MMT, and 12.5 mg TT at the pH value of 4 and temperature of 25 ℃ was chosen for further studies as it had a high EE%. The particle sizes and zeta potentials of pristine MMT dispersions and the optimized TT-MMT were determined by the Malvern zeta sizer. The results showed that intercalation of the drug in the MMT increased the particle sizes from 1.532 ± 0.01 to 4.215 ± 0.35 µm. In contrast, this caused a decrease in the absolute value of the zeta potential from -43.85 ± 0.63 to -39.35 ± 1.06 mV.

PXRD

The physical status of TT in the optimized MMT formulation was evaluated using PXRD analysis. Figure 2 shows the PXRD patterns of the intact TT, pristine MMT, and TT-MMT. The pure TT showed peaks at 2θ° of 11.85°, 15.85°, 18.3° 21.95°, which was due to the crystalline nature of the drug, whereas these peaks were not observed in TT-MMT. This, thus, indicated that TT was intercalated in the MMT interlayer space in an amorphous or molecular state. PXRD was also used to determine the d-spacing distance in clay particles (17). According to the obtained results, the characteristic peak for the pure MMT was seen at 2θ = 5.4°, which was shifted to 4.4° for TT-MMT, indicating the intercalation of TT in TT-MMT. This also indicated that, during intercalation, the insertion of TT into the organoclay galleries forced the platelets apart and increased the d-spacing from 16.35 to 19.91 Å (18,19).

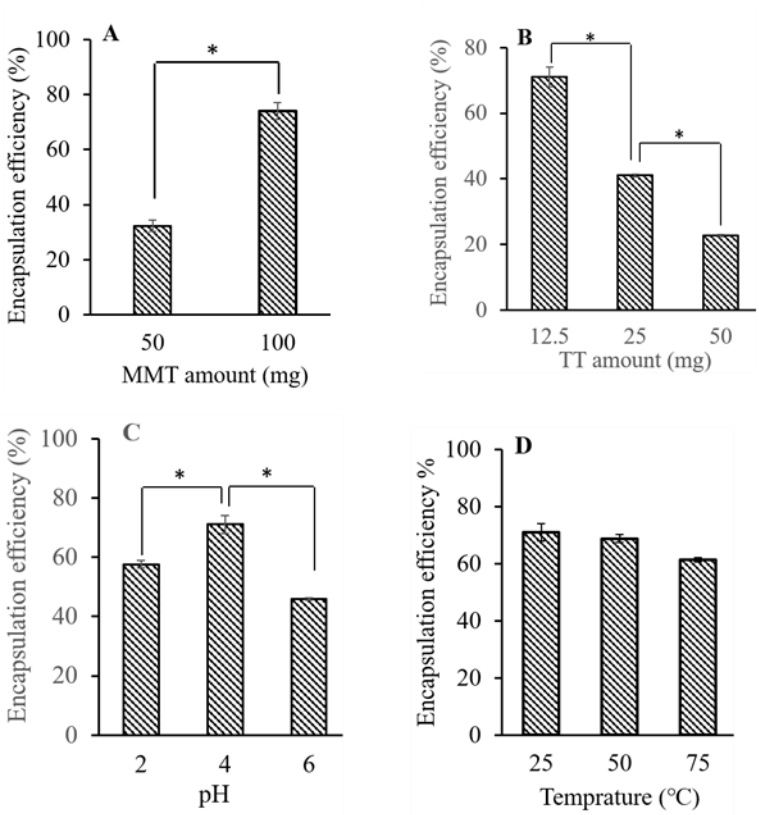

Fig. 1. The effect of (A) MMT content, (B) drug content, (C) pH, and (D) temperature on the drug intercalation capacity of MMT. * Indicates significant differences between groups. MMT, Montmorillonite; TT, tolterodine tartrate.

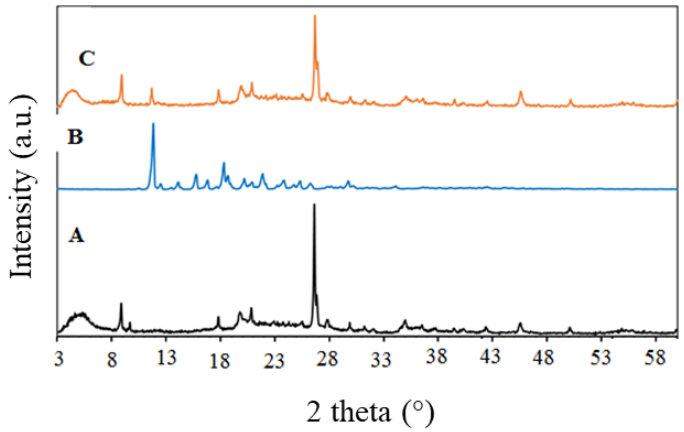

Fig. 2. Powder X-ray diffraction analysis pattern for (A) montmorillonite, (B) tolterodine tartrate, (C) tolterodine tartrate-montmorillonite hybrid.

DSC analysis

In addition to the PXRD analysis, DSC analysis was used to determine the physical status of the drug in the optimized MMT formulation. The results are illustrated in Fig. 3. The DSC curve of TT showed a sharp endothermic peak at 219 ºC corresponding to the melting point of the drug. The DSC curve of the intercalated products did not, however, show any peaks related to TT, indicating that TT was present in an amorphous or molecular state in the MMT (20).

FTIR analysis

FTIR analysis was also carried out to investigate the possible intermolecular interactions between TT and MMT. The FTIR spectra of TT, MMT, and TT-MMT are shown in Fig. 4.

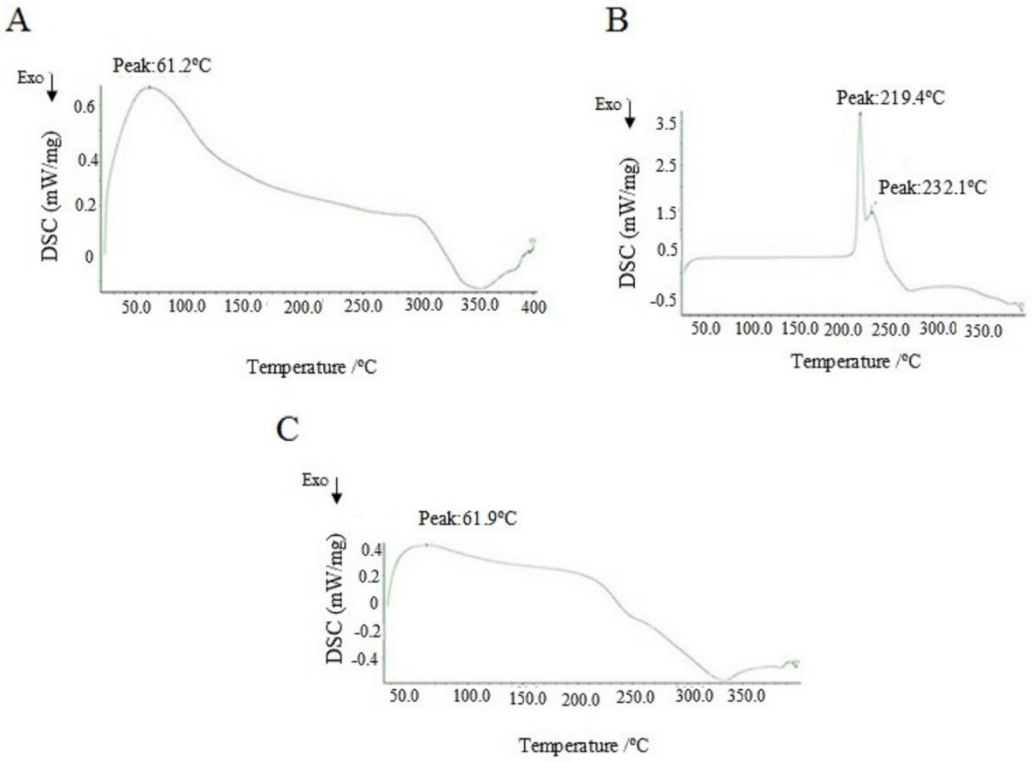

Fig. 3. DSC of for (A) montmorillonite, (B) tolterodine tartrate, (C) tolterodine tartrate-montmorillonite hybrid

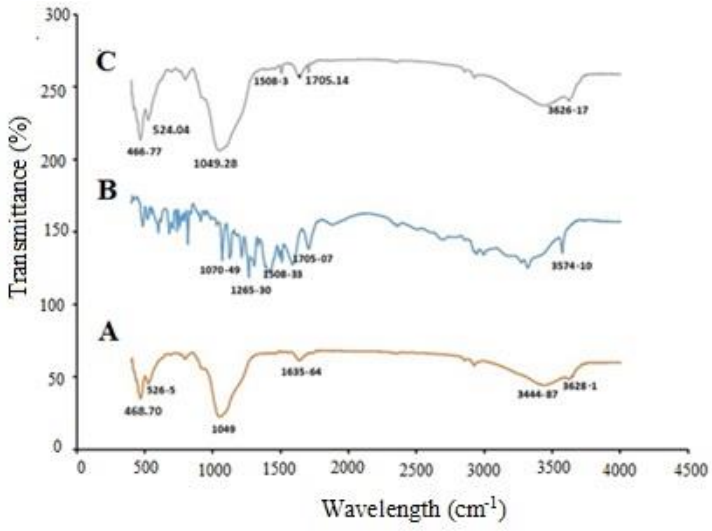

Fig. 4. Fourier-transform infrared spectrum of (A) montmorillonite, (B) tolterodine tartrate, (C) tolterodine tartrate-montmorillonite hybrid.

The FTIR spectrum of MMT showed a band at 3628 cm^{-1} that was related to the OH band stretch of Al-OH and Si-OH. The broad bound around 3444 cm^{-1} was due to the -OH stretching band of the adsorbed water. The peak at 1049 cm^{-1} and 1635.64 cm^{-1} was due to Si-O-Si stretching vibrations and deformation vibration mode, respectively. The bands at 468.70 and 526.57 cm^{-1} were due to the bending vibrations of Si-O-Si and Si-O-Al, respectively (21). The FTIR spectra of TT also showed a band at 3574 cm^{-1}, which was due to the stretching vibrations of the OH group. The bands at 1508 and 1705 cm^{-1} were due to the aromatic phenyl ring and C=O stretching vibrations of the carbonyl group of tartrate, respectively. On the

other hand, the peaks at 1070 and 1205 cm^{-1} were attributed to the C-O and C-N stretching, respectively (22). Although the spectra of TT-MMT closely resembled those of MMT, the presence of the peaks at 1508 and 1705 cm^{-1} proved that the drug existed in the hybrid. In addition, a broad hump in the region of 3400 to 3100 cm^{-1} was probably due to hydrogen bonding between the silanol group of MMT with OH and the amine functional groups of TT.

Morphology

From the SEM image of the pure MMT (Fig. 5), we could see flake-shaped particles, which adhered to each other. After the intercalation of TT into the MMT layers, a structural free space appeared to be filled with TT, and the surface of the TT-MMT hybrid was found to be smoother than the free MMT.

In-vitro release study

This system was designed to mask the taste of TT. To evaluate this, an *in vitro* release study was carried out in PBS (pH = 6.8) for 3 min to simulate the situation of the buccal cavity. It was found that approximately 49% of the free drug was released during 3 min. However, almost no TT was released from TT-MMT during this time, which was desirable for masking the taste of TT. Although the suppressed drug release is required for taste masking, TT should still be delivered efficiently through the gastrointestinal tract to retain its therapeutic efficacy. So, we also performed drug-release experiments in the simulated gastric juice. As shown in Fig. 6, about 80.95 ± 6.39% TT was released within 2 h.

Evaluation of the powder blends

Table 4 shows the properties of the blended powders, including ρb, ρt, Carr's index, angle of repose, and Hausner ratio. The angle of the repose of the powder blend was found to be in the range of 31.20 to 37.24° (Table 4). According to the scale of flowability given in USP (12), the powder with an angle of repose below 35° or between 36-40° showed a good and fair flowing properties, respectively. Hausner ratio and Carr's index were in the range of 1.27-1.37 and 21.31-26.98%, respectively. As stated in USP (12), Hausner's ratio between 1.35-1.45 and Carr's index between 26-31 indicate poor flow. These results indicated various blends showing flow properties from good to poor.

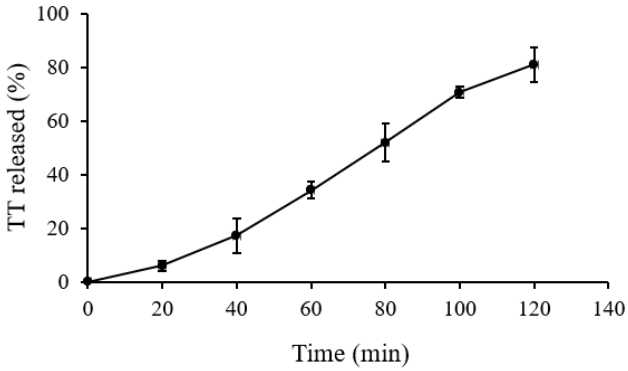

Fig. 6. Release profiles of TT from TT-MMT hybrid in simulated gastric medium, pH = 1.2. TT-MMT, Tolterodine tartrate-montmorillonite hybrid.

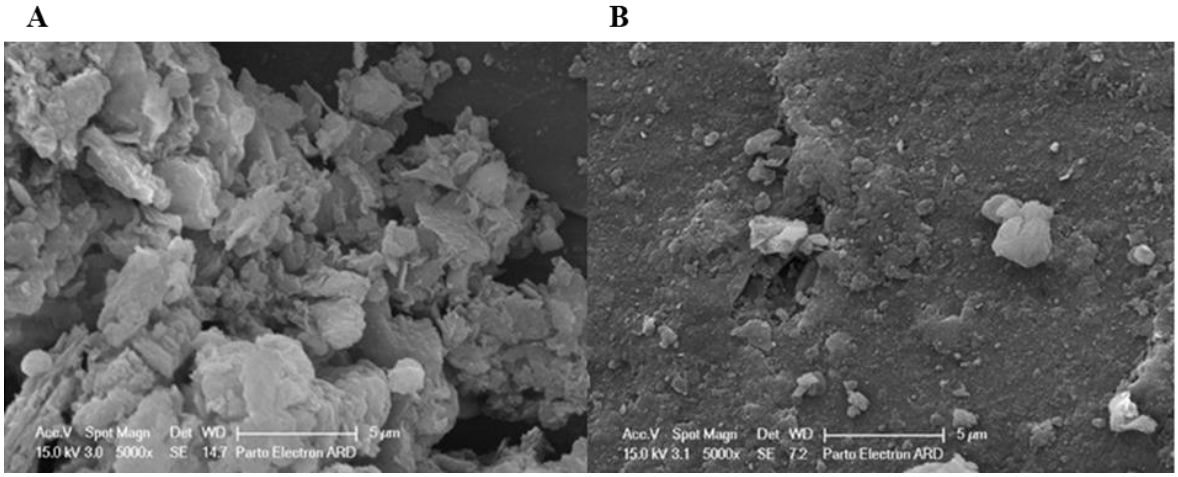

Fig. 5. Scanning electron microscope images for (A) drug free montmorillonite (B) tolterodine tartrate-montmorillonite hybrid.

Table 4. Physical properties of the powder blend. Data are presented as mean ± SD, (n = 3).

Formulations	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner ratio	Angle of repose (°)
F1	0.47 ± 1.21	0.62 ± 0.41	24.19 ± 1.42	1.32 ± 1.03	36.78 ± 0.25
F2	0.43 ± 0.015	0.55 ± 0.85	21.81 ± 0.75	1.27 ± 0.92	37.24 ± 0.37
F3	0.49 ± 0.27	0.66 ± 1.05	25.75 ± 0.31	1.35 ± 0.14	36.41 ± 1.33
F4	0.48 ± 1.02	0.61 ± 0.11	21.31 ± 0.18	1.27 ± 0.66	31.20 ± 0.82
F5	0.51 ± 0.75	0.67 ± 0.78	23.88 ± 1.05	1.29 ± 1.05	34.80 ± 1.55
F6	0.46 ± 0.66	0.63 ± 0.45	26.98 ± 1.42	1.37 ± 0.19	34.74 ± 0.73
F7	0.43 ± 0.42	0.58 ± 1.20	25.86 ± 0.67	1.35 ± 1.27	36.11 ± 0.37
F8	0.45 ± 1.09	0.61 ± 0.23	26.22 ± 0.42	1.35 ± 0.82	36.42 ± 2.14
F9	0.44 ± 0.16	0.59 ± 0.36	25.42 ± 1.07	1.34 ± 0.56	35.12 ± 1.28

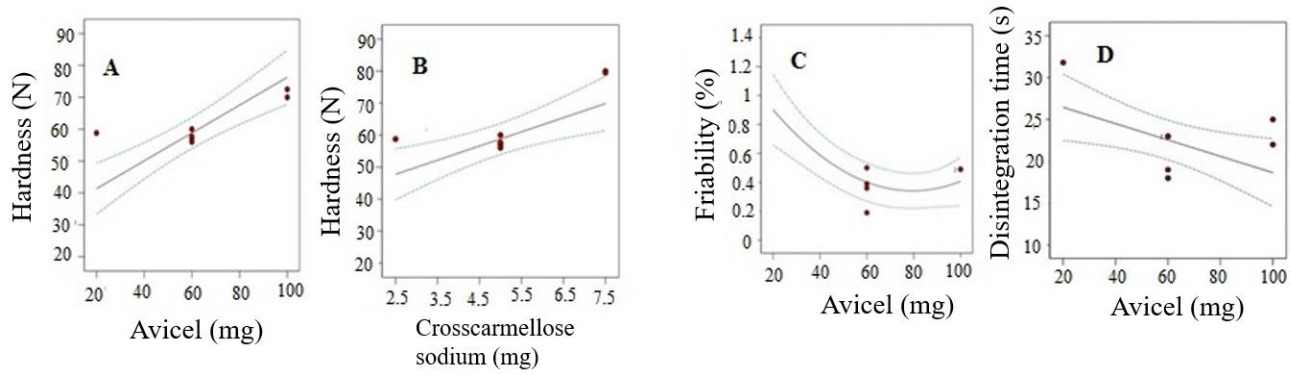

Fig. 7. The effect of different levels of studied parameters on tablet hardness, friability, and disintegration time

Physicochemical evaluation of tablets

The results of the physicochemical evaluation of ODT formulations containing TT-MMT are reported in Table 5. For content uniformity, the obtained values ranged from 0.29 to 5.29% (Table 5) which met the passing criteria of 15% (12). As can be seen in Table 5, the thickness of the prepared tablets was approximately the same. Die and punch selected for compression influenced tablet thickness; in the case of powder with good flow properties, it was expected that the thickness of tablets would remain the same (23). The effect of different levels of studied parameters on physicochemical properties of tablets are shown in Fig. 7A-D. As shown in Table 5, the hardness of the tablets ranged from 24 to 81.5 N. Analysis of the data showed that the hardness of tablets was significantly affected by the amount of Avicel® and CS (*P* value < 0.05). According to the literature (12,24), the acceptable limit of friability is less than 1%. The friability of the prepared ODT was in the range of 0.13 to 1.39% (Table 5). Except for the formulation of F1, all others had friability to an acceptable limit. The results of the experimental design also indicated that the amount of Avicel® significantly affected the tablet's friability (*P* value < 0.05). According to European Pharmacopoeia (16), the disintegration time of ODT must be faster than 3 min. From Table 5, the obtained disintegration time values were in the range of 16-35 s, thus complying with the pharmacopeial requirement. It could be concluded from ANOVA results that the disintegration time was significantly affected by the amount of Avicel® (*P* value < 0.05).

Optimization

The optimal condition for the preparation of optimized formulation was determined using the design expert software, based on some set criteria including constraints and target goals of all dependent variables. Optimization was done in a way that the disintegration time and friability% were the minimum, while hardness was the maximum. The optimum formulation was suggested by the software with a desirability of 89.2%; this consisted of 99.14 mg Avicel® and 6.26 mg CS.

Table 5. Post compressional parameters of formulations. Data are presented as mean ± SD, (n = 3).

Formulations	Hardness (N)	Disintegration time (s)	Friability (%)	Thickness (mm)	Acceptance value (%)
F1	24 ± 0.83	19 ± 0.13	1.39 ± 0.29	3.66 ± 0.01	1.34
F2	58.80 ± 0.65	31.80 ± 0.86	0.13 ± 0.34	3.69 ± 0.02	0.29
F3	37 ± 0.97	35 ± 0.29	0.94 ± 0.52	3.67 ± 0.02	2.33
F4	58.75 ± 0.45	26 ± 0.30	0.73 ± 0.14	3.58 ± 0.03	1.81
F5	56 ± 0.43	19 ± 1.10	0.39 ± 0.28	3.50 ± 0.01	2.70
F6	79.50 ± 0.32	21 ± 1.05	0.49 ± 0.18	3.49 ± 0.02	2.13
F7	68 ± 0.20	17 ± 0.96	0.60 ± 0.28	3.51 ± 0.02	4.77
F8	72.50 ± 1.03	22 ± 0.26	0.49 ± 0.18	3.61 ± 0.03	3.86
F9	81.50 ± 0.71	16 ± 0.90	0.49 ± 0.12	3.74 ± 0.01	5.29

Table 6. Predicted values, observed values and error % for optimized oral-disintegrating tablet containing tolterodine tartrate-montmorillonite complex. Data are presented as mean ± SD, n = 3.

Response variables	Predicted values	Observed values	Error (%)
Disintegrating time (s)	16	16.30 ± 0.56	1.84
Hardness (N)	81.32	81.50 ± 0.73	0.22
Friability (%)	0.463	0.478 ± 0.12	3.13

Table 7. Result of taste masking evaluation and disintegration time *in vivo*. Data are presented as mean ± SD, n = 3.

Formulation	Disintegrating time (s)	Taste-masking score of ODT (0-5)
Pure tolterodine oral-disintegrating tablet	40.76 ± 0.94	1.33 ± 0.56
Tolterodine tartrate-montmorillonite oral-disintegrating tablet	41.63 ± 1.02	5.00 ± 0.00

The optimized formulation was prepared, and the observed responses were determined; the error% was determined using equation 6 (25). According to the obtained error% (in Table 6), there was an acceptable agreement between the observed values and those predicted by the Design-Expert. This confirmed that our method was valid and reliable, with adequate precision for the prediction of the optimized conditions for the preparation of ODT.

$$\text{Error (\%)} = \left(\frac{Observed\ value - predicted\ value}{Predicted\ value}\right) \times 100 \qquad (6)$$

Panel test

The results of the human taste panel, as summarized in Table 7, revealed that the bitterness score of TT-MMT-ODT decreased compared with TT-ODT. The mean results of the *in-vivo* disintegration time for the pure TT ODT and TT-MMT-ODT were 40.76 and 41.63 s (Table 7), which were acceptable based on European Pharmacopoeia (≤ 3 min).

DISCUSSION

In the present study, we have developed ODT containing the TT-MMT hybrid for the taste masking of TT. To achieve optimal preparation conditions for the TT-MMT hybrid, several parameters including the initial concentration of TT and MMT, temperature, and pH were assessed. According to Fig. 1A, increasing the amount of MMT significantly raised EE% from 32.30% to 71.06%, which could be due to more drugs adsorbed and intercalated with the higher MMT. This was also in line with the results obtained by Hou and his coworker (26) on MMT for the drug delivery of betaxolol hydrochloride. As can be seen in Fig. 1B, when the drug amount increased from 12.5 mg to 50 mg, a significant decrease in EE% from 71.06% to 22.67% was observed. This could be explained by the lack of available adsorption sites for the greater concentration of the drug (27). In agreement with our findings, Kaur *et al*. (27) observed that

a decrease in diclofenac sodium concentration led to the rise of the intercalated drug. It could be observed from Fig. 1C that an increase of pH up to 4 raised the EE% of TT. TT is a weak base with a pKa value of about 9.9 (28). The pH of the zero-point charge of MMT was also around 7.2. In pH 2, the competition between the cationic drug and H^+ protons, present on the silanol groups of the MMT surface caused a decrease in EE% compared with pH 4 (P value < 0.05). However, a further increase of pH from 4 to 6 decreased EE% from 71.06 to 45.92 (P value < 0.05), which was possibly due to the increase in the neutral species of TT. This was in line with the results obtained from other studies (29,30). The effect of temperature was also evaluated, as can be seen in Fig. 1D, showing no significant differences between samples (P value > 0.05).

The particle sizes and zeta potentials of pristine MMT dispersions and the optimized TT-MMT were determined. According to the obtained results, after intercalation of the drug into the MMT, particle size was increased (P value < 0.05) possibly due to drug intercalation within the interlayer space of MMT or adsorption of some portion of the drug on the surface of the clay. This finding was in line with another study as well (31). The absolute value of the zeta potential was decreased from -43.85 ± 0.63 to -39.35 ± 1.06 mV (P value < 0.05) due to the neutralization of the negative charge of MMT with the amine functional groups of TT (32). As another group of scientists, Silva and colleagues (32) also found out that zeta potential tended to decrease following the tamoxifen adsorption. The optimized TT-MMT exhibited no release during 3 min in PBS (pH = 6.8), which was due to a strong ionic interaction between the TT and the MMT interlayers (7). This result was in agreement with similar studies reporting considerable suppression of drug release after loading sildenafil into MMT (7). Nine different ODT formulations containing TT-MMT were developed by the direct compression method, using CS and Avicel® as superdisintegrants. Physicochemical tests were then conducted on the prepared tablets; these included hardness, friability, thickness, disintegrating time, and drug content. Tablets must have an optimum mechanical strength to tolerate the mechanical shocks of handling during their manufacture, packaging, and transport (23). As can be seen in Fig. 7 A and B, raising the amount of Avicel® and CS increased the tablet hardness (P value < 0.05), which was in line with the previous studies (33-36). This finding could be related to numerous hydrogen binding sites in cellulose excipients, such as Avicel® and CS, which enhanced particles interlocking. From Fig. 7C, at higher Avicel®, a decrease in friability was observed (P value < 0.05). These changes were parallel with those in tablet hardness. Thus, the higher the hardness, the lower the friability of the tablet. By increasing the amount of Avicel®, the disintegration time was also decreased (P value < 0.05, Fig. 7D). This could be due to the porous morphology of Avicel®, which caused the penetration of hydrophilic liquid (water) into the tablet matrix employing capillary pores and the subsequent breaking of hydrogen bonds between cellulose microcrystals (37). The results of the human taste panel also revealed that the bitterness score of TT-MMT-ODT was decreased, as compared with TT-ODT, which could be due to the negligible TT release in the first 3 min. It was found that the *in vivo* disintegration time for TT-MMT-ODT was longer than the *in vitro* disintegration time because the available water absorbed by the tablet in the mouth was less compared with that in the vessel. This was in line with our previous study too (38).

CONCLUSION

In the present study, we successfully prepared a new ODT using MMT as a taste-masking agent. The study demonstrated that TT was present in an amorphous or molecular state in MMT. The MMT formulation in the tablets delayed the initial release of TT, which was considered advantageous concerning the bitter taste of TT. The results of the human taste panel also revealed that the optimal ODT tablet remarkably improved the taste of TT. Therefore, the ODT containing TT-MMT could be used as a substitute for TT for further clinical applications following pharmacokinetic studies.

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Conflict of interest statement

The authors declared no conflicts of interest in this study.

Authors' contributions

H. Talabaki contributed to the investigation; S. Taymouri contributed to the conceptualization, methodology, analysis, writing, reviewing, and editing of the article, and supervised the study; A. Mostafavi contributed to the conceptualization, methodology, and supervision of the study. The finalized article was approved by all authors.

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