Magnetic triazine-based dendrimer as a versatile nanocarrier for efficient antiviral drugs delivery

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Nanoscale engineering is an efficient method for the treatment of multiple infectious diseases. Due to the controllable functionalities, surface properties, and internal cavities, dendrimer-based nanoparticles represent high performance in drug delivery, making their application attractive in pharmaceutical and medicinal chemistry. In this study, a dendritic nanostructure (Fe3O4@SiO2@TAD-G3) was designed and fabricated by grafting a triazine-based dendrimer on a magnetic nanomaterial. The structure of synthesized hybrid nanostructure was characterized by Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), energy-dispersive X-ray (EDX) spectroscopy, elemental mapping, scanning electron microscopy (SEM), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), and vibrating sample magnetometry (VSM). The prepared nanostructure (Fe3O4@SiO2@TAD-G3) combines the unique properties of magnetic nanoparticles and a hyperbranched dendrimer for biomedical applications. Its dual nature and highly exposed active sites, could make the transportation of drugs to targeted sites of interest through the magnetic field. A study was conducted on model drugs loading (Favipiravir and Zidovudine) and in vitro release behaviour of Fe3O4@SiO2@TAD-G3, which was monitored by ultraviolet spectroscopy. The dendritic nanostructure exhibited high drug-loading capacity for Favipiravir (63.2%) and Zidovudine (76.5%). About (90.8% and 80.2%) and (83.5% and 83.4%) of loaded Favipiravir and Zidovudine were released from Fe3O4@SiO2@TAD-G3 at pH 1.5 and 6.8 respectively, within 600 min and at 37 °C. The initial fast release attributed to the drug molecules on the surface of nanostructure while the drugs incorporated deeply into the pores of the Fe3O4@SiO2@TAD-G3 released with a delay. We proposed that Fe3O4@SiO2@TAD-G3 could be tested as an effective carrier in the targeted (cellular or tissue) delivery of drugs. We think that the prepared nanostructure will not deposit in the liver and lungs due to the small size of the nanoparticles.

In recent years, the use of metallic, bimetallic, and superparamagnetic iron oxide nanoparticles (Fe3O4) has gained significant importance for biomedical applications, including magnetic resonance imaging contrast agent (MRI), hyperthermia, bio-sensing, tissue engineering and cell separation, and targeted drug and gene delivery1–8. The iron oxide nanoparticles have elegant properties including reactive surface, high magnetization value, narrow size distribution, high stability, and biocompatibility which are required for these biomedical applications9,10. Therefore, preparation of the monodispersed Fe3O4 nanoparticles and functionalization of the surface of these particles by coating biocompatible polymers or targeting ligands are much desired.

Dendrimers are nano-sized tree-like molecules with precise architecture and low polydispersity, consisting of a core and branches extending outward, which are synthesized in a layer-by-layer fashion and provide suitable well-defined structures for drug solubilization and delivery applications. There is a high control over the size, branching points, and active group functionality of dendrimers to achieve the proper applications11,12. Dendrimers, based on the size, surface properties, and functional groups, can be chemically attached to various molecules and encapsulate cargos to protect these molecules against the harmful effects of external factors. In addition, they can release these molecules into their targeted environment13,14. Furthermore, they could have a significant application in the co-delivery of hydrophobic/hydrophilic drugs for increased synergistic treatment. Over the last decades, several nano-sized and shaped dendritic scaffolds have been synthesized, which have various functionalities and applications including poly(amidoamine) (PAMAM), poly(propylene imine) (PPI), triazine, and polyester dendrimers2,15–23.

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Novel drug delivery systems (NDDS) have many advantages, including enhanced therapy by increasing the productivity and duration of drug activity, increased patient compliance through minimized dosing frequency and appropriate routes of administration and improved site-specific delivery to reduce the undesirable adverse effects.

Human immunodeficiency virus (HIV) and Coronaviruses are serious issues for the new century. HIV disrupts T cells thereby compromising the host’s immune system. Zidovudine, known as a nucleoside reverse transcriptase inhibitor, is designed for the treatment of human immunodeficiency virus (HIV-1) in conjunction with other antiretroviral medications. It is also specified for avoiding vertical transmission of the human immunodeficiency virus (HIV-1) between mother and fetus. Zidovudine indications also include the treatment of adult T-cell leukemia25–30. A worldwide spreading viral disease known as a novel severe acute respiratory syndrome called coronavirus 2 (SARS-CoV-2) abbreviated as COVID-19 pandemic (starts spreading in December 2019) which endangered seriously public health and created an urgent need for effective drugs to treat COVID-19 infection.

Considering the unique properties of both magnetic nanoparticles (MNPs) and dendrimers, we have investigated the modification of silica-coated magnetite nanoparticles (Fe3O4@SiO2) with triazine-based polyethanolamine dendrimer of generation 3 to construct an efficient drug delivery system (Fe3O4@SiO2@TAD-G3).

Results and discussion
In this work, a divergent strategy used for decorating solid supports with dendrimers by introducing a linker on the surface of magnetic nanoparticles. The triazine-based poly(ethanolamine) (PETAM) dendrimer was selected because of its highly exposed active sites which could have good interactions with guest molecules. So, the dendrimer grafted step by step on the surface of silica-coated magnetite nanoparticles (Fig. 1). Initially, magnetic Fe3O4 nanoparticles were prepared by co-precipitation and then coated with a silica layer via the Stöber method.

Figure 1. Synthetic pathway for construction of dendrimer-coated magnetite nanoparticles (Fe3O4@SiO2@TAD-G3).
provide an amino group as a starting point (linker). The nucleophilic substitution of amino group on cyanuric chloride produced Fe₃O₄@SiO₂@Pr-TCl₂. PETAM Dendron up to generation three (G3) were then fabricated by stepwise consecutive nucleophilic aromatic substitution of ethanolamine on aromatic triazine ring.

Figure 2 shows the FT-IR spectra of Fe₃O₄ (a), Fe₃O₄@SiO₂ (b), Fe₃O₄@SiO₂-PrNH₂ (c), Fe₃O₄@SiO₂-TzCl₂ (d), Fe₃O₄@SiO₂@D-G₁ (e), Fe₃O₄@SiO₂-Tz-BEA-TzCl₄ (f), Fe₃O₄@SiO₂@D-G₂ (g), Fe₃O₄@SiO₂-Tz-TEA-TzCl₈ (h), Fe₃O₄@SiO₂@TAD-G₃ (i).

The crystallinity of Fe₃O₄ (a), Fe₃O₄@SiO₂-TzCl₂ (b), and Fe₃O₄@SiO₂@TAD-G₃ (c) was characterized by X-ray powder diffraction patterns (XRD, Fig. 3). Comparing the XRD patterns of Fe₃O₄, Fe₃O₄@SiO₂-TzCl₂, and Fe₃O₄@SiO₂@TAD-G₃ in the wavenumber range 400–4000 cm⁻¹. The FT-IR spectrum of the bare magnetic Fe₃O₄ nanoparticles indicated the characteristic Fe–O absorption band around 580 cm⁻¹ (Fig. 2a). The bands at 1101, 900–800, and 450 cm⁻¹ relating to the asymmetric stretching, symmetric stretching, in-plane bending, and rocking mode of the Si–O-Si and Si–O bonds, are appeared in the Fe₃O₄@SiO₂ spectrum (Fig. 2b). The broad band in the range 3200–3500 cm⁻¹ appertained to the stretching vibration mode of Si–OH bonds and the weak band at 1630 cm⁻¹ related to the twisting vibration mode of H–O-H adsorbed in the silica layer. The presence of alkyl groups has been corroborated by the weak symmetric and asymmetric stretching vibrations at 2980 and 2895 cm⁻¹ (Fig. 2c–i). Also, the bands corresponding to C=N, C=C, and C–N appeared at 1350–1600 cm⁻¹ (Fig. 2d–i). The N–H bending vibrations are overlapped with O–H vibrations. Therefore, the above results confirm the successful grafting of different functional groups in each fabrication step.

The crystallinity of Fe₃O₄ (a), Fe₃O₄@SiO₂-TzCl₂ (b), and Fe₃O₄@SiO₂@TAD-G₃ (c) was characterized by X-ray powder diffraction patterns (XRD, Fig. 3). Comparing the XRD patterns of Fe₃O₄, Fe₃O₄@SiO₂-TzCl₂, and
Fe3O4@SiO2@TAD-G3 indicate the same peaks, confirming the stability of the ferrite core without any phase changing during the functionalization process. The XRD patterns of the prepared Fe3O4@SiO2@TAD-G3 show diffraction peaks at 2θ = 30.2°, 35.4°, 43.7°, 56.6°, and 63.0°, which can be assigned to the (220), (311), (400), (422), (511), and (440) Miller planes of Fe3O4 nanoparticles. These XRD patterns confirm that the material structure has a cubic spinel phase (Fig. 3a–c) and match with the standard Fe3O4 sample (JCPDS file No. 19–0629). The appearance of a broad peak at 2θ = 18° to 25° confirms the presence of a SiO2 amorphous layer (Fig. 3b,c).

The average crystallite size of Fe3O4@SiO2@TAD-G3 was estimated by the Scherrer equation (d = 0.9λ/βcosθ). In this equation, λ, β and θ are x-ray Cu wavelength, line broadening at half the maximum intensity (FWHM), and Bragg angle, respectively. The crystallite size as calculated from the width of the peak at 2θ = 35.4° (311), is 21 nm which is approximately in the range determined using FE-SEM and TEM analysis.

The size and morphology of Fe3O4@SiO2@TAD-G3 are investigated by field emission scanning electron microscopy (FE-SEM). As shown in Fig. 4a–c, the Fe3O4@SiO2@TAD-G3 nanostructure possesses nearly spherical morphology with an average diameter of about 15–35 nm. The energy-dispersive X-ray spectroscopy (EDS), obtained from SEM analysis of Fe3O4@SiO2@TAD-G3 (Fig. 4d) displays the presence of Fe, Si, O, N, and C in the nanostructure. Moreover, the higher peak intensity of the Si element compared to the Fe peak indicates that Fe3O4 nanoparticles are trapped by SiO2 and organic molecules and confirms the synthesized core–shell structure.

The transmission electron microscopy (TEM) analysis provides additional visualization of the size and morphology of the Fe3O4@SiO2@TAD-G3 structure (Fig. 5). The structure is almost spherical. This technique displays a dark nano-Fe3O4 core surrounded by a grey silica shell, and the average size of the synthesized nanomaterial is estimated to be 15–30 nm.

Thermal stability of Fe3O4@SiO2-PrNH2 (a), Fe3O4@SiO2@D-G1 (b), Fe3O4@SiO2@D-G2 (c), Fe3O4@SiO2@TAD-G3 (d) is considered at 25–950 °C (Fig. 6). The TGA curves of all samples exhibited apparent weight losses from 150 to 700 °C, correlated to the decomposition of grafted organic moieties. It is worth noting that the weight losses of Fe3O4@SiO2@TAD-G3, and Fe3O4@SiO2@D-G2 were higher and sharper than Fe3O4@SiO2@D-G1.
which strongly proves the successful growth of triazine dendrimer onto the surface of Fe₃O₄@SiO₂ particles. A slight weight loss (3–5%) below 175 °C has appeared for all samples, which related to the loss of physically adsorbed water or solvent. In Fig. 2a, an apparent weight loss (10%) was seen in the range of 200–700 °C, which can be attributed to the anchored aminopropyl groups on Fe₃O₄@SiO₂ nanoparticles.

The magnetization curves of Fe₃O₄ (a), Fe₃O₄@SiO₂-PrNH₂ (b), and Fe₃O₄@SiO₂@TAD-G3 (c) were measured by the VSM analysis in the range ± 8000 Oe at room temperature (Fig. 7). The S-like magnetization curves, the coincidence of the hysteresis loop, and the low remanence and coercivity confirm the superparamagnetic properties of these hybrid materials. The maximum saturated magnetization of Fe₃O₄ nanoparticles was 45 emu/g which was dropped to 35 emu/g and 15 emu/g for Fe₃O₄@SiO₂-PrNH₂ (b) and Fe₃O₄@SiO₂@TAD-G3 (c) respectively, which confirm the successful anchoring of the linkers, and dendrons on nanoparticles surface.

**Drug loading and In vitro drug release from dendritic nanostructure.** In this study, drugs were incorporated into dendritic nanostructure (as a drug carrier) by the post-loading procedure. Drug loading on the synthesized dendritic nanostructure was evaluated by X-ray powder diffraction patterns for Zidovudine (Fig. 8), and Favipiravir (Fig. 9), respectively. The X-ray analyses results confirm apparently the successful

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**Figure 5.** TEM images of Fe₃O₄ (a) and Fe₃O₄@SiO₂@TAD-G3 (b).

**Figure 6.** TGA analyses of Fe₃O₄@SiO₂-PrNH₂ (a), Fe₃O₄@SiO₂@D-G1 (b), Fe₃O₄@SiO₂@D-G2 (c), Fe₃O₄@SiO₂@TAD-G3 (d).
drugs loading into the nanostructure. The loading Favipiravir and Zidovudine onto the nanostructure was measured by UV–Vis spectrometer at 235 nm and 266 nm, respectively. Then, a calibration curve and the absorbance value obtained for the Fe₃O₄@SiO₂@TAD-G3/Drug NPs were used to calculate the concentration of Favipiravir and Zidovudine. Based on the determined concentration, drug loading was respectively calculated as 63.2 and 76.5% for Favipiravir and Zidovudine, at pH 6.8 (Fig. 10).

In vitro controlled release behavior of Favipiravir and Zidovudine as model drugs were studied for ~ 600 min in simulated gastric fluid (SGF, pH 1.5) and simulated intestinal fluid (SIF, pH 6.8) at physiological temperature (37 °C). The percentages of drug releases were measured by UV–Vis spectroscopy and is plotted as a cumulative release versus time for Favipiravir and Zidovudine (Fig. 11). In vitro drug release experiments were replicated three times and the standard deviations represented in the Fig. 11. The pooled standard deviations are calculated to be 0.27, and 0.61 for release of Favipiravir and Zidovudine, respectively.

As can be seen in Fig. 11, the maximum Favipiravir and Zidovudine release has occurred at pH 1.5. Initially, a burst release from Fe₃O₄@SiO₂@TAD-G3 was observed in the Favipiravir and Zidovudine first 90 min, whereby almost (76% and 63%) and (78% and 69%) of them were released at pH 1.5 and 6.8, respectively. In addition,
about (90.8% and 80.2%) and (95.5% and 83.4%) of loaded Favipiravir and Zidovudine were released from Fe3O4@SiO2@TAD-G3 at pH 1.5 and 6.8, respectively, within 600 min.

In fact, after burst release, the rate of release decreased and the Favipiravir and Zidovudine entrapped into Fe3O4@SiO2@TAD-G3 were released moderately over the 24 h. The initial release could be ascribed to part of the drug molecules located on or close to the dendrimer surface. When the Fe3O4@SiO2@TAD-G3 contacts with the release medium, it diffuses faster than the drug incorporated deeply into the pores of the Fe3O4@SiO2@TAD-G3.

The mechanism of drug release from the prepared nanostructure depends on various factors such as the composition of dendrimers (type of the branches, type of drug and additives), size and shape of the nanostructure, and the environmental conditions during drug release. To confirm the proposed release mechanism, the zeta potential of nanocarrier was studied at different pHs. When the pH increased from 3 to 9, the zeta potential of the nanostructure decreased from +16.15 mV to -33.31 mV (Fig. 12). It is anticipated a low pH causes the -NH and -OH groups to become protonated and exist in the form -NH2+ and -OH2+. Thus, these groups are ionized and their charges repel each other. This force expands dendrimer leading to more space among the branches of dendrimer which facilitates the migration of drug molecules. While, at high pH, both forms of NH groups are present and the repulsion force decreases and less drug is released. As shown in Fig. 10, the release of synthesized nanostructure was more desirable for zidovudine.

**Conclusion**

In conclusion, a dendritic nanostructure (Fe3O4@SiO2@TAD-G3) was designed and synthesized by grafting a triazine-based dendrimer on a magnetic nanomaterial. The structure of synthesized hybrid nanostructure was characterized by FT-IR, XRD, EDX, SEM, TEM, TGA, and VSM techniques. The drugs (Favipiravir and Zidovudine) were loaded at pH 1.5 and 6.8, respectively, with high entrapment efficiency.
Zidovudine) loading on Fe₃O₄@SiO₂@TAD-G3 and its in vitro release behaviour as a drug carrier was investigated and monitored by ultraviolet spectroscopy. The dendritic nanostructure exhibited high drug-loading capacity for Favipiravir (63.2%), and Zidovudine (76.5%). In vitro drug release behaviour in simulated gastric buffer and simulated intestinal buffer was evaluated at physiological temperature (37 °C) and it was found that about (90.8% and 80.2%) and (95.5% and 83.4%) of loaded Favipiravir and Zidovudine were released from Fe₃O₄@SiO₂@TAD-G3 at pH 1.5 and 6.8 respectively, within 600 min. Finally, we suggest that the biocompatibility and effectiveness of this nanostructure in the targeted drug delivery could be investigated in the future works.

Figure 11. Drug release study of Fe₃O₄@SiO₂@TAD-G3/Drug in simulated gastric fluid (SGF, pH 1.5) and simulated intestinal fluid (SIF, pH 6.8) for (a) Zidovudine, and (b) Favipiravir as model drugs.

Figure 12. The zeta potential of Fe₃O₄@SiO₂@TAD-G3 at different pHs.
Methods
All reagents for the synthesis and analysis were commercially available from Aldrich and Merck Companies and used as received without further purification. Favipiravir (Mw = 267.104 g/mol) was purchased from Actoverco Pharmaceutical Company (Isfahan, Iran). Zidovudine (Mw = 267.242 g/mol) was purchased from Bakhtar Biochemical Pharmaceutical Company (Isfahan, Iran). Deionized water was used in all experiments. Fourier transform infrared spectroscopy (FT-IR) was recorded using KBr pellet by Alpha Bruker Fourier transform (FT-IR) spectrophotometer in the range of 400–4000 cm⁻¹. The crystallinity of nanomaterials was evaluated by Philips Xpert X-ray powder diffraction (XRD) instrument (Cu-Kα radiation and λ = 0.15406). A MIRA 3-XMU field emission scanning electron microscope (FE-SEM) with energy dispersive X-ray analysis (EDX) was used to elucidate the surface morphology and elemental distribution. Transmission electron microscopy (TEM) was performed on a CM120 apparatus. The thermogravimetric analysis (TGA) was studied on a Metler TA4000 system under a nitrogen atmosphere in the range of 25–700 °C at a heating speed of 15 °C/min. The magnetic properties of nanoparticles were studied by a 730 vibrating sample magnetometer (VSM) at room temperature. Total C, N, and H contents were measured using dry combustion (975 °C) on a CHNS analyzer (Vario EL III). UV–Vis spectroscopy (Perkin-Elmer Lambda double beam) in the range 190–900 nm was used to study the release of Favipiravir and Zidovudine.

Statistical analysis. The standard deviation is simply the square root of the variance. For each time of the drug release under the same conditions, three tests were repeated, and the standard deviation was calculated for each time using following formula. The sample statistic follows the same convention and is given as $S_i$ is each of the values of the obtained data, $N$ is the total number of tests (data points), and $\bar{x}$ is the mean of the obtained data.

$$S = \sqrt{\frac{\sum_{i=1}^{N} x_i^2}{N}}$$

The pooled standard deviation is the average spread of all data points about their group mean (not the overall mean). It is a weighted average of each group’s standard deviation. So, the pooled standard deviation was calculated following equation.

$$S_{pooled}^2 = \frac{(N_1 - 1)S_1^2 + (N_2 - 1)S_2^2 + (N_3 - 1)S_3^2 + \cdots}{N_1 + (N_2 - 1) + (N_3 - 1) + \cdots}$$

Preparation of Fe$_3$O$_4$ MNPs. Fe$_3$O$_4$ MNPs were synthesized by the co-precipitation method$^{39}$. FeCl$_2$.4H$_2$O (5 mmol, 0.99 g) and FeCl$_3$.6H$_2$O (10 mmol, 2.7 g) were dissolved in 100 mL of deionized water and stirred at 80 °C for 1 h. Then, NH$_4$OH (10 mL, 25 w%) was added to the mixture and stirred for 1 h under the same conditions. Finally, the precipitate was separated by a magnet, washed with deionized water and ethanol, and dried at 50 °C in a vacuum oven.

Synthesis of silica-coated magnetite nanoparticles (Fe$_3$O$_4$@SiO$_2$). Fe$_3$O$_4$@SiO$_2$ MNPs were prepared using Stöber method$^{40}$. In this synthetic procedure, Fe$_3$O$_4$ MNPs (1 g) were dispersed in EtOH (40 mL) and H$_2$O (20 mL) under ultrasound irradiation for 30 min. Then, NH$_3$ (10 mL, 25 w%) was added to the mixture and stirred for 1 h under the same conditions. Afterward, tetraethyl orthosilicate (1.4 mL) was added and stirred at room temperature for 12 h. The final precipitate (Fe$_3$O$_4$@SiO$_2$) was recovered, washed with deionized water and ethanol, and dried at 50 °C in a vacuum oven.

Synthesis of 3-Aminopropyl-functionalized silica-coated magnetite nanoparticles (Fe$_3$O$_4$@SiO$_2$@PrNH$_2$). 3-Aminopropyl-functionalized magnetite nanoparticles (Fe$_3$O$_4$@SiO$_2$@PrNH$_2$ MNPs) were prepared based on our previous work$^{41}$. Fe$_3$O$_4$@SiO$_2$ (1 g) and 20 mL toluene were poured into a round-bottomed flask (100 mL) and dispersed under ultrasound for 30 min. Then, 1.4 mL of (3-Aminopropyl) trimethoxysilane (APTMMS) was added to the mixture and sonicated for 10 min. The mixture was refluxed for 24 h at 110 °C. Then, the black precipitate was separated by an external magnet, washed with toluene, and dried at 50 °C in a vacuum oven.

Triazine dichloride-functionalized silica-coated magnetite nanoparticles (Fe$_3$O$_4$@SiO$_2$-TzCl$_2$). Fe$_3$O$_4$@SiO$_2$-TzCl$_2$ was prepared according to the reported method$^{42}$. The mixture of Fe$_3$O$_4$@SiO$_2$-PrNH$_2$ nanoparticles (1 g), THF (10 mL), and Et$_3$N (0.7 mL) was sonicated for 10 min to produce a uniform suspension. Then, 1 g of cyanuric chloride was added to the suspension and stirred at room temperature for 24 h. The black solid was isolated by a magnet and washed with hot toluene and ethanol to remove unreacted cyanuric chloride. This solid was dried at 60 °C under a vacuum.

The preparation of dendrimer-coated magnetic nanoparticles (Fe$_3$O$_4$@SiO$_2$-D-G1). The coating of dendrimer generation 1 on MNPs (MNPs@G1) was performed according to the literature$^{43}$. Fe$_3$O$_4$@SiO$_2$-TzCl$_2$ (1 g) was dispersed in dioxane (40 mL) 20 min. Then K$_2$CO$_3$ (5 mmol, 0.7 g) and ethanolamine (10 mmol, 0.7 g) was added to mixture and refluxed at 100 °C for 24 h. The solid was gathered using an external magnet, washed with dioxane, and dried at 50 °C under vacuum.
The preparation of dendrimer-coated magnetic nanoparticles (Fe₃O₄@SiO₂@D-G2). MNPs@G (1 g) was poured into a round-bottomed flask and dispersed in dichloromethane (50 mL) for 10 min. Cyanuric chloride (10 mmol, 1.8 g), tetrabutylammonium bromide (TBAB) (0.001 g) and NaOH (1 M) were added to the suspension and stirred for 2 h at 5 °C in an ice water bath. Subsequently, the mixture was stirred at room temperature for 24 h. The black magnetic precipitate was isolated by a magnet, washed with dichloromethane, and dried at 50 °C under a vacuum. After that, 10 mg of Fe₃O₄@SiO₂@D-G2/Drug was mixed with a phosphate buffer solution (100 mL) with pH 6.8 in a round-bottomed flask. The solution was stirred for 12 h at 25 °C, and filtered by a membrane filter with 0.40 μm pores. The drugs content of the obtained filtrates was estimated by measuring their absorbance at 235 nm for Favipiravir, and at 266 nm for Zidovudine, respectively. The percentage of drug loading and the drug entrapment efficiency were calculated based on the reported procedure45.

Drug loading on dendritic nanostructure. The nanostructure Fe₃O₄@SiO₂@TAD-G3 (20 mg) were added to a 3 mL of aqueous solution of drugs (100 ppm) separately at 25 °C for 24 h under stirring. After that, 10 mg of Fe₃O₄@SiO₂@TAD-G3/Drug was mixed with the phosphate buffer solution (100 mL) with pH 6.8 in a round-bottomed flask. The solution was stirred for 12 h at 5 °C, and filtered by a membrane filter with 0.40 μm pores. The drugs content of the obtained filtrates was estimated by measuring their absorbance at 235 nm for Favipiravir, and at 266 nm for Zidovudine, respectively. The percentage of drug loading and the drug entrapment efficiency were calculated based on the reported procedure45.

In vitro drug release from dendritic nanostructure. Drug release was considered for dendritic nanostructure in simulated gastric buffer (pH 1.5, 7 mL HCl, 2 g NaCl and 1000 mL distilled water) and simulated intestinal buffer (pH 6.8, 6.8 g K₂HPO₄, 1.6 g NaOH and 1000 mL distilled water). The drug-loaded magnetic nanoparticles Fe₃O₄@SiO₂@TAD-G3 were added to 200 mL of buffer solution at 37 °C (physiological temperature) under mild agitation with a shaking rate of 80 rpm. At specific time intervals, 1 mL of the release medium was removed and replaced with a 1 mL of fresh buffer solution. Then, samples were filtered by a magnet, and the concentration of the released drug was measured by a UV spectrophotometer (at 235 nm for Favipiravir and 266 nm for Zidovudine) and compared to the standard calibration curve (the absorbance as a function of drug concentration) was studied in the UV spectrophotometer.

Data availability. All data generated or analysed during this study are included in this article and its supplementary information file.

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R.A. and M.A.B. conceived and planned the experiments and also they contributed to the interpretation of the results. R.A. carried out the experiments and products synthesis and also provided the primary draft of the manuscript. S.A. contributed to the interpretation of data and visualisation of the manuscript. M.A.B. supervised the project and revised the final version of the manuscript. All authors approved the final version of the manuscript to be published.

Competing interests
The authors declare no competing interests.

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