

Fabrication and characterisation of new type of magnetic nanoanion exchanger particles for enteric losartan potassium delivery

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Magnetite nanoparticles (MNPs) were synthesised and grafted with polymer containing brilliant cresyl blue for the exchange of losartan potassium. The resulted polymeric nanoparticles were characterised with Fourier transform infrared spectroscopy, elemental analysis, thermogravimetric analysis and transmission electron microscopy. The effects of the exchange parameters such as sample pH, temperature and contact time on sorption of losartan potassium were investigated. The sorption capacity of the functionalised sorbent was 19.4 mg g^{-1} . The equilibrium adsorption data of losartan potassium on modified nanoparticles were analysed by Langmuir, Freundlich, Temkin, Dubinin–Radushkevich and Redlich–Peterson equations. Nearly, 74% of losartan potassium was released in simulated gastric fluid of pH 1.2 in 15 h and 50% in simulated intestinal fluid pH 7.4 in 30 h. These results have shown the utility of losartan potassium loaded–modified MNPs for enteric drug delivery.

1. Introduction: Hypertension (high blood pressure) is a general status, in which the long-term force of the blood against the artery walls is adequately high that it may in the long run cause health problems such as heart disease. Losartan, 2-butyl-4-chloro-1-[[2%-(1H-tetrazol-5-yl) [1,1%-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol, acts by selectively binding to and blocking the angiotensin II type 1 receptor, thus interfering with the rennin angiotensin system, an important regulator of normal blood pressure [1–4]. Losartan can be found in the form of standard pills. A literature survey revealed special studies for the analysis of losartan potassium in biological fluid and tablet formulations [5, 6]. Losartan is a distinguished solid with light yellow colour, molecular weight of 461, melting point of 184°C , aqueous solubility 3.3 mg l^{-1} at pH 7.8 and pKa value of 4.9 [6, 7].

Recently, the application of magnetic adsorption technology to pharmaceuticals such as drug delivery and cancer therapy has received significant attention. After magnetic adsorbents are used to adsorb species of drug from aqueous solutions, they can be separated conveniently from the medium by a simple magnetic process [8].

In drug delivery, magnetic fields can be used to direct the particles to specific locations within the body. However, before magnetic nanoparticles can act as drug delivery agents, they must be examined in simulated physiological fluids [9–13]. In this research, magnetite nanoparticles (MNPs) were synthesised by the co-precipitation method, and then grafted with a polymer containing of brilliant cresyl blue as a new anion exchanger. The chloride ions of brilliant cresyl blue could be easily exchanged with anionic losartan in aqueous solution. The particles which resulted were used for effective enteric drug delivery.

2. Experimental results

2.1. Materials: Brilliant cresyl blue, ferric chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), ferrous chloride ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), anhydrous 1,4-dioxane, ammonia, acetic acid, sodium acetate, sodium dihydrogen phosphate, disodium hydrogen phosphate, hydrochloric acid, sodium chloride (NaCl), sodium hydroxide and acetone were purchased from Merck (Darmstadt, Germany). 2, 2'-azobis (2-methylpropionitrile) (AIBN) was obtained from Acros (NJ, USA). Allyl glycidyl ether (AGE) was purchased from Fluka (Buchs Switzerland).

3-Mercaptopropyltrimethoxysilane, *N*, *N*-dimethylformamide (DMF) were purchased from Aldrich (Steinheim, Germany).

2.2. Equipment: Fourier transform infrared (FT-IR) spectra were recorded on a Jasco FT-IR spectrometer (FT-IR-410, Jasco Inc., Easton, MD). Elemental analysis was carried out on a Thermo-Finnigan (Milan, Italy) model Flash EA elemental analyser. Thermogravimetric analysis (TGA) was carried out using a TGA-50H (Shimadzu Corporation, Kyoto, Japan). The transmission electron microscopy (TEM) images were obtained using a TEM-PHILIPS model CM 120 Netherlands.

2.3. Functionalisation of Fe_3O_4 MNPs: The preparation of primary MNPs was based on precipitation method [14]. Ammonia solution was added to solutions of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ dropwise during 2 h under nitrogen atmosphere. The MNPs were washed with ethanol and deionised water and finally dried. Dried MNPs (3 g) in 5% solution of 3-mercaptopropyltrimethoxysilane in 1, 4-dioxane was refluxed at boiling temperature for 48 h. The coated MNPs were separated magnetically, washed with 1, 4-dioxane twice and then dried. The resulting MNPs were grafted with AGE. The coated MNPs in 10 ml AGE as monomer, 20 ml ethanol as solvent and 0.1 g pure AIBN as initiator were refluxed at 70°C and under nitrogen atmosphere for 8 h. The resultant grafted polymer was washed with ethanol and then stirred with solution of brilliant cresyl blue (0.5 g) in NaCl 0.1M (40 ml) and DMF (10 ml) 50°C for 10 h; thereafter, the modified MNPs were washed with distilled water until a colourless filtrate was obtained. The methodology used for the synthesis of modified MNPs is summarised in Fig. 1.

2.4. Isotherm studies: Isotherm studies were carried out by adding 0.02 g to a series of solutions of losartan potassium ($2\text{--}80 \mu\text{g ml}^{-1}$) at optimum (pH 7) and 20°C . The final concentration of losartan potassium in the solution was measured using a ultraviolet–visible spectrophotometer. The amount of losartan potassium at equilibrium q_e (mg g^{-1}) on modified MNPs was calculated from the following equation:

$$q_e = (C_0 - C_e) V/W \quad (1)$$

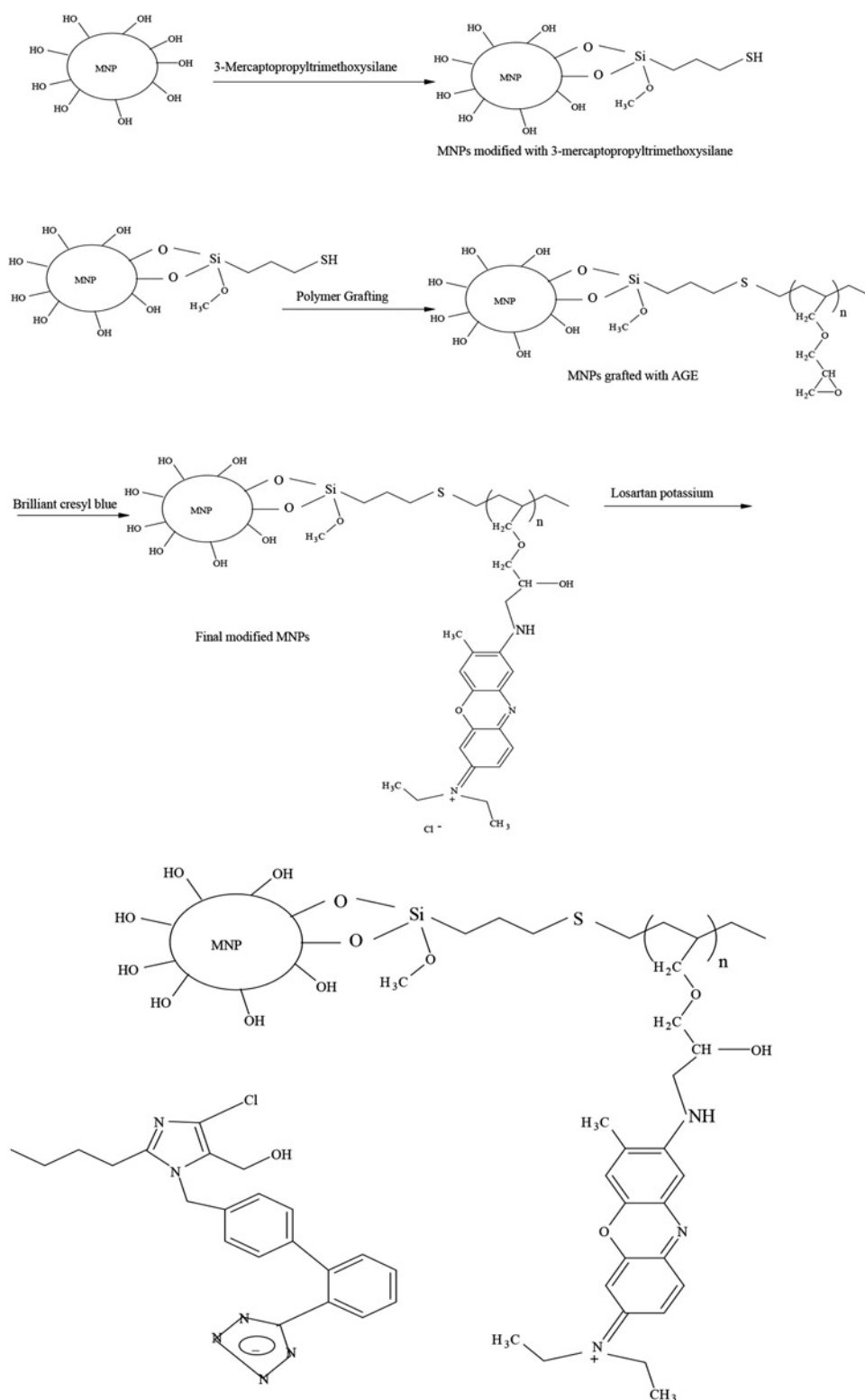


Fig. 1 Schematic presentation of synthesis and grafting process of modified MNPs

where C_0 and C_e (mg l^{-1}) are initial and equilibrium concentrations of losartan potassium, respectively; $V(L)$ is the volume of the solution and $W(g)$ is the mass of the adsorbent used.

2.5. *In vitro* drug release: The release profiles of losartan potassium from modified MNPs were examined in the simulated gastric fluid and simulated intestinal fluids. The phosphate buffer, 0.01 mol l^{-1} , (pH 7.4) and HCl solution pH 1.2 were used as simulated intestinal and gastric fluids, respectively. The losartan potassium loaded in modified MNPs were put into the beakers with shaking (50 rpm)

and without shaking at different temperatures. At scheduled time intervals, the sampling was achieved. The losartan potassium content in the samples was determined spectrophotometrically at 234 nm.

3. Results and discussion

3.1. Characterisations: FT-IR was carried out to ensure that cresyl blue was correctly immobilised on the MNPs according to Fig. 1. The spectrum of MNPs showed peaks at 579.21 and 3391.41 cm^{-1} , which were related to Fe-O stretching band and

O–H stretching, respectively. Additional peaks in MNPs modified with 3-mercaptopropyltrimethoxysilane indicated the existence of S–H groups on the MNPs. The peak for C–O in MNPs grafted with AGE and subsequent C–N for the final modified MNPs confirmed successful modification. According to Table 1, increasing the sulphur and carbon percentages in MNPs modified with 3-mercaptopropyltrimethoxysilane, carbon percentage in MNPs grafted with AGE as well as carbon and nitrogen percentages in the final modified MNPs, confirmed the structure of the modified MNPs as presented in Fig. 1. The thermal behaviour of MNPs in comparison with modified MNPs was studied by TGA. The thermal decomposition of MNPs and modified MNPs proceed in one and two steps, respectively. The thermogravimetry of both the MNPs and modified MNPs showed a weight loss at 600–800°C due to the removal of water molecules in the structure of the particles, whereas modified MNPs indicated an additional weight loss at 150–300°C as a result of the decomposition of the polymeric matrix on the MNPs. The morphology and particle size of the modified MNPs were analysed by using TEM. Fig. 2 indicates the smooth and spherical agglomerated nanoparticles with an average diameter of about 10–80 nm.

3.2. Optimisation of parameters: The modified MNPs were subjected to losartan potassium sorption at different pH levels. Fig. 3

Table 1a FT-IR and elemental analysis information

FT-IR		
MNPs	579.21 cm ⁻¹	3391.41 cm ⁻¹
	Fe–O stretching	O–H stretching
MNPs modified with	2919.34 cm ⁻¹	2309.39 cm ⁻¹
3-mercaptopropyltrimethoxysilane	C–H stretching	S–H stretching
MNPs grafted with AGE	1248.62 cm ⁻¹	—
	C–O stretching	
final modified MNPs	1076.24 cm ⁻¹	—
	C–N stretching	

Table 1b

Elemental analysis				
	C, %	N, %	H, %	S, %
MNPs	0.017	0.0522	0.535	0.0196
MNPs modified with	3.299	0.0513	0.903	2.201
3-mercaptopropyltrimethoxysilane				
MNPs grafted with AGE	6.475	0.0520	1.090	2.510
final modified MNPs	6.962	0.799	1.029	2.801

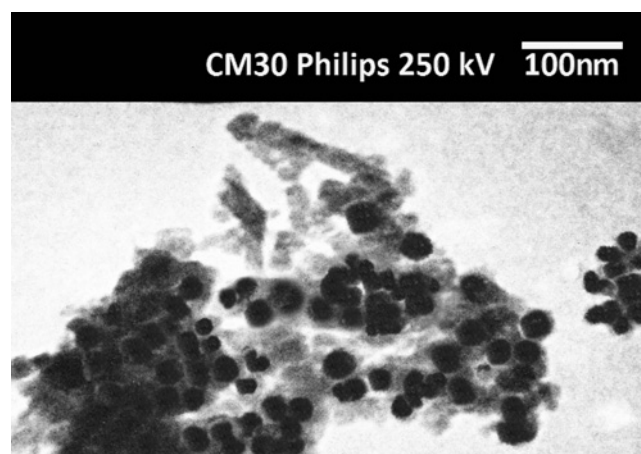


Fig. 2 TEM images of modified MNPs

shows that the maximum adsorption of losartan potassium by modified MNPs was achieved at moderate pH (pH 7). pH higher than 8 was not considered because MNPs dissolved in alkaline pH. The sorption, as a function of contact time for losartan potassium, was studied in different periods of time. Fig. 4 indicates

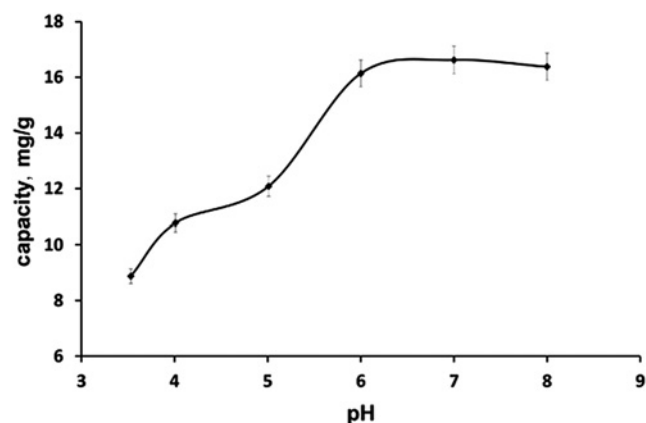


Fig. 3 Effect of pH on sorption of losartan potassium onto modified MNPs. Volume of each 1 ml containing 20 µg mL⁻¹ of losartan potassium. Their pH values were adjusted with buffer solutions. The 0.01 g of modified MNPs was added to each solution and the mixture was shaken for 1 h

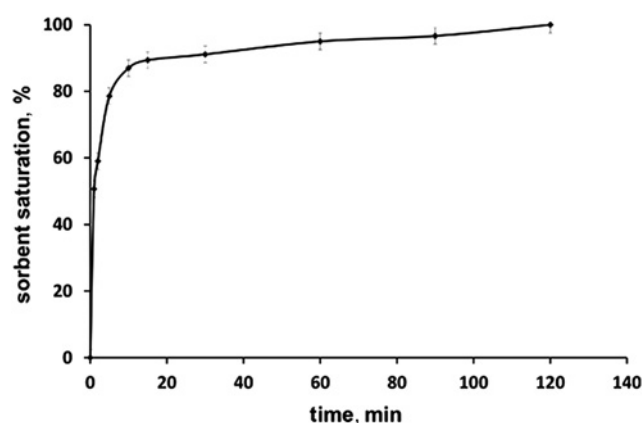


Fig. 4 Kinetics of losartan potassium sorption on modified MNPs. Volume of each 1 ml containing 20 µg mL⁻¹ of losartan potassium. Their pH values were adjusted with buffer solutions. The 0.01 g of modified MNPs was added to each solution and the mixture was shaken for a different time

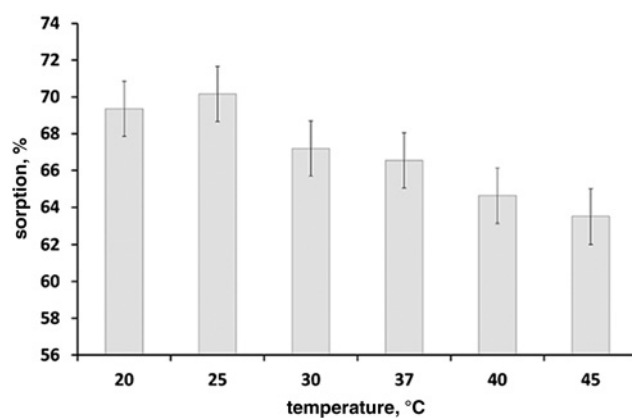


Fig. 5 Effect of temperature on sorption of losartan potassium onto modified MNPs. Volume of each 1 ml containing 20 µg mL⁻¹ of losartan potassium. Their pH values were adjusted with buffer solutions. The 0.01 g of modified MNPs was added to each solution and the mixture was shaken for 1 h at different temperatures

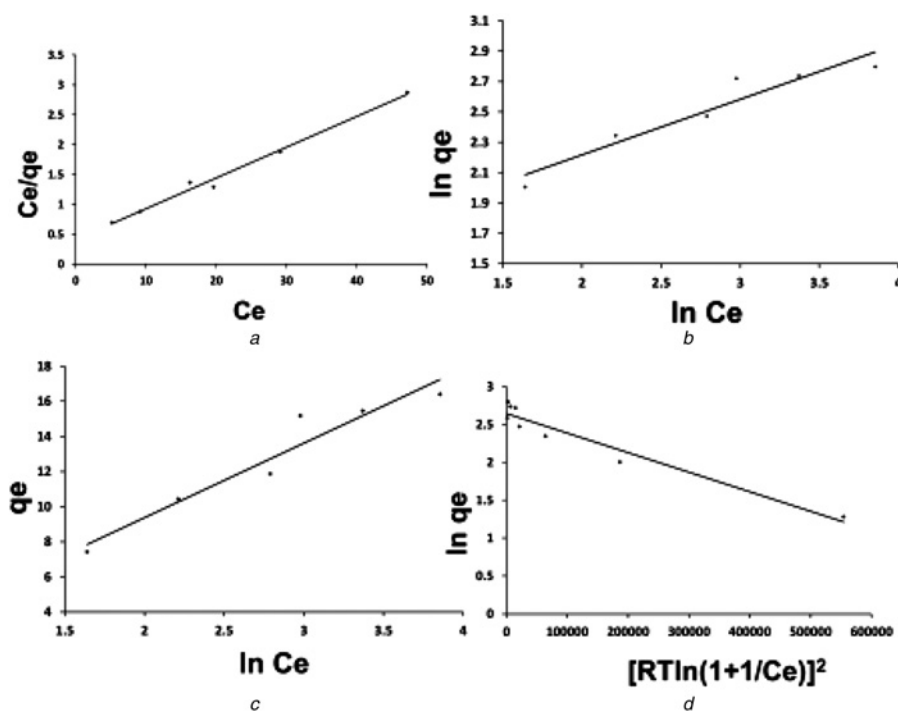


Fig. 6 Isotherms for losartan potassium adsorption onto modified MNPs at 20°C

- a Langmuir
b Freundlich
c Temkin
d Dubinin–Radushkevich

that just 1 min was sufficient for more than 50% sorption. The profile of losartan potassium uptake by modified MNPs reflects good accessibility of the sorption sites in the modified MNPs. Adsorption of losartan potassium by the modified MNPs in different temperatures (20–45°C) was studied (Fig. 5). The maximum adsorption occurred at 25°C. At a temperature higher than 25°C, the sorption decreased, and this may be as a result of more drug movement in the solution.

3.3. Adsorption isotherms: Adsorption isotherms, which present the amount of losartan potassium exchanged per unit of modified MNPs, as a function of equilibrium concentration in aqueous solution at 20°C, were investigated to optimise the design of a sorption system to remove losartan potassium from the drug solutions.

In Langmuir isotherm, the assumption is that maximum adsorption occurs when a saturated monolayer of solute drugs is present on the adsorbent surface, the energy of sorption is constant and there is no migration of adsorbate drug in the surface plane.

Fitting experimental data to the linearised form of Langmuir isotherm (Fig. 6) [15]

$$C_e/q_e = (1/q_{\max} K_L) + (C_e/q_{\max}) \quad (2)$$

where $q_{\max}$ is the maximum adsorption capacity corresponding to complete monolayer coverage on the surface (mg g^{-1}) and K_L is the Langmuir constant (L mg^{-1}), which indicates the homogeneous nature of modified MNPs. Table 2 presents a list of Langmuir parameters calculated from the mentioned equation.

Table 2a Isotherm parameters obtained by using a linear method

Langmuir isotherm model				
Temperature, °C	$q_{\max}$, mg/g	K_L , L/mg	R_L	R^2
20	19.380	0.125	0.091	0.9893

Table 2b

Freundlich isotherm model			
Temperature, °C	K_F , (mg/g) (L/mg) ^{1/n}	n	R^2
20	4.424	2.736	0.9109

Table 2c

Temkin isotherm model				
Temperature, °C	A , L/g	B , J/mol	b , J/mol	R^2
20	1.237	4.237	575.28	0.9269

Table 2d

Dubinin–Radushkevich				
Temperature, °C	$q_{m,DR}$, mg/g	β , mg^2/J^2	E , kJ/mg	R^2
20	14.058	3×10^{-6}	0.408	0.9371

Table 2e

Redlich–Peterson isotherm model			
g	B , (dm^3/mg) ^g	A , dm^3/g	R^2
1.006	0.113	2.3	0.9938

The essential characteristics of the Langmuir equation can be expressed in terms of a dimensionless separation factor, R_L , defined as [16]

$$R_L = 1/(1 + K_L C_0) \quad (3)$$

Table 2 shows that the values of R_L (0.091) are in the range of 0–1 at optimum pH which confirms the favourable uptake of losartan potassium.

The Freundlich model is an empirical relationship describing the adsorption of dissolved drugs from a liquid to a solid surface and assumes that different sites with several adsorption energies are involved.

The Freundlich equation employed to describe heterogeneous systems, which are characterised by the heterogeneity factor $1/n$ with an empirical equation written as [17]

$$q_e = KF C_e^{1/n} \quad (4)$$

where KF is the Freundlich constant (mg g^{-1}) (L mg^{-1}) $1/n$ and $1/n$ is the heterogeneity factor. A plot of $\ln q_e$ versus $\ln C_e$ enables the constant KF and exponent $1/n$ to be determined (Fig. 7). The constants were listed in Table 2.

The Temkin isotherm model contains a factor that obviously takes into consideration sorbing drugs–sorbent interactions. The Temkin model [18] assumes that (i) the heat of sorption of all the drugs in the layer decreases linearly with coverage due to sorbent–drug–sorbate interactions and that (ii) the sorption is characterised by a uniform distribution of binding energies, up to some maximum binding energy. The Temkin equation is

$$q_e = B \ln A + B \ln C_e \quad (5)$$

where $B = RT/b$ and b is the Temkin constant related to the heat of sorption (J mol^{-1}). A is the Temkin isotherm (Fig. 6) constant (L g^{-1}), R is the gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$) and T is the absolute temperature (K). Table 2 presents a list of Temkin parameters calculated from the equation.

The Dubinin–Radushkevich isotherm was also considered [19]

$$\ln q_e = \ln q_m, \quad DR - \beta \varepsilon^2 \quad (6)$$

where q_m , DR is the Dubinin–Radushkevich monolayer capacity (mg/g), β is a constant related to sorption energy and ε is the Polanyi potential which is related to the equilibrium concentration

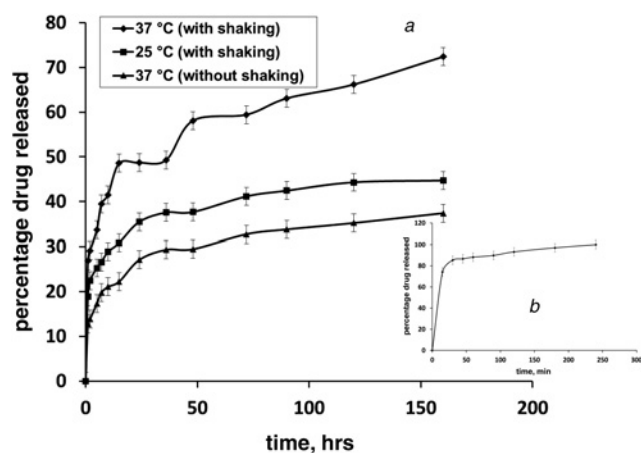


Fig. 7 Losartan potassium release profile in
a Simulated intestinal fluid (pH 7.4)
b Simulated gastric fluid (pH 1.2)

as follows:

$$e = RT \ln(1 + 1/C_e) \quad (7)$$

The constant β gives the mean free energy, E , of sorption per molecule of losartan potassium when it is transferred to the surface of the solid from infinity in the solution and can be computed using the relationship

$$E = \frac{1}{\sqrt{2\beta}} \quad (8)$$

Table 2 (see Fig. 6) lists the constants in this isotherm.

The Redlich–Peterson isotherm contains three parameters and incorporates the features of both the Langmuir (at $g=1$) and the Freundlich (at $g=0$) isotherms [20]

$$\ln\left(A \frac{C_e}{q_e} - 1\right) = g \ln(C_e) + \ln(B) \quad (9)$$

The three isotherm constants, A , B and g evaluated from the equation, using best fitting computer calculations, are shown in Table 2. The g values were close to unity, indicating that the isotherms are approaching the Langmuir form rather than the Freundlich isotherm.

3.4. Losartan potassium release: Fig. 7 showed the release behaviour of losartan potassium from modified MNPs in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4). About ~72 and 44% of losartan potassium was released in the simulated intestinal fluid over a period of 160 h at 37 and 25°C, respectively. This amount was decreased to 38% without shaking mode at 37°C. About 50% of losartan potassium was released in 30 h at 37°C. However, in simulated gastric fluid due to acetic media, the nitrogen in the brilliant cresyl blue was protonated to improve drug release. Around 90% of losartan potassium can be released in about 30 h.

4. Conclusion: In this paper, a polymer grafted with magnetic nanoparticles was prepared by subsequent chemical reaction. This modified MNP was characterised and showed good potential for the removal of losartan potassium. The grafted nanoparticles also present the advantage of high adsorption capacity and high chemical stability. The sorption of losartan potassium is fast and increases with increase in contact time. Owing to prolonged drug release, the loaded–modified MNPs can be used for sustained release drug delivery.

5 References

- [1] Etcheverry S.B., Ferrer E.G., Naso L., *ET AL.*: ‘Losartan and its interaction with copper(II): biological effects’, *Bioorg. Med. Chem.*, 2007, **15**, pp. 6418–6424
- [2] Darwish I.A.: ‘Analytical study for the charge-transfer complexes of losartan potassium’, *Anal. Chim. Acta*, 2005, **549**, pp. 212–220
- [3] Brunetto M.R., Contreras Y., Clavijo S., *ET AL.*: ‘Determination of losartan, telmisartan, and valsartan by direct injection of human urine into a column-switching liquid chromatographic system with fluorescence detection’, *J. Pharm. Biomed. Anal.*, 2009, **50**, pp. 194–199
- [4] Seburg R.A., Ballard J.M., Hwang T.L., *ET AL.*: ‘Photosensitized degradation of losartan potassium in an extemporaneous suspension formulation’, *J. Pharm. Biomed. Anal.*, 2006, **42**, pp. 411–422
- [5] Hertzog D.L., McCafferty J.F., Fang X., *ET AL.*: ‘Development and validation of a stability-indicating HPLC method for the simultaneous determination of losartan potassium, hydrochlorothiazide, and their degradation products’, *J. Pharm. Biomed. Anal.*, 2002, **30**, pp. 747–760
- [6] Lastra O.C., Lemus I.G., Sanchez H.J., *ET AL.*: ‘Development and validation of an UV derivative spectrophotometric determination of

- losartan potassium in tablets', *J. Pharm. Biomed. Anal.*, 2003, **33**, pp. 175–180
- [7] Williams R.C., Alasandro V.L., Fasone V.L., *ET AL.*: 'Comparison of liquid chromatography, capillary electrophoresis and super-critical fluid chromatography in the determination of losartan potassium drug substance in Cozaar tablets', *J. Pharm. Biomed. Anal.*, 1996, **14**, pp. 1539–1546
- [8] Euliss L.E., Grancharov S.G., O'Brien S., *ET AL.*: 'Cooperative assembly of magnetic nanoparticles and block copolypeptides in aqueous media', *Nano Lett.*, 2003, **3**, (11), pp. 1489–1493
- [9] Gao Q., Liang Q., Yub F., *ET AL.*: 'Synthesis and characterization of novel amphiphilic copolymer stearic acid-coupled F127 nanoparticles for nano-technology based drug delivery system', *Colloids Surf. B, Biointerfaces*, 2011, **88**, pp. 741–748
- [10] Veisheh O., Gunn J.W., Zhang M.: 'Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging', *Adv. Drug Deliv. Rev.*, 2010, **62**, pp. 284–304
- [11] Sun C., Lee J.S.H., Zhang M.: 'Magnetic nanoparticles in MR imaging and drug delivery', *Adv. Drug Deliv. Rev.*, 2008, **60**, pp. 1252–1265
- [12] Ai H.: 'Layer-by-layer capsules for magnetic resonance imaging and drug delivery', *Adv. Drug Deliv. Rev.*, 2011, **63**, pp. 772–788
- [13] Kumar C.S.S.R., Mohammad F.: 'Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery', *Adv. Drug Deliv. Rev.*, 2011, **63**, pp. 789–808
- [14] Mahdavian A.R., Mirrahimi M.A.S.: 'Efficient separation of heavy metal cations by anchoring polyacrylic acid on superparamagnetic magnetite nanoparticles through surface modification', *Chem. Eng. J.*, 2010, **159**, pp. 264–271
- [15] Langmuir I.: 'The adsorption of gases on plane surfaces of glass, mica and platinum', *J. Am. Chem. Soc.*, 1918, **40**, (8), pp. 1361–1403
- [16] Hall K.L., Eagleton L.C., Acrivos A., *ET AL.*: 'Pore and solid-diffusion kinetics in fixed bed adsorption under constant pattern conditions', *Ind. Eng. Chem. Fundam.*, 1966, **5**, pp. 212–218
- [17] Freundlich H.M.F.: 'Over the adsorption in solution', *J. Phys. Chem.*, 1906, **57**, pp. 385–471
- [18] Temkin M.J., Pyzhev V.: 'Recent modifications to langmuir isotherms', *Acta Physicochim. URSS*, 1940, **12**, pp. 217–222
- [19] Dubinin M.M., Radushkevich L.V.: 'Equation of the characteristic curve of activated charcoal', *Chem. Zent.*, 1947, **1**, (1), pp. 75–882
- [20] Ho Y., Ofomaja A.E.: 'Biosorption thermodynamics of cadmium on coconut copra meal as biosorbent', *Biochem. Eng. J.*, 2006, **30**, pp. 117–123