Magnetoresponsive biocomposite hydrogels comprising of gelatin and valine based magnetic ionic liquid surfactant as controlled release nanocarrier for drug delivery

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1. Structural scheme of synthesized [ValC\textsubscript{16}][FeCl\textsubscript{4}].

**Fig. S1.** Synthetic procedure of [ValC\textsubscript{16}][FeCl\textsubscript{4}].
2. $^1$H NMR of the synthesis of [ValC$_{16}$][FeCl$_4$]

Fig. S2: $^1$H NMR of [ValC$_{16}$][Cl]

$^1$H NMR chemical shift values of [ValC$_{16}$][Cl] CDCl$_3$, 500MHz: $\delta_H$ (ppm) 8.43 (s, 3H), 4.16(m, 3H), 3.98(t,2H ), 2.16(s,1H), 1.60 (m,2H), 1.25-1.29(m, 26H,CH$_2$), 0.96(dd, 6H), 0.85(t,3H).
3. LCMS of the synthesis of [ValC$_{16}$][FeCl$_4$]

LCMS of [ValC$_{16}$][FeCl$_4$]: ESI+ 342.3, ESI – 197.8

**Fig. S3** LCMS of [ValC$_{16}$][FeCl$_4$].
4. Raman spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]

![Raman spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]](image)

Fig. S4. Raman spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]

5. UV spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]

![UV spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]](image)

Fig. S5. UV spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]

6. EPR spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]

![EPR spectra graph](image)

**Fig. S6.** EPR spectra of [ValC\textsubscript{16}][FeCl\textsubscript{4}]

7. DSC thermogram of [ValC\textsubscript{16}][FeCl\textsubscript{4}] & [ValC\textsubscript{16}][Cl].
Fig. S7 DSC thermogram of [ValC₁₆][FeCl₄] & [ValC₁₆][Cl].
8. Thermogravimetric analysis and parameters

![TGA analysis of [ValC\textsubscript{16}][FeCl\textsubscript{4}] & [ValC\textsubscript{16}][Cl].](image)

**Fig. S8** TGA analysis of [ValC\textsubscript{16}][FeCl\textsubscript{4}] & [ValC\textsubscript{16}][Cl].

9. Thermal parameters of [ValC\textsubscript{16}][FeCl\textsubscript{4}] & [ValC\textsubscript{16}][Cl].

**Table S1**: \( T_\text{d} \), \( T_\text{start} \) and \( T_\text{onset} \) of [ValC\textsubscript{16}][FeCl\textsubscript{4}] & [ValC\textsubscript{16}][Cl].

| SAILs       | \( T_\text{start} \) (°C) | \( T_\text{d} \) (°C) | \( T_\text{onset} \) (°C) |
|-------------|-----------------------------|------------------------|---------------------------|
| [ValC\textsubscript{16}][Cl] | 174                        | 242                    | 193                       |
| [ValC\textsubscript{16}][FeCl\textsubscript{4}] | 180                        | 251                    | 207                       |
10. Wavelength vs $I_1/I_3$ graph

![Graph showing wavelength vs $I_1/I_3$ on increasing concentration of [ValC$_{16}$][FeCl$_4$].](image)

Fig. S9 Wavelength vs $I_1/I_3$ on increasing concentration of [ValC$_{16}$][FeCl$_4$].

11. Concentration dependent morphological transitions in [ValC$_{16}$][FeCl$_4$].

![Micrographs showing concentration dependent morphological transitions](images)

Fig. S10 Concentration dependent morphological transitions in [ValC$_{16}$][FeCl$_4$].
12. DLS plot of micelle formation using [ValC\textsubscript{16}][FeCl\textsubscript{4}]

![DLS plot of micelle formation using [ValC\textsubscript{16}][FeCl\textsubscript{4}]](image)

**Fig. S11** DLS plot of micelle using [ValC\textsubscript{16}][FeCl\textsubscript{4}]

13. Autocorrelation function of [ValC\textsubscript{16}][FeCl\textsubscript{4}].

![Autocorrelation function of [ValC\textsubscript{16}][FeCl\textsubscript{4}]](image)

**Fig. S12.** Autocorrelation function of [ValC\textsubscript{16}][FeCl\textsubscript{4}].
14. Zeta Potential of Micelles and vesicles of [ValC₁₆][FeCl₄]

![Zeta Potential of Micelles and vesicles of [ValC₁₆][FeCl₄]](image)

*Fig. S13* Zeta Potential of Micelles and vesicles of [ValC₁₆][FeCl₄]

15. EDX elemental mapping of Gelatin- [ValC₁₆][FeCl₄] biocomposite gel

![EDX elemental mapping of Gelatin- [ValC₁₆][FeCl₄] biocomposite gel](image)
**Fig. S14** EDX elemental mapping of Gelatin-[ValC$_{16}$][FeCl$_4$] biocomposite gel

16. Stability of gelatin- [ValC$_{16}$][FeCl$_4$] biocomposite gel

![Image of stability experiment](image_url)

**Fig. S15** Stability of gelatin-[ValC$_{16}$][FeCl$_4$] biocomposite gel.

17. Swelling behavior of gelatin-[ValC$_{16}$][FeCl$_4$] biocomposite gel

![Image of swelling experiment](image_url)

**Fig. S16** Swelling behavior of gelatin-[ValC$_{16}$][FeCl$_4$] biocomposite gel
18. Comparison of previously reported ornidazole drug loading efficiency in various systems.

Table S2 Comparison of previously reported ornidazole drug loading efficiency in various systems.

| S.No | Materials                                                                 | Loading efficiency of Oridazole(%) | Author                                     | Year |
|------|---------------------------------------------------------------------------|-----------------------------------|--------------------------------------------|------|
| 1    | Present work (magnetic biocomposite gel)                                  | 69.3%                             | -                                          | -    |
| 2    | Beta-cyclodextrin polymer microspheres (βCDPM)                            | 8.86%                             | Y. Liu et al.²                             | 2020 |
| 3    | PVP electrospun fibers                                                   | -                                 | S. Tort et al.³                           | 2018 |
| 4    | Polyethylene glycol-based micron-level particle                          | 15-20%                            | S. Tamilvanan et al.⁴                     | 2019 |
| 5    | Ornidazole-Loaded Graphene Paper                                         | 10-17.3%                          | W. Quian et al.⁵                          | 2018 |
| 6    | Biopolymer-dextrin and poly(methyl methacrylate) microgel                | 30.54%                            | D. Das et al.⁶                            | 2016 |
| 7    | Biocompatible hydrogel derived from glycogen and poly(N-isopropylacrylamide) | 19-31%                            | Priyapratim Patra et al.⁷                | 2016 |
19. Comparison of previously reported 5-Fluoro uracil drug loading efficiency in various systems.

Table S3 Comparison of previously reported 5-Fluoro uracil drug loading efficiency in various systems.

| S.No | Materials                                                                 | Loading efficiency of 5-FU (%) | Author                  | Year  |
|------|---------------------------------------------------------------------------|-------------------------------|-------------------------|-------|
| 1.   | Present work (magnetic biocomposite gel)                                  | 78.3%                         | -                       | -     |
| 2.   | Poly(ε-caprolactone) with 6-(chloromethyl)uracil                          | 42%                           | S. Zhu et al.           | 2020  |
| 3.   | Gelatin–rosin gum complex nanoparticle                                    | 50%                           | S. Joshi                | 2020  |
| 4.   | polyurethane-based hydrogels                                             | 45-54 %                       | M. Kamaci et al.        | 2020  |
| 5.   | PEGylated Ag2S QDs functionalized with Cetuximab (Cet) antibody           | 7.34%                         | F. D. Duman et al.      | 2019  |
| 6.   | zinc nanoMOFs functionalized with folate                                  | 24%                           | B. Yang et al.          | 2017  |
| 7.   | Self-Assembling Monomeric Nucleoside Molecular Nanoparticle              | 53%                           | H. Zhao et al.          | 2015  |
20. Kinetics study of drug release pattern using mathematical models

Table S4: Kinetics study of release of guest drugs by various mathematical models.

| Guest Molecule | Release condition | *Zero Order | *First order | *Higuchi Model | *KorsMeyar Peppas | *Hixon Crowell |
|----------------|-------------------|-------------|--------------|----------------|-------------------|----------------|
|                |                   | \( R^2 \)  | Slope        | \( R^2 \)  | Slope            | \( R^2 \)  | Slope |
| Ornidazole     | pH 7.4            | 0.83       | 0.75         | 0.89          | 0.006             | 0.93       | 8.3   |
| 5-Fluoro Uracil| pH 7.4            | 0.72       | 0.42         | 0.85          | 0.005             | 0.86       | 6.88  |

21. Drug release pattern in different electrolyte solutions

Fig. S17 Drug release pattern in different electrolyte solution
Annexure I

The Surface parameter equations are as follow:

1. The Adsorption efficiency ($pC_{20}$) and Effectiveness of Surface tension reduction ($\Pi_{CAC}$) of surfactant at air-water interface is estimated by using the relation (1)

$$pC_{20} = -\log C_{20}, \quad \Pi_{CMC} = \gamma_{H,0} - \gamma_{CAC}$$

where, $C_{20}$ is the concentration reduce by 20mNm$^{-1}$ from the surface tension of the solvent (water)$^1$, $\gamma_{H,0}$ stands for the surface tension of the pure water and $\gamma_{CMC}$ stands for the surface tension of the solvent medium at CAC.

2. The amount of surfactants adsorbed at the interface is estimated from relative surface excess concentration ($\Gamma_{max}$). The values $\Gamma_{max}$ of at the CMC have been calculated using Gibbs adsorption Eq. 2.

$$\Gamma_{max} = -\frac{1}{nRT} \frac{\partial \gamma}{\partial \ln C}$$

where “$\frac{\partial \gamma}{\partial \ln C}$” is the slope of $\gamma - \ln C$ plot in the pre CMC region and $n$ is Gibbs adsorption coefficient.

3. Minimum area occupied by monomers at the interface was calculated using equation 4.

$$A_{min} = \frac{10^{16}}{\Gamma_{max} \cdot N_A}$$

where $N_A$ is Avogadro number and the Unit of $A_{min}$ is Å$^2$.

4. The $\beta$ value is obtained from the formula ($\beta = 1 - \alpha$) where the $\alpha$ is the degree of counterion dissociation which is obtained by ratio of the slope post micellar region and the pre micellar region ($S_2/S_1$) then the $\beta$ value is further used to derive the value of standard free energy of micellization from the equation as follow:

$$\Delta G_{mic}^\alpha = (1 + \beta)RT \ln X_{cmc} \quad \text{.................. (4)}$$
Annexure-II

Various mathematical models and their equations

1. Zero order mathematical model:

   \[ C_o - C_t = K_o t \]

   where \( C_o \) = initial concentration of the drug at time, \( t = 0 \), \( C_t \) = amount of drug released at time \( t \), \( K_o \) = zero order constant

2. First Order mathematical model:

   \[ \ln C = \ln C_o - K_1 t \]

   where \( C_o \) = initial concentration of the drug at time \( K_1 \) = first order rate constant, \( C \) = percent of drug remaining at time

3. Higuchi model:

   \[ Q = A\sqrt{D(2C_o - C_S)C_s t} \]

   \( Q \)=Cumulative amount of drug released at time per unit area, \( C_S \) is the drug solubility in the matrix and \( D \) is the diffusion coefficient of the drug molecule in the matrix, \( C_S \) =drug solubility in the matrix.

4. Korsmeyer- Peppas model

   \[ \frac{M_t}{M_\infty} = K_{kp} t^n \]

   \( M_t \) = amount of drug released in time \( t \), \( M_\infty \) = amount of drug released after time \( \infty \), \( n \) = diffusional exponent or drug release exponent, and \( K_{kp} \) = Korsmeyer release rate constant.

5. Hixson–Crowell model

   \[ C^{1/3}_0 - C^{1/3}_t = K_{HC} t \]

   \( K_{HC} \)= Hixson–Crowell constant

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