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Hybrid materials for drug delivery of rifampicin: evaluation of release profile

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ABSTRACT

The aim of the present investigation was to evaluate the dissolution profile of rifampicin, to study the design parameters of magnetic scaffolds and to evaluate the in vitro release characteristics. A series of magnetic hybrid materials were developed with different release rates using chitosan (Ch) and diethylaminoethyl-cellulose (DeaeC). The duration of rifampicin release could be tailored by varying the polymer type. Rifampicin was found to follow a linear release profile with time from all magnetic polysaccharide scaffolds. Using suitable polysaccharide scaffolds and proper optimization of the processing techniques, it was possible to design the controlled release formulations of rifampicin that could provide the sufficient initial release and release extension up to 24 h for the drug despite of the wide variations in their physicochemical properties.

Keywords: *magnetic scaffolds, polysaccharide, drug targeting, controlled release, rifampicin*

1. Introduction

Modern drug carrier systems play an important role in controlled release of a pharmaceutical agent to the target at a therapeutically optimal rate and dose [1]. Polymers have been paid considerable attention in the controlled release formulations for various drugs. This can be achieved by incorporation of drugs into polymeric materials that release the drug at a predefined and reproducible rate for a prolonged period of time [2]. Active targeting of magnetic hybrid materials that carry entrapped drugs can achieve drug delivery to target cells *in vivo* [3], thus increase the therapeutic efficacy of the drug and reducing its systemic side-effects, simplifies drug administration procedures, reduces the quantity of drug required to reach therapeutic levels and decreases the concentration of the drug at non-target sites. Polysaccharides (Ch and DeaeC) are biocompatible and biodegradable products. Due to their biocompatibility and advantageous functional groups (amino and hydroxyl), Ch and DeaeC are widely used in medicine. Produced by fermentation of *Streptomyces mediterranei*, rifampicin is a strategic medication, recommended by the World Health Organization for the treatment of endemic diseases. It shows effective action against both gram-negative and gram-positive bacteria [4], and is one of the principal chemical therapies employed in combating tuberculosis. For oral administration, rifampicin is present as separate formulation in the form of suspension, capsule and tablet or combined with other anti-tuberculosis drugs like isoniazid, pyrazinamide and ethambutol in a fixed ratio[5]. However, these conventional formulations have

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been associated with many serious drawbacks like development of microbial drug resistance, improper bioavailability of drugs and, toxico-allergic side effects. These problems can be alleviated by the use of controlled release drug delivery systems [6]. In light of the above discussed aspects, the main objective of our present study was to evaluate the release profile of rifampicin, first line anti-tubercular drug, from (magnetic) Ch and (magnetic) DeaeC. The present research also aimed the development of an once-a day controlled release of rifampicin from magnetic scaffolds in order to increase the therapeutic efficacy.

2. Experimental section

2.1. Preparation of magnetic polymer composites

2.1.1. Magnetic DeaeC fibers and magnetic Ch beads. Magnetic hybrid materials were prepared and characterized according to our previous studies, as follow: DeaeC or Ch was added in aqueous solution of NaOH (2%) and then Fe^{2+} and Fe^{3+} (in 1:2 molar ratio) were dissolved in ultrapure water and were added drop-wise under constant stirring at 25 °C. The DeaeC/Fe_3O_4 [7,8] and Ch/Fe_3O_4 [9] (magnetic hybrid materials) were separated by applying a magnetic field, and washed several times with water and then with ethanol.

2.2. Characterization of magnetic hybrid materials

2.2.1. Confocal Scanning Electron Microscopy. The surface morphology of DeaeC and Ch samples were carried out before and after magnetite coating by using Leica microscope (TCS-SP CSLM), equipped with PL FLUOTAR (40X NA0.5) and an He-Ne laser tuned on 633 nm wavelength. Samples were visualized, in reflection mode. Leica software was used for surface topography [10].

2.2.2. Fourier Transform InfraRed Spectroscopy. The DeaeC/Fe_3O_4/rifampicin and Ch/Fe_3O_4/rifampicin hybrid materials were characterized by FT-IR. A Nicolet 6700 FT-IR spectrometer (Thermo Nicolet, Madison, WI) connected to software of the OMNIC operating system (Version 7.0 Thermo Nicolet) was used to obtain FT-IR spectra of hybrid materials. The samples were placed in contact with attenuated total reflectance (ATR) on a multibounce plate of ZnSe crystal at controlled ambient temperature (25°C). FT-IR spectra were collected in the frequency range of 4,000–650 cm^{-1} by co-adding 32 scans and at a resolution of 4 cm^{-1} with strong apodization. All spectra were ratioed against a background of an air spectrum.

2.3. Rifampicin loading and release

2.3.1. Preparation. After drying, the magnetic materials were dispersed in minimum quantity of chloroform and the rifampicin was added. The mixture was grounded until complete evaporation of chloroform and this step was repeated 3 times. The concentration of deposited rifampicin was 10 %.

2.3.2. Evaluation of dissolution profile of rifampicin from magnetic hybrid materials. The rifampicin dissolution release profile from the hybrid materials was studied using a high pressure liquid chromatograph (HPLC) according to our previous study [7]. Dissolution profiles of rifampicin were performed with a modified Agilent 1100 series HPLC (Agilent Technologies, Palo Alto, USA) equipped with quaternary pump, vacuum degasser and UV-VIS detector. HP ChemStation software was used for data collection and processing. The samples were introduced in the working station, thermostated at 25°C, under controlled and continuous stirring. Ultra-pure water was used as mobile phase with a flow rate of 1.5 mL/min.

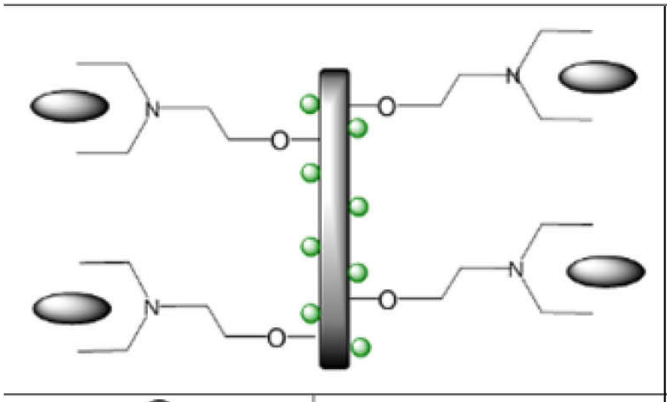


Figure 1: Magnetic DeaeC as a drug carrier for rifampicin

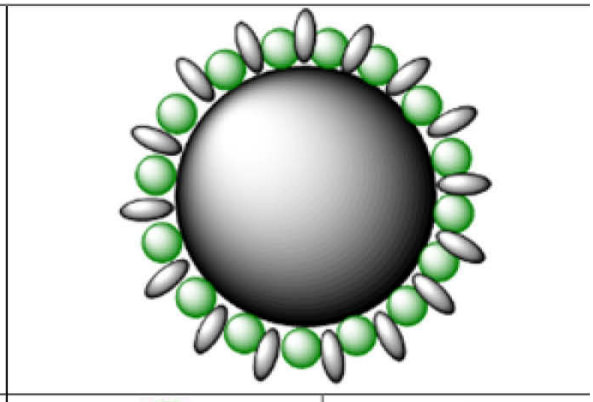
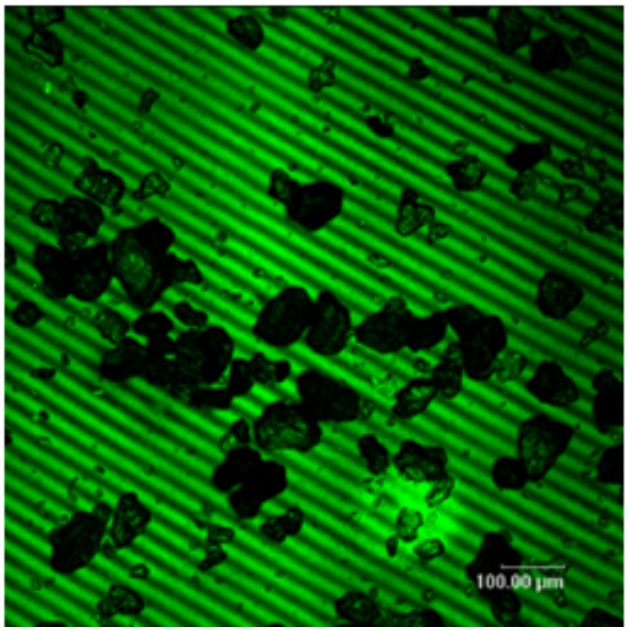


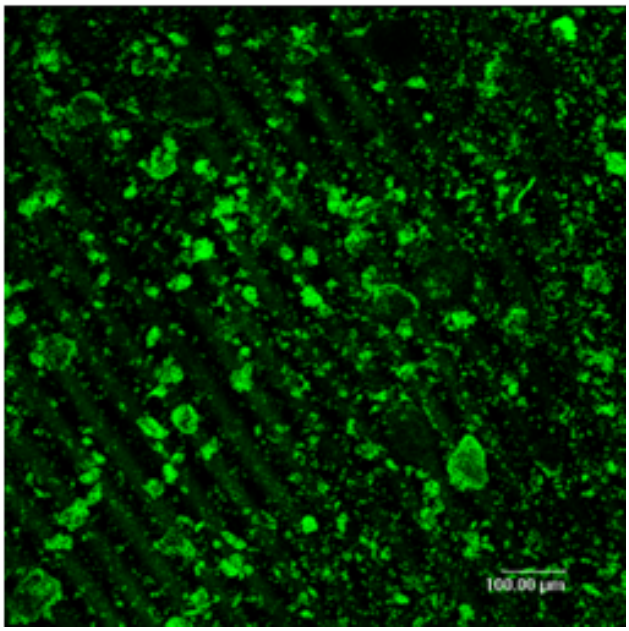
Figure 2: Magnetic Ch as a drug carrier for rifampicin

3. Results section

3.1. Confocal Scanning Electron Microscopy (CLSM). Different morphologies have been obtained by employing different polysaccharides like Ch or DeaeC.

CLSM images of pure Ch beads and Ch beads coated magnetite are illustrated in figure 3. Magnetite particles are well visualized and form agglomerates on the surface of Ch beads. Magnetic Ch beads under CLSM are present in the form of agglomerated ellipsoidal particles with dimensions that do not exceed 80 µm. Figure 4 shows the shape and size distribution of DeaeC fibers. Magnetite particles form agglomerates on the surface of fibers and this hybrid material has lengths of 100-150 µm and diameters of 10–20 µm.





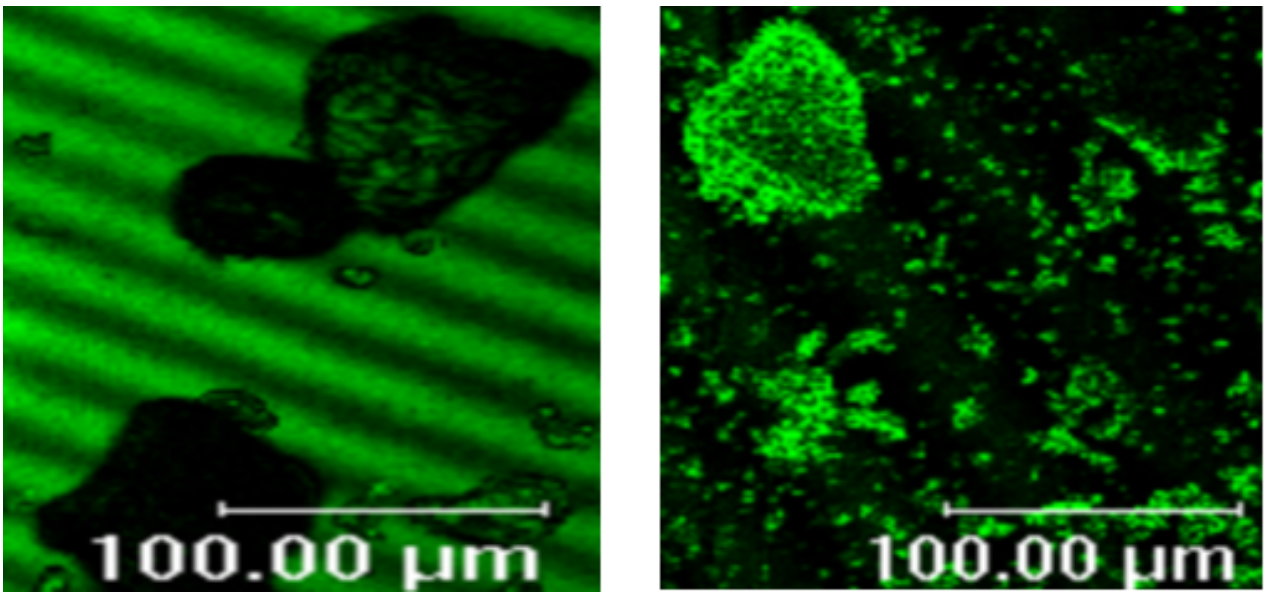


Figure 3: CLSM images of magnetic chitosan beads

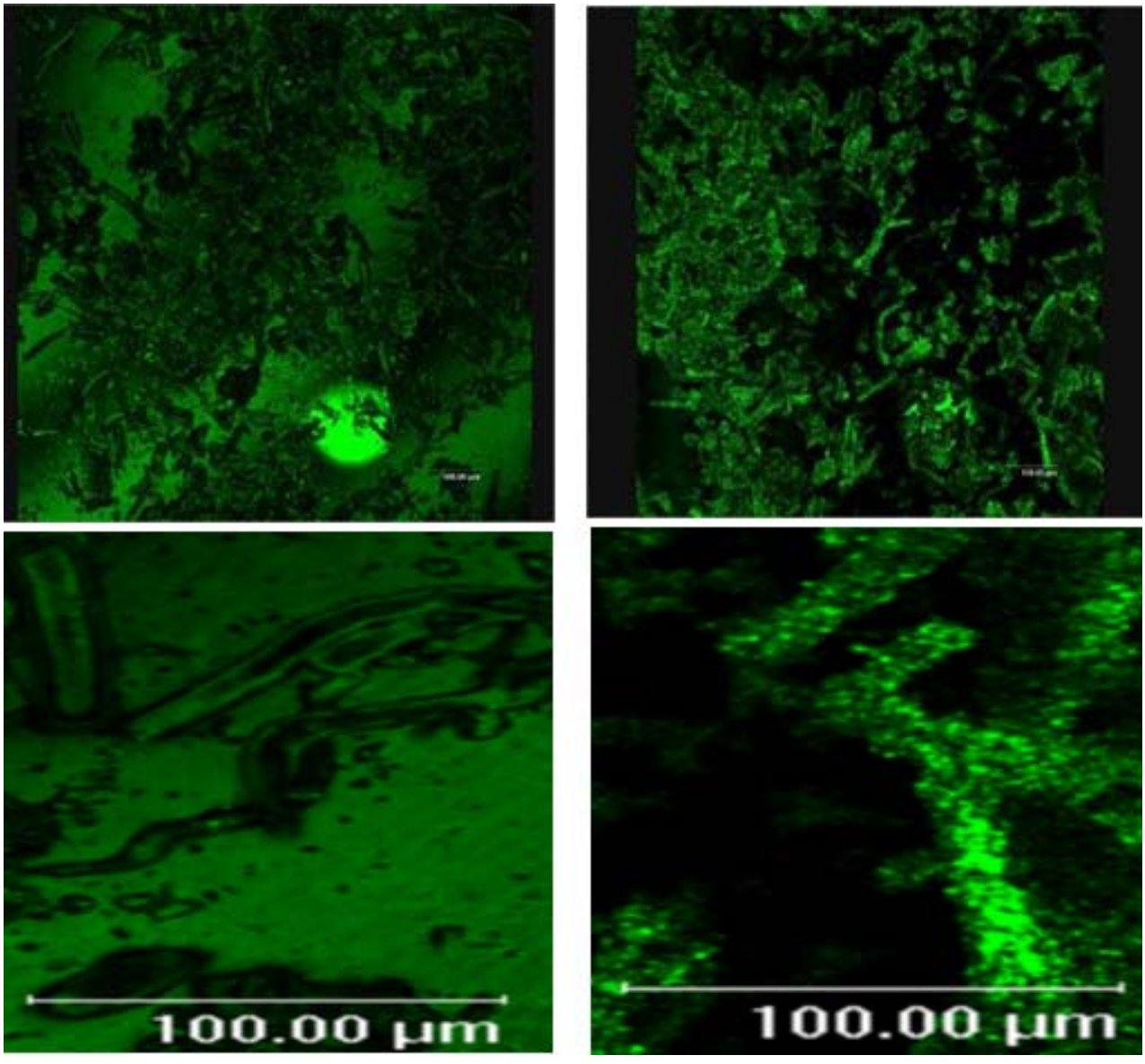
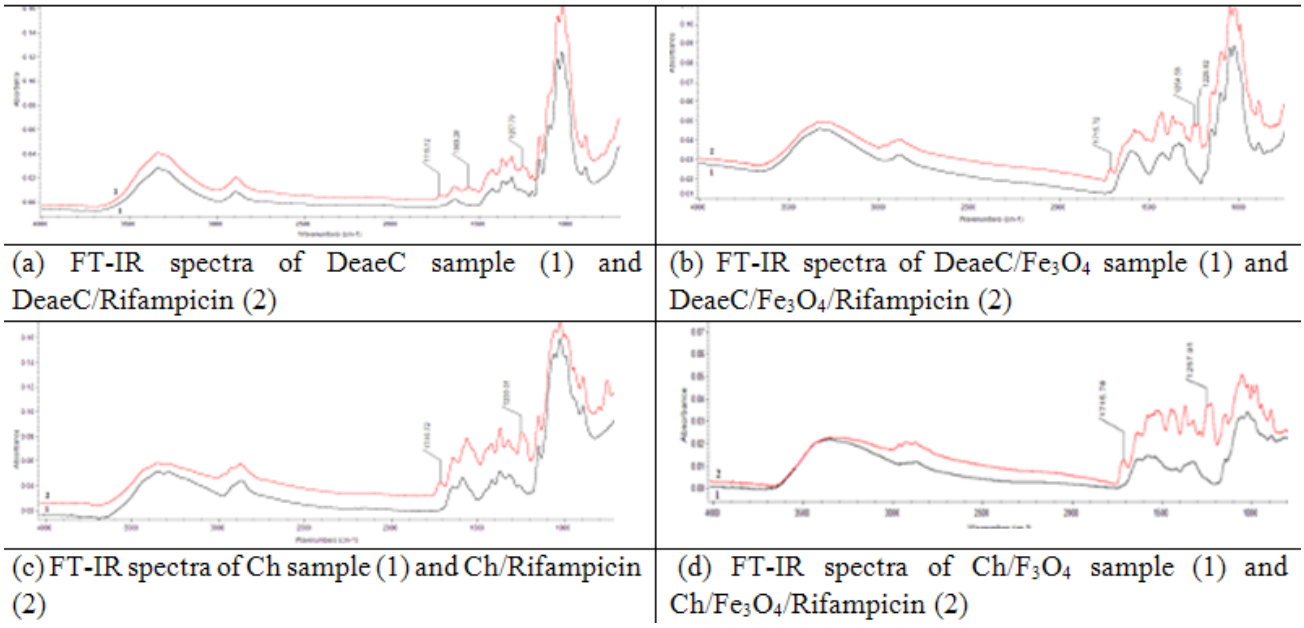


Figure 4: CLSM image of fibrillated magnetic cellulose

3.2. Fourier Transform Infrared analysis.

The drug and (magnetic) hybrid materials interactions were studied by FT-IR. The FT-IR spectra were recorded in the wavelength region 600-4000 cm^{-1} for pure Ch beads, DeaeC fibers, rifampicin loaded polymers and rifampicin loaded magnetic polymers. In order to compare the obtained spectra, an overview is given in Figure 5. Each spectrum is the average of three tests and all spectra are shifted upwards to prevent overlap. The spectra plotted in figure 2(a-b) refer to the DeaeC and (magnetic) DeaeC/rifampicin hybrid materials. The bands at 1047, 1104 and 1158 cm^{-1} are well-defined in the "fingerprint" region. Also, absorption bands at 1715 cm^{-1} and 1255 cm^{-1} corresponding to rifampicin are observed in the FT-IR spectra of (magnetic) DeaeC/rifampicin. FT-IR spectra of the obtained (magnetic) Ch hybrid materials in Figure 5(c-d) showed the characteristic bands of Ch at 1089 cm^{-1} for C–O–C bonds, 1559 cm^{-1} for free NH_2 groups and 1658 cm^{-1} for the residual acetamido groups. In addition, there is an absorption band at 2938 cm^{-1} attributed to C–H bonding. Also rifampicin absorption bands are are observed in the FT-IR spectra of (magnetic) Ch/rifampicin and (magnetic) DeaeC/rifampicin at 1715 cm^{-1} and 1255 cm^{-1}.



(a) FT-IR spectra of DeaeC sample (1) and DeaeC/Rifampicin (2)

(b) FT-IR spectra of DeaeC/Fe_3O_4 sample (1) and DeaeC/Fe_3O_4/Rifampicin (2)

(c) FT-IR spectra of Ch sample (1) and Ch/Rifampicin (2)

(d) FT-IR spectra of Ch/F_3O_4 sample (1) and Ch/Fe_3O_4/Rifampicin (2)

Figure 5: FT-IR spectra of (magnetic) deae-cellulose and (magnetic) chitosan loaded with rifampicin

3.3. Evaluation of release profile of rifampicin.

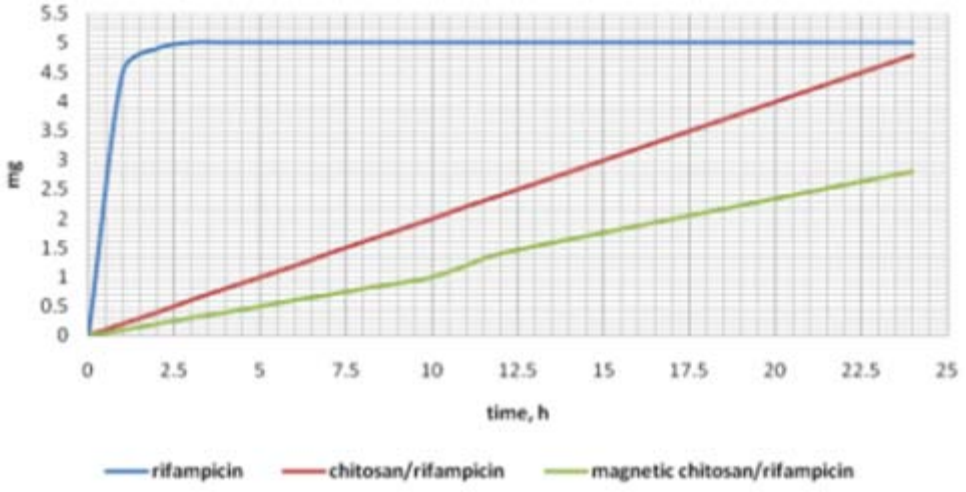


Figure 6: Comparative release profile of rifampicin from (magnetic) Ch

The effect of (magnetic) hybrid materials on rifampicin loading and release from (magnetic) Ch beads and (magnetic) DeaeC fibers was evaluated. Figure 6 shows the release profiles of rifampicin from polymer beads. As evident from the figure, absence of (magnetic) beads caused nearly immediate release of rifampicin. However, (magnetic) beads loaded with rifampicin, caused dramatic reduction in the amount of released rifampicin.

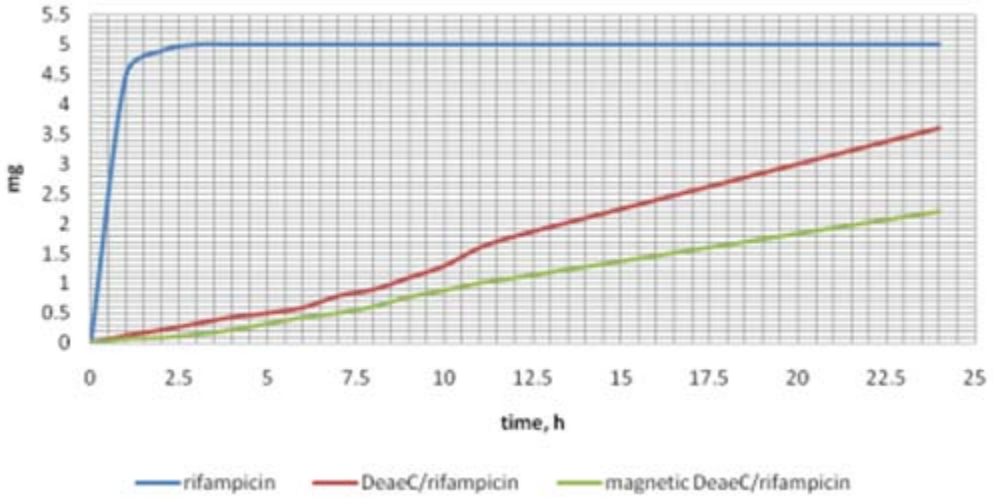


Figure 7: Comparative release profile of rifampicin from (magnetic) DeaeC

4. Conclusions

In the present investigation, an attempt has been made to develop controlled release of rifampicin using different (magnetic) polymers. The designed hybrid materials presented good and reproducible physical properties indicating that the methods of preparation are suitable. The duration of rifampicin release could be tailored by varying the polymer type. Rifampicin was found to follow linear release profile with time from all magnetic polysaccharide scaffolds. Using suitable polysaccharide scaffolds and proper optimization of the processing techniques, it was possible to design the controlled release formulations of rifampicin that could provide the sufficient initial release and release extension up to 24 h for the drug despite of the wide variations in their physicochemical properties. The present study was also focused on evaluating the applicability of HPLC for releasing profiles and showed that a modified HPLC system is useful for rapid evaluation of profiles of rifampicin release from magnetic polysaccharide scaffolds. This method can be viewed as a useful method for the evaluation of many other sustained-release formulations. More detailed studies of this method are expected in the future.

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