

Magnetic fluids as drug carrier in magnetically assisted chemotherapy - an experimental study

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The present study is dedicated to the biomedical utilization of magnetic fluids. Drug delivery under magnetic control was the application studied experimentally by using two different magnetic fluids in combination with the same pharmaceutical molecule. The aqueous magnetic fluids were consistent with magnetite and maghemite nanoparticles coated with citric acid and respectively tetramethyl ammonium hydroxide while the rifampin molecule was taken as pharmaceutical principle – used in lung disease treatment. Spectral measurements both in the visible (474 nm) and ultraviolet (334 nm) range were carried out to assess the drug delivery dynamics under magnetic control. The optimal ferrofluid dilution was established in the case of each ferrofluid - to about 66% -and the most convenient spectral band –the visible range one - when the rate of drug molecule releasing was the highest and best evidenced during the observation time of 48 hours. The basic protocol of the utilization of rifampin in combination with ferrofluids for targeted drug delivery in living tissues was shaped in the frame of this study.

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1. Introduction

The utilization of magnetic fluids in biology and medicine could represent more and more a complex research direction for both physicians and physicists. Diagnostics applications are related mainly to MRI contrast enhancement, i.e. the adding of the contrast agent (biocompatible magnetic fluid) at a given site can enhance the contrast between normal and diseased tissue. Therapeutic applications of biocompatible magnetic fluids concern, in the first place, tissue local hyperthermia; the raise of the temperature of a region of the body for the treatment of target malignant cells by heating enables preferential killing of cancer cells without damaging normal cells since the high absorption rate of ferrofluids localized in the tumor allows the heating to be restricted to the tumor volume. Tissue local hyperthermia intensifies the efficiency of radiotherapy and/or chemotherapy while reducing the toxic side effects. Then, the use of ferrofluids in tumor therapy regards the drug targeted delivery. Selective delivery of drug molecules to the diseased site by using a combination of drug and biocompatible magnetic carrier makes chemotherapy more effective by increasing the drug concentration at the tumor site, while limiting the systemic drug concentration. More, the associated side effects are reduced, as well as the dosage required - by more efficient, localized targeting of the drug molecules. Drug targeting represents the ability of the drug molecules to accumulate in the target organ or tissue selectively and quantitatively, independent of the site and methods of its administration.

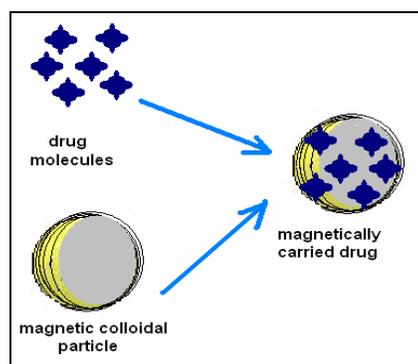


Fig. 1. The complexation of magnetic nanoparticles with drug molecules.

An interesting example of targeted drug delivery by external physical force is the magnetic drug transport. For this purpose, the drug is immobilized on a microparticulate carrier possessing ferromagnetic properties; so we have to do with magnetic targeting of drugs attached to paramagnetic carriers under the action of external magnetic field. In the following the authors present a spectral study on the capacity of two ferrofluids to form reversible complexes with rifampin molecules.

2. Experimental

Rifampin or rifampicin (Fig. 1) is a bactericidal antibiotic drug of the rifamycin group resulting as

semisynthetic compound derived from *Streptomyces mediterranei*. This medication is typically used to treat mycobacterium infections, including tuberculosis and leprosy, having a considerable role in the treatment of methicillin-resistant *Staphylococcus aureus*. Being a colored crystalline substance (Fig. 2) the light absorption either in the visible or the ultraviolet range could be utilized for quantitative studies.

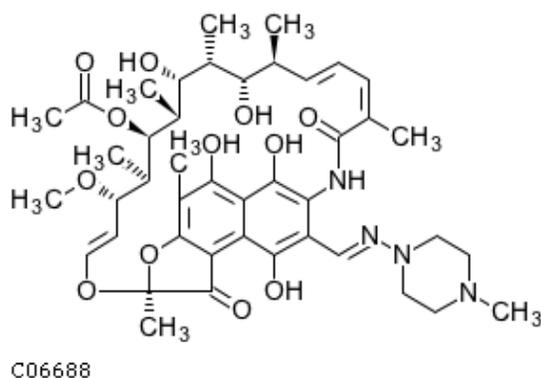


Fig. 1. The structure of rifampin.

Two aqueous magnetic fluids were used for the experimental investigation, both based on magnetite and maghemite nanoparticles stabilized with citric acid (CA – magnetic fluid) and respectively tetramethyl ammonium hydroxide (TMA-magnetic fluid).

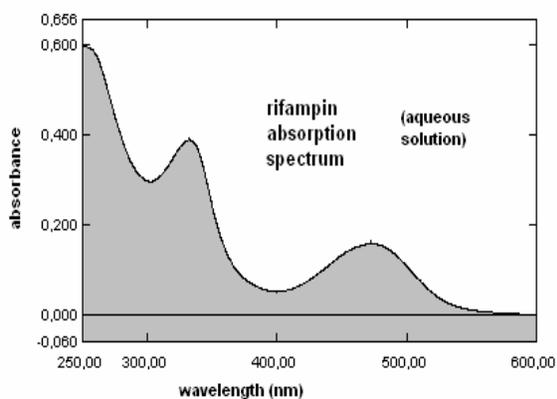


Fig.2. Electronic absorption spectrum of rifampin aqueous solution – the two maxima from visible range and respectively ultraviolet range were used for the quantitative assay of drug delivery.

The distribution curves of the nanoparticle physical diameter showed maximum frequency to about 10.9 nm in CA - magnetic fluid and respectively 8.1 nm in TMA - magnetic fluid while the saturation magnetization reached 20 kA/m and respectively 10 kA/m as described in [6].

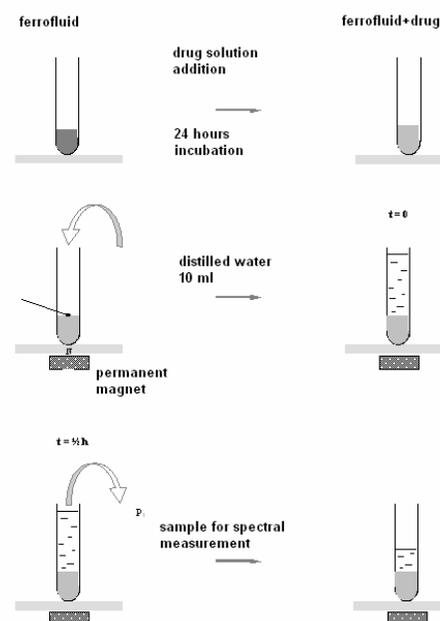


Fig. 3. The schematic representation of the main experimental steps.

Three dilutions in distilled water were tested in each case: C1: 1 ml magnetic fluid + 9 ml distilled water; C2: 2 ml magnetic fluid + 8 ml distilled water; C3: 4 ml magnetic fluid + 6 ml distilled water. The rifampin aqueous solution contained 50 mg powder and 15 ml distilled water. The magnetic induction of the permanent magnets utilized to control the drug delivery was of 120 mT as measured with a Hall probe teslameter. The spectral device utilized for the quantitative assay of rifampin released in distilled water after decomplexation was a Shimadzu UV 1700 provided with 1 cm width quartz cells. For each magnetic fluid dilution the percentage of rifampin solution added for complexation was of 50%; careful stirring was carried out and 24 hours pause at room temperature (24.0 C 0) was assured (Fig. 3). Further, the careful and slow addition of 10 ml water column was performed in each tube - with the above mentioned mixture - brought in contact with a permanent magnet - to simulate wet tissue, i.e. target organ of the rifampin molecules. Light extinction was measured in both VIS and UV bands of rifampin at $t=0$, $t=0.5$ h, $t=1.0$ h, $t=1.5$ h, $t=2.0$ h and $t=2.5$ h and 24 hours after the period of the magnetic exposure (24 hours).

3. Results and discussion

The dynamics of rifampin decomplexation was followed by using the values of light absorbance – the initial zero value - corresponding to the moment of the first contact of the target tissue with the complex rifampin-magnetic fluid - was included as starting point in all graphs; consequently the time axis was scaled from “0” to “48 h”.

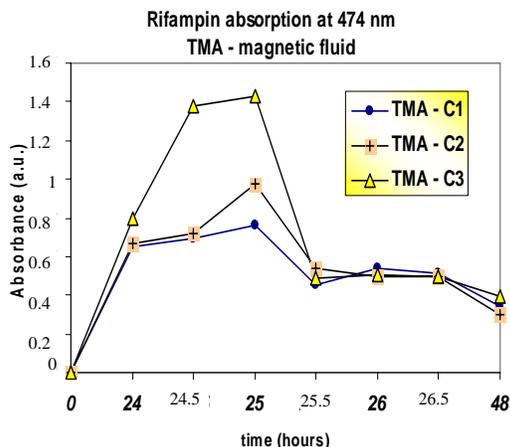


Fig. 4 a. The dynamics of rifampin decomplexation from the TMA-magnetic fluid as resulted from measurements on the visible absorption band.

The results obtained for TMA-magnetic fluid investigation are given in Figs. 4 a-b. For all concentrations of the TMA-magnetic fluid tested in here the maximum concentration of rifampin released in the water column simulating the target organ reached its maximum value at 25 hours (i.e. 1 hour after spectrophotometric assay debut). The highest concentration of magnetic fluid (C3) led to the highest rate of rifampin decomplexation. Peculiar behavior seems to be provided by the dynamics of the ultraviolet absorption intensity (Fig. 4 b) where considerable increase toward the final of the recording was noticed. This could be an indication upon a quasi-stable complex, characterized by its own absorption band in the ultraviolet range that is accumulated in time within the investigated solution. It is possible to be a complex between the tetramethyl ammonium ion and the rifampin molecules. In the case of the second complex rifampin-magnetic fluid - with higher magnetization and particle size - the graphs are presented in Figs. 5 a-b. Comparing with previous two graphs the tendency of drug molecule rapid delivery seems to be evidenced by both the visible and ultraviolet absorption band.

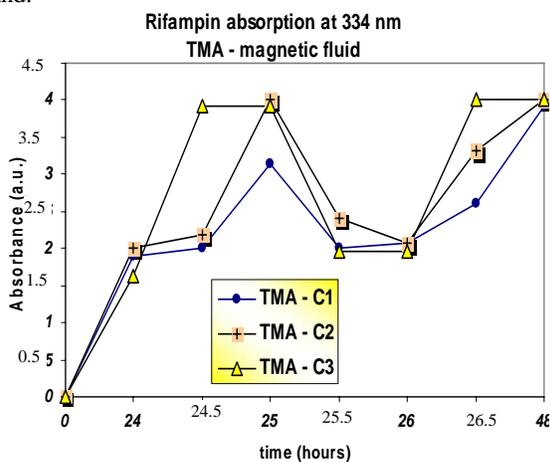


Fig. 4 b. Rifampin decomplexation from the TMA-magnetic fluid assessed from measurements on the ultraviolet absorption band.

This could be taken as an indirect indication of the fact that the interaction rifampin-magnetic particle is not so strong when the ferrophase is coated with citric acid in comparison to the case when the colloidal particles are coated with tetramethyl ammonium hydroxide. More, it seems that the interaction of magnetite and maghemite with rifampin molecules is favored by the smaller size of the magnetic cores.

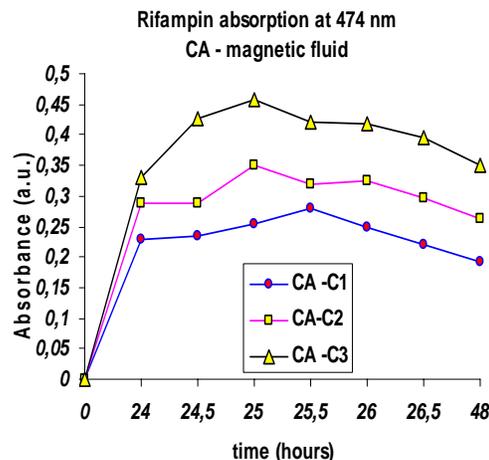


Fig. 5 a. The dynamics of rifampin decomplexation from the CA-magnetic fluid as resulted from measurements on the visible absorption band.

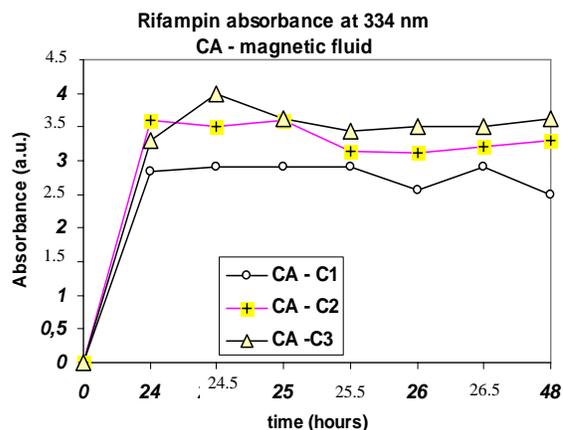


Fig. 5 b. Rifampin decomplexation from the CA-magnetic fluid assessed from measurements on the ultraviolet absorption band.

In both cases the band from the visible range of rifampin absorption spectrum is the most sensitive for the study of reversible complex formation with ferrophase particles.

4. Conclusions

The possibility of the utilization of the two magnetic fluids as magnetic drug carriers for the rifampin molecules is suggested by this study results. The targeted drug delivery to the lung tissue – where tuberculosis disease is often found – seems to be possible using magnetic field of about 100 mT induction. The generalization to the case of living tissues of this experimental model based on pure water as decomplexation medium need to be adjusted properly following in vivo experiments – the goal of our next experimental stage dedicated to magnetic targeting of drugs attached to paramagnetic carriers under the action of external magnetic field.

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