SISTEME CU ELIBERARE CONTROLATĂ PE BAZĂ DE SILICE CU ELIBERARE PRELUNGITĂ DE ACID FOLIC
DRUG DELIVERY SYSTEMS BASED ON SILICA WITH PROLONGED DELIVERY OF FOLIC ACID

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The aim of this work is to obtain new drug delivery systems with prolonged release of biological active folic acid. The prolonged delivery of folic acid, a component of the B complex is essential during the life being responsible with many essential functions including cell division and growth. The obtained materials were characterized by, FTIR and XRD as well as by studying the release profiles of folic acid and water uptake. It can conclude that the release rate is influenced by the used silica precursors.

Scopul acestei lucrări este de a obține noi sisteme cu eliberare controlată, cu eliberare prelungită de acid folic, componentă biologic activă. Eliberarea prelugită/susținută a acidului folic, componentă a complexului de vitamine B este esențială pe parcursul vieții, acidul folic îndeplinind funcții esențiale precum diviziunea celulară şi creştere. Materialele obținute au fost caracterizate prin, FTIR şi XRD precum şi din punct de vedere a capacității de eliberare a acidului folic şi absorbției de apă. Se poate concluziona că viteza de eliberare este influențată de tipul precursorilor de silice utilizați.

Keywords: *biocomposite materials, silica, DDS, sustained delivery*

1. Introduction

Drug delivery systems (DDSs) are of real interest for both biomedical and industrial applications. Numerous drug-delivery systems are developed with significant clinical applications. Some of the most important applications of silica based DDSs are: cancer treatment and diagnosis [1-5], treatment of cardiac diseases [6], therapy of ulcer [7], tuberculosis [8] or retinoblastoma [9].

Oral administration of the drugs has some very attractive advantages which recommend it any time when possible [10]. A major disadvantage of this form of administration is the chemical instability of many active components in the stomach conditions (low value of pH, presence of enzymes, etc).

Silica is mainly obtained starting from tetraethyl orthosilicate - TEOS or sodium silicate. Silica synthesis starting form TEOS consist of two consecutive steps meaning hydrolysis followed by condensation/dehydrating. The properties of the synthesized silica are strongly influenced by numerous factors: pH, concentrations, TEOS:H_2O ratio and temperature. Higher temperature and more acid media induce a quicker hydrolysis and low degree of polymerization [11-13]. Silica synthesis from silicate is also influenced by preparation conditions such as pH and temperature [14, 15].

Even if silica is a very attractive material [16] a lot of improvements were done. Based on the processing conditions structural improvement can be realised, the obtained mesoporous silica being valuable materials for drug delivery, sensors or for environmental applications. [1, 17, 18].

Another important way to improve characteristics of the silica based materials is to combine with other components, organic or inorganic, resulting composite materials [5, 19, 20] or materials with core-shell structure [21-24].

Folic acid is an essential component of the B vitamin complex being responsible with cell division and cell growth. Folic acid insufficiency leads to tiredness, weakness, diarrhoea, appetite and weight loss. An increasing level of folic acid is necessary, especially in pregnancy and during lactation [25].

The main purpose of this study is to obtain silica based drug delivery systems with prolonged release of folic acid.

The control of the folic acid delivery is assured by the low solubility of folic acid in acidic media, folic acid being especially released in intestines where the pH is higher.

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2. Experimental

Silica was obtained by two classical routes, starting from TEOS and sodium silicate. When TEOS is the precursor of silica the folic acid is mixed with TEOS and stoichiometric quantity of water followed by acidulation with HCl 1M, until pH became 2. When sodium silicate is used as silica precursor folic acid is firstly added and mixed few minutes till complete dissolution and then HCl 0.1M is added until neutral/slightly acidic pH. In both cases the silica precursor was calculated to assure a SiO_2:folic acid ratio of 1:1. Finally, the precipitates were filtered under vacuum and dried by freeze drying (Christ Alpha 2.4).

The obtained materials were investigated by X-ray diffraction, IR spectroscopy as well as delivery studies using UV-Vis spectroscopy.

X-ray diffraction analyses were performed using a Shimadzu XRD 6000 diffractometer at room temperature. In all cases, Cu Kα radiation from a Cu X-ray tube was used. The samples were scanned in the Bragg angle, 2θ range of 10 – 70.

For IR measurements, Brucker–VERTEX V70 spectrophotometer with ATR unit was used. The spectra were recorded over the wave number range of 400–4000 cm^{-1} with a resolution of 2 cm^{-1}.

UV-Vis measurements were made using a Thermo Evolution 300 spectrometer operated in transmission mode. The maximum absorption was determined by recording the spectrum of folic acid in 190-1100nm range. Both delivery systems were analyzed from the point of view of the release kinetic in simulated gastric fluid – SGF as well as in simulated intestinal fluid – SIF [10], by monitorizing the absorbance of the solution for 24h. In order to obtain the release profile the solution was continuously pumped throw the flow cell (quartz cell, 1mm pathlength, 37 ± 1^0C) and readings were done from 5 to 5 minutes at selected wavelength (350nm - wavelength corresponding to the maximum of absorptivity of folic acid) using QUANT mode. Prior analysis, a 5 points calibration curve is obtained, at same wavelength versus distilled water.

3. Results and discussion

The two types of SiO_2/FA are expected to exhibit different release profiles because of the different processing conditions. In the case of silica prepared from TEOS, the pH is maintained at acid value and consequently only a limited amount of folic acid is dissolved. In the case of sodium silicate derived silica, the pH is basic during the precipitation of silica and consequently a large amount of folic acid is dissolved. FTIR spectrum of pure silicate (obtained from sodium silicate) was recorded in order to relieve the characteristic absorption bands of silica. The main bands are: 1056cm^{-1} assigned to the antisymmetric motion of silicon atoms in siloxane bonds ν_{as}(Si-O-Si) and 793cm^{-1} corresponding to transverse-optical (TO2) mode, ν_s(Si–O–Si) of the O atom along a line bisecting the Si–O–Si angle [26].

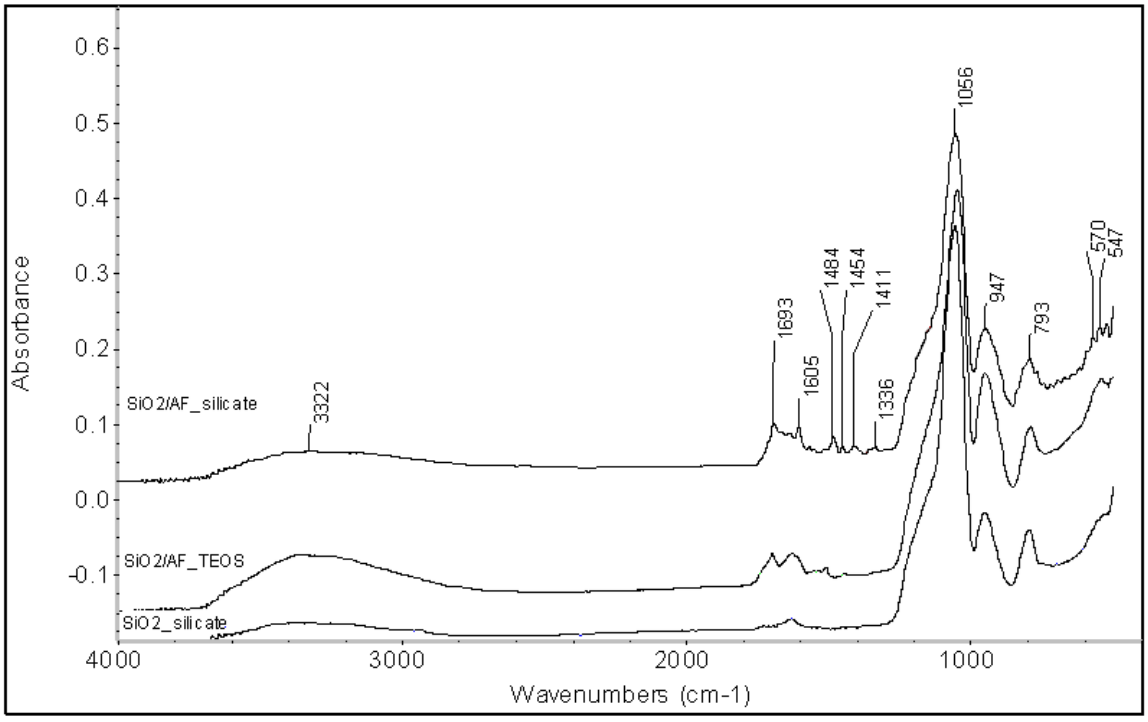

Fig. 1 - FTIR spectra of a. pure SiO_2 obtained from sodium silicate; b. SiO_2/AF obtained from TEOS and c. SiO_2/AF obtained from sodium silicate / *Spectrele FTIR ale: a. SiO_2 pur obținut pornind de la silicat de sodiu; b. SiO_2/AF obținut pornind de la TEOS şi c. SiO_2/AF obținut pornind de la silicat de sodiu.*

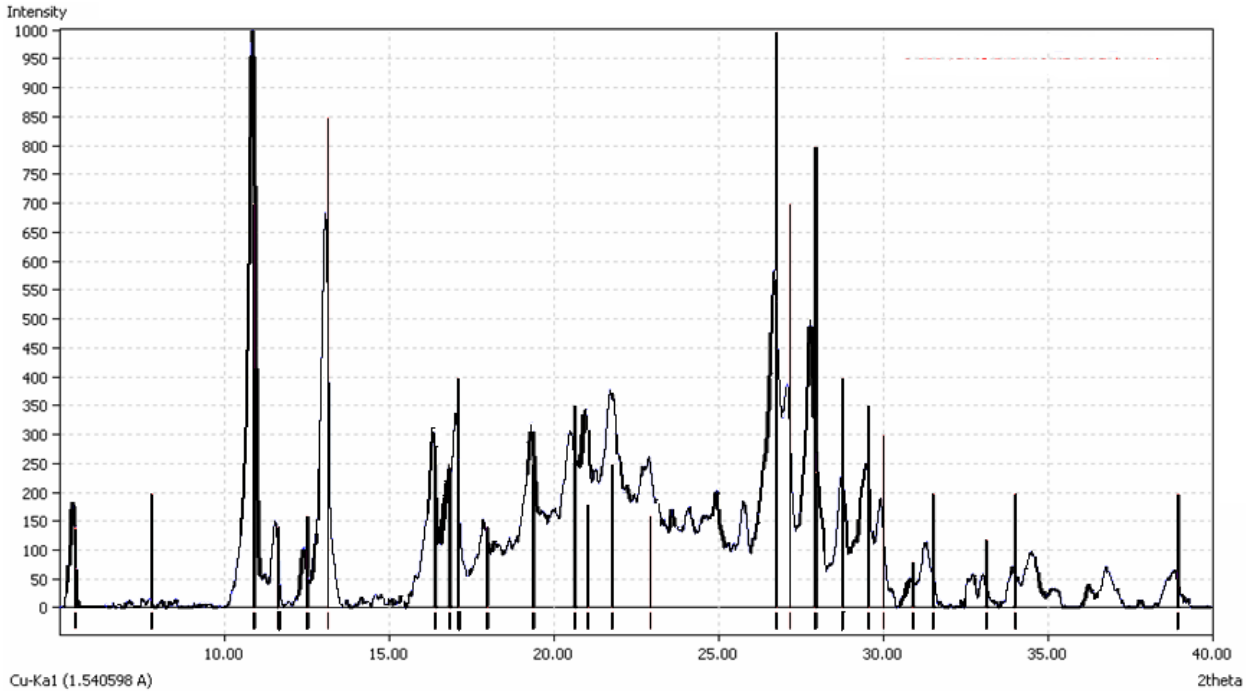

Fig. 2 - XRD diffraction pattern of silica/folic acid drug delivery system / *Difractograma de raze X a sistemului cu eliberare controlată SiO_2/acid folic.*

In fact, the large band from ~1100cm^{-1} is composed by three absorption bands: (i) the broad shoulder from 1115–1130cm^{-1} assigned to longitudinal optical mode (LO v_{as}(Si-O-Si); (ii) a strong peak centered at 1056cm^{-1} (transverse optical mode TO v_{as}(Si-O-Si); and (iii) a medium absorption band at 950 cm^{-1} due to silanol (Si-OH) stretching vibrations [28]. Comparing the intensity of the silanol group it can conclude that the silica obtained from TEOS has an increased density of the silanol groups (Fig. 1). The increase number of hydroxyl groups could induces differences between the release curves of folic acid from the two silica based DDS.

The FTIR spectra of both SiO_2/FA samples present suplimentary bands in 1300-1700 cm^{-1} range, bands assigned very probably to folic acid.

The diffraction pattern of folic acid is rich in diffraction peaks, the most important peaks appearing between 2Theta = 5 and 40° (ASTM 29-1716). The drug delivery systems of folic acid based on silica obtained from TEOS or sodium silicate exhibit the diffraction peaks of folic acid as well as a broad peak centred at ~ 22° [23], both being similar (Fig. 2). It is also worth to mention that the peaks of folic acid became narrower and even a better peak separation occurs when folic acid is embedded in a silica based drug delivery system. Sherrer's rule was used to estimate the crystallites size of folic acid for both pure folic acid and silicate based drug delivery systems. Based on the main five diffraction peaks of folic acid the mean size of folic acid is ~36.46nm in the case of pure folic acid and ~12.36nm in the case of TEOS derived DDS. The purity of the silica based DDS was proved by XRD by the lack of any supplementary diffraction peaks.

The release process of the folic acid was evaluated in two media each of them being relevant to the two segments of the digestive tract (SGF and SIF, Fig. 3). Important differences appear between the release of the folic acid in different media but also function of the used precursor. By short the release process is much more slower in SGF than in SIF and also the in the case of folic acid delivery system obtained by using sodium silicate as precursor.

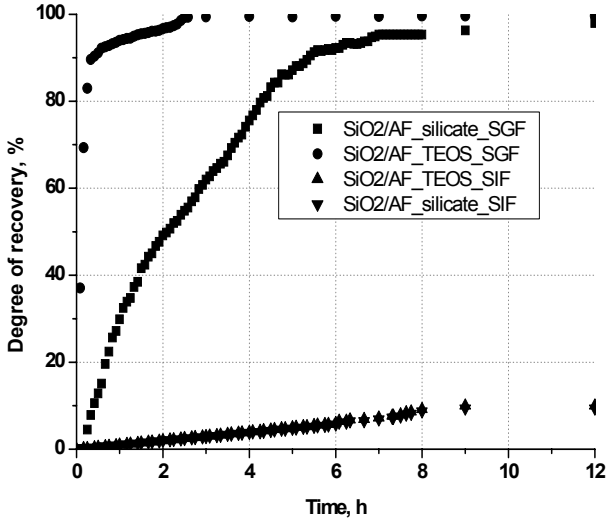

Fig. 3 - Folic acid release in SGF and SIF from both SiO_2/AF system / *Curbele de eliberare a acidului folic din sistemele SiO_2/AF obținute în SGF şi SIF.*

4. Conclusion

This work presents the synthesis and characterisation of new silica based drug delivery systems of folic acid. The influence of the silica precursors was analyzed from the point of view of release process. The faster release of folic acid is proper to the silica based drug delivery system obtained from TEOS. It is very important to mention that both drug delivery systems exhibit a very low release in SGF (due to the low solubility of the folic acid in acidic media) that make it suitable for oral administration because folic acid is not released in the stomach but in the intestine where the pH increase to slightly alkaline pH (because of the increasing solubility of folic acid in more basic solutions).

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