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Application of nuclear magnetic resonance spectroscopy to investigate the encapsulation of selected drugs into mesoporous silica nanoparticles

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Streszczenie w języku angielskim

The effectiveness of the therapy depends not only on the pharmacological activity, but also on an Active Pharmaceutical Ingredient form. Due to the fact that as many as 40% of known pharmacologically active compounds do not dissolve in water, which significantly reduces their bioavailability, improvement of this parameter is extremely important. A partial solution to the problem can be micronization or salt formation. Unfortunately, there are a lot of restrictions which preclude the application of these methods. Another method is to use systems capable of delivering drugs (***D**rug **D**elivery **S**ystems*, ***DDS***).

Drug delivery systems are also needed when the action of the active substance in the body is not satisfactory due to the low chemical stability and/or non-selective action of a drug. The pharmaceutical industry spent more and more money in search of new formulations of existing formulations to obtain systems with specific physicochemical properties. Using a specially designed carriers, it is expected that the encapsulation can provide the necessary protection active compound, a higher selectivity and therapeutic efficacy as well as safety of use, particularly in the case of anticancer drugs, wherein a common problem is their high toxicity. Among them an important group of DDS are mesoporous silica nanoparticles (***M**esoporous **S**ilica **N**anoparticles*, ***MSP***) such as MCM-41 (***M**obile **C**rystalline **M**atter/**M**obile **C**omposite **M**atter*) and SBA-15 (***S**anta **B**arbara **A**morphous*).

Mesoporous silica nanoparticles are inorganic polymers having a porous microstructure and a large adsorption surface. Among such materials, those having a well-defined structure and pore size (MCM-41, SBA-15), have become particularly important in modern chemical materials because of the variety of possibilities for their use. The possibility of simple modification of their surface consisting in the introduction of additional functional groups, or a suitable targeting particle makes these systems as indicators of diseased tissues. In addition, the host-guest interactions can also support the process of purification of water with certain chemicals, drugs or metals.

In the case of MSPs, the embedding of API into the pores is mainly based on soaking of a suitable matrix by ethanol, methanol or hexane solution of API. The applicability of these method we showed employing ibuprofen and MCM-41 as DDS. It turned out that obtained filling factor of the tested matrix pores is not fully satisfactory and fluctuates around 20%. Larger values (about 30%) was obtained only if the solvent used for the ibuprofen solution

was hexane. Hexane, because of its toxicity, will never be used for the preparation systems of the drug/DDS.

In the course of my research I have shown the cause of low filing factor of drug into matrix in the case of standard methods employing solvents. For this purpose the first time so successfully been used advanced experiments of NMR spectroscopy in the solid state. I found that the affinity of solvent molecules to the free silanol groups of silica matrix in comparison to the drug molecules are much greater and in the process of soaking they rapidly fill the pores blocking access of active pharmaceutical substance. The described phenomenon was unfortunately neglected in previous studies on the subject, although the "activate" the pores of the matrix before impregnation by calcining silica at a temperature of approx. 300 ° C to remove water molecules, it is standard procedure.

Small efficiency of impregnation of the above-mentioned methods was the basis for the search for a new, more efficient, as well as fulfilling the requirements green chemistry, solvent-free thermal method (***T**hermal **S**olvent-**F**ree, **TSF***) of incorporation of pharmaceutical active ingredients into the pores of mesoporous silica nanoparticles.

Using the specific physicochemical properties of the selected model compounds (relatively low melting point) I attempted to incorporate of selected drugs silicon matrix into MSN pores using a thermal solvent free process, TSF. This process based on melting of physical mixture of the drug and a matrix at a temperature above about 5 ° C than the melting point of the drug. This approach eliminates the system of media other than a drug and matrix, and significantly shortens the process of incorporation into the MSN pores.

Due to the high melting point and low thermal stability of some pharmaceutical active ingredients, the TSF method it can not be regarded as a universal tool for carrying out the encapsulation process. This is extremely important in the case of APIs melting at a very high temperature, which may start the process of degradation. The change of these properties can be achieved by cocrystal engineering.

The next stage of my research was to design, obtain and analyze cocrystals of the relevant physicochemical properties. Cocrystals consist of two or more different chemicals and has different physicochemical properties of the starting components. My aim was to change the melting point to allow for impregnation of the pores of the MCM-41 / SBA-15 by TSF. During the research, I observed that the process of incorporating cocrystals into MSN can take place in different ways. The first leads to a fusion of the material retaining complete or partial crystal structure of the starting cocrystal in the pores of the MSN. In the latter case, I noted

partial or complete separation of cocrystal components by preferential binding of one of these with MSN functional groups.

The primary technique used to analyze the drug/MSN or cocrystal/MSN systems was nuclear magnetic resonance spectroscopy and related techniques, such as infra-red spectroscopy (***F**ourier **T**ransformation **I**nfra **R**ed, **FT-IR***) or thermal methods such as TGA (***T**hermal **G**ravimetric **A**nalysis, **TGA***) and DSC (ang. ***D**ifferential **S**canning **C**alorimetry, **DSC***).

In my researchers, the classic experiments of NMR spectroscopy in the solid allowing for the registration of the spectra of nuclei with non-zero magnetic moment, ^{1}H, ^{13}C, ^{15}N and ^{29}Si present in the tested systems have been used. ^{1}H NMR spectra MAS because of the strong dipolar interactions are characterized by significant broadening the signals, which inevitably makes it difficult to interpret. The solution to this problem is a technique Very Fast (VF) MAS NMR, in which the test substance is spun at the magic angle at up to 65kHz.

Spin samples at such rate eliminates receiving adverse effects of NMR as homo- and heteronuclear dipolar coupling and chemical shift anisotropy. Despite the fact that NMR spectroscopy in solid is a fundamental technique used in structural studies of the compounds in the solid phase, only a small extent was used to describe the MSN interactions with medication. An additional advantage of NMR spectroscopy in the solid state is possible to carry out a complete characterization of the molecular dynamics of drug molecules into silicon matrix, including the pore size and topology as well as drug-matrix interactions.

Made research described a "guest-host" interaction, the structure of the drug embedded into silica matrix as well as to carry out full characterization of mesoporous silica materials as drug carriers using NMR techniques in the solid phase. Moreover, the knowledge of the analysis of the drug release mechanisms, which is not without significance for the design and control the release ratio have been completed. In addition, studies allowed for development of other systems cocrystal/DDS, which in the future may allow for more effective drug therapy. A small number of works taking place on the cocrystal incorporated into MSN is no doubt about the novelty of presented dissertation.