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Tetrabutylammonium methacrylate as a novel receptor for selective extraction of sulphonylurea drugs from biological fluids using molecular imprinting

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Glibenclamide (GLIB), an oral antidiabetic medication of the sulphonylurea drug family, was stoichiometrically imprinted using tetrabutylammonium methacrylate as the functional monomer, for the first time in molecular imprinting, and utilising the sulphonylurea affinity for carboxylate anions. Solution association between the drug and the novel functional monomer was studied by ^{1}H-NMR titrations, whereby evidence of sulphonylurea deprotonation followed by the formation of "narcissistic" GLIB dimers was found when tested in $CDCl_3$, while an affinity constant in excess of 10^5 L mol^{-1} was measured in DMSO-d_6. Detailed analysis of GLIB binding on the subsequently prepared imprinted and non-imprinted polymers confirmed the deactivation of binding sites by exchange of a proton between GLIB and methacrylate, followed by extraction of the tetrabutylammonium counterion from the polymer matrix, resulting in overall reduced binding capacities and affinities by the imprinted material under equilibrium conditions. An optimised MI-SPE protocol, which included a binding site re-activation step, was developed for the extraction of GLIB from blood serum, whereby recoveries of up to 92.4% were obtained with an exceptional sample cleanup.

Introduction

Glibenclamide (GLIB), also known as glyburide, is an oral antidiabetic medication and belongs to the second generation sulphonylurea drug family, used in the treatment of diabetes mellitus. It acts by stimulating the release of insulin from pancreatic β-cells and peripheral tissue sensitivity to insulin.[1] Glibenclamide is more potent than the first generation sulphonylurea drugs and is a medication of choice for initiating treatment for non-insulin dependent diabetes mellitus when diet fails. Controlling the therapeutic concentration of glibenclamide in blood as well as the study of its pharmacokinetic profile requires rapid and sensitive analytical methods. The most commonly employed method for the analysis of glibenclamide is by HPLC, with UV or mass spectrometry detection, GC, and MEKC using non-ionic surfactants.[2] All of the above methods reported in the literature require a liquid–liquid extraction step for blood sample pre-treatment, which is a labour intensive, time consuming process and is often associated with sample loss. Solid phase extraction (SPE) methods for glibenclamide extraction from human plasma have been reported using C8 or C18 cartridges coupled in line with HPLC and capillary electrophoresis.[3]

Herein, we wish to report on the development of novel Molecularly Imprinted Solid-Phase Extraction (MI-SPE) materials for the rapid pre-concentration and cleanup of glibenclamide in biological fluid samples prior to HPLC analysis. Molecular imprinting is a technique that enables the generation of selective binding sites within the matrix of a synthetic polymer by co-polymerisation of selected functional and cross-liking monomers in the presence of a target substance.[4] Thus, solution phase complexes between the so-called template and functional monomers are locked in place upon cross-linking of the growing polymer chains. The resulting binding sites are revealed by removal of the template by simple solvent wash and are thus capable of selective rebinding of the template or closely related substances.[5] Such materials have already shown promise in bioanalytical applications combining high selectivity and sample cleanup prior to subsequent analysis.[6]

Our approach was inspired by our previous work in the development of custom functional monomers for the recognition of anionic species.[7] In particular, we have demonstrated that urea-based functional monomers are powerful receptors for carboxylate anions and have employed them in the recognition

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