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Extraction of non-steroidal anti-inflammatory drugs using an octyl-hybrid silica monolith.

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ABSTRACT

The process of the extraction and preconcentration of drugs is usually complicated, labour-intensive and time consuming. Therefore, the selection of an appropriate sample preparation procedure is a key factor in a successful sample analysis, while the whole analytical process can be wasted if an unsuitable sample preparation method is used. The aim of this work was to fabricate a material with the ability to preconcentrate drugs of abuse in biological fluids with a high extraction efficiency. This was achieved by the fabrication of a monolithic materials, followed by modification of the surface of the silica-based monolith with octyl groups, and then placing the octyl-hybrid silica monolithic disc inside a plastic syringe for the subsequent analysis. The fabricated materials were characterised using different techniques, such as SEM coupled with EDAX analysis and BET analysis. In this study, the isolation of non-steroidal anti-inflammatory drugs (NSAIDs), namely ketoprofen (KEP) and ibuprofen (IBP), was achieved using an octyl-hybrid silica monolith onto which the drugs were adsorbed on a solid support while any contaminants were removed by washing the monolithic materials; finally the purified drugs were eluted from the monolithic material. The results showed that the extraction efficiencies of the two NSAIDs were both more than 95%. Linearity (R^2, 0.9974 – 0.9978) was obtained in the range of 40-800 µg mL^{-1}. The intra- and inter-monolithic columns indicated good monolith reproducibility, with relative standard deviations (RSDs) of less than 5.9% and 7.6%, respectively.

Keywords: silica-based monolith, octyl group, extraction, ketoprofen, ibuprofen.

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INTRODUCTION

The utilisation of pharmaceutical products such as non-steroidal anti-inflammatory drugs (NSAIDs) are highly important in modern society, where they have been used in clinical practice since 1898. Hundreds of other NSAIDs have been fabricated and used in anti-inflammatory medicine (Luo, Zheng et al. 2011). Ketoprofen (KEP) and Ibuprofen (IBP) are the most widely used NSAIDs and have analgesic and antipyretic functions (Bempong and Bhattacharyya 2005); the former is widely utilised for the treatment of arthritis and as an antipyretic (Richardson 2003), while the latter is widely utilised for the treatment of pain, inflammation, vascular headaches, dysmenorrhoea and fever (Basheer, Chong et al. 2007). NSAIDs are a major category of drug residues found in effluents as higher therapeutic doses of pharmaceutical residues are excreted via urine into environmental aqueous media, which can be toxic to animal species and human beings and thus represent a health hazard (Tixier, Singer et al. 2003); albeit, the concentration of pharmaceutical residues in environmental aqueous are usually relatively low (Richardson 2003). Therefore, it is important to develop a suitable sensitive analytical method to monitor the levels of pharmaceutical drugs in environmental aqueous media for proper risk assessment.

Most analytical instruments cannot handle such sample matrices directly, or the target analytes may be masked by interfering compounds during the analysis. Therefore, sample preparation is essential in order to remove any interfering materials and to preconcentrate the analytes of interest. As a result, the signal intensities of the target analytes will be improved and the quantities of the target analytes can then be easily measured (Alzahrani 2012) . For sample preparation in drug analysis, liquid-liquid extraction (LLE) is the oldest and the most common technique utilised (Jönsson and Mathiasson 1999). However, LLE is complicated, tedious, labour-intensive, time consuming, non-selective, susceptible to errors and depends on the use of hazardous organic solvents. Moreover, LLE can cause the loss of the analyte of interest because of an incomplete extraction, and also, generally it has problems regarding emulsion formation (Moeder, Schrader et al. 2000, Vas and Vekey 2004, Fan, Feng et al. 2005, Nováková and Vlčková 2009). To overcome these problems other kinds of extraction have been considered, such as the solid-phase extraction (SPE) technique.

Common materials that can be used as an SPE sorbent include monolithic materials, namely organic and inorganic monolithic materials. Most of the publications dealing with organic polymer monoliths are focused on using these types of monoliths for the extraction of different types of drugs. For example, Chen et al. (Ma, Chen et al. 2009) fabricated a poly(*N*-isopropylacrylamide-*co*-ethylene dimethacrylate) organic monolith that was investigated in an in-tube solid-phase microextraction for antidepressant drugs. Zheng et al. (Luo, Zheng et al. 2011) synthesised a poly(VP-*co*-ethylene dimethacrylate) organic monolithic polymer as a robust stationary phase for the extraction of NSAIDs. However, organic monolithic materials have some drawbacks, such as poor hydrophobicity, small surface area and low mechanical stability (Yu, Wang et al. 2011), and, as a result, the wider application of monolithic materials is limited.

To the best of our knowledge, there have been few reports on the preparation of inorganic silica monoliths for the purpose of the extraction of NSAIDs. Herein, the aim of the current work was to fabricate an inorganic monolithic material, followed by modification of the surface of the monolithic silica rod with octyl groups to form hydrophobic materials. The modified silica monolith with octyl groups was then cut and placed into a plastic syringe in order to use it as a sorbent for the extraction of KEP and IBP. The reason for choosing these types of NSAIDs in this study was because they are the most common drugs found in untreated waste-water samples (Nakada, Tanishima et al. 2006). Characterisation of the fabricated monolithic materials was performed using different techniques in order to study the physical properties of the fabricated monolithic materials; for example, their surface area, porosity and the structural morphology of the monolith. In addition, reproducibility of the performance of the fabricated silica materials was checked by calculating the relative standard deviation.

EXPERIMENTAL

Chemicals and materials

Polyethylene oxide (PEO) with an average relative molecular mass MW of 10,000 Da, trimethylchlorosilane (TMCS), tetramethylorthosilicate (TMOS, 99%), chloro(dimethyl)octylsilane (97%), 2,6-lutidine (99%), ketoprofen (KEP) and ibuprofen (IBP) were purchased from Sigma-Aldrich (Poole, UK) and used

as received without any further purification. Nitric acid, ammonia, toluene, acetonitrile (ACN), analytical-grade methanol (MeOH), sodium acetate buffer and phosphate buffer were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Disposable plastic syringes (1 mL) were purchased from Scientific Laboratory Supplies (Nottingham, UK). Falcon™ conical centrifuge tubes (50 mL) were purchased from Fisher Scientific (Waltham, USA).

Instrumentation

A hot-plate stirrer from VWR International LLC (West Chester, PA, USA) was used. The Brunauer-Emmett-Teller (BET) model used a Surface Area and Porosity Analyser from Micromeritics Ltd. (Dunstable, UK). The transmission electron microscopy (TEM) system was from JEOL Ltd. (Welwyn Garden City, UK). The scanning electron microscope and energy dispersive X-ray spectroscopy (SEM-EDAX) system was a Cambridge S360 from Cambridge Instruments (Cambridge, UK). A WiseTherm high-temperature muffle furnace from Wisd Laboratory Instruments (Wertheim, Germany) was used. The instrument used for HPLC-UV detection was a 785A UV/Visible Detector from PerkinElmer (California, USA). The symmetry C_8 column, 4.6 mm × 250 mm packed with silica particles (size 5 mm), was purchased from Thermo Fisher Scientific (Loughborough, UK).

Fabrication of the octyl-hybrid silica monolith

Preparation of a monolithic silica rod

The monolithic silica rod was synthesised by the hydrolysis and polycondensation of precursors via a two-step sol-gel method following the previously reported procedure (Alzahrani and Welham 2011). The porous silica rod was fabricated by mixing 0.282 g of polyethylene oxide (PEO), 2.537 mL of 1 M nitric acid solution, 0.291 mL of distilled water and 2.256 ml of tetramethyl orthosilicate (TMOS) in a Falcon™ conical centrifuge tube (50 mL). The solution was violently agitated to promote a hydrolytic reaction while immersed in an ice bath until the two phase mixture gradually became a homogeneous solution.

The acidified polymer solution was slowly poured in to a 1 mL disposable plastic syringe (internal diameter 4.5 mm). When the mixture was in the syringe, it was shaken carefully to remove any air bubbles. The thin end of the syringe was sealed using PTFE thread seal tape. The syringe was placed in an oven at 40 ºC for 24 h. Afterwards, the wet silica monolith rod was released slowly from the plastic syringe. The silica rod was soaked in a water bath for 2 h at room temperature. The resulting monolithic silica rod was treated with a basic environment, produced by the thermal decomposition of 1 M aqueous ammonia solution in a conical flask (100 mL) at elevated temperature (85 ºC) for 24 h. Then, the rod was rinsed with distilled water to remove the ammonia solution. Subsequently, the monolithic silica rod was dried in an oven for 24 h at 40 ºC, followed by a further 24 h at 100 ºC, and finally the rod was placed in an oven at 500 ºC for 2 h.

Modification of the surface of the silica monolith with octyl groups

The surface of the monolithic silica rod was chemically modified by adding octyl groups. The derivatisation reagent was 0.5 g chloro(dimethyl)octylsilane as the silanisation reagent in 5 mL of dried toluene and 10 drops of 2,6-lutidine. The monolithic silica rod was continuously fed with the mixture for 3 h and washed with toluene. Subsequently, the monolithic silica rod modified with octyl groups was rinsed with 0.5 g trimethylchlorosilane (TMCS) in 5 mL of dried toluene for 3 h. After derivatisation, the monolith was flushed with toluene and then with methanol, and finally the modified silica rod was placed in an oven for 24 h at 40 ºC prior to use.

Characterisation of the fabricated materials

The fabricated material was characterised using techniques such as SEM analysis. In addition, a compositional analysis was performed using the energy dispersive analysis of X-ray spectroscopy (EDAX). The physical properties of the fabricated materials were studied using BET isotherms of nitrogen adsorption and desorption at 77 K. The monolithic rods were dried using N_2 gas. The isotherms were analysed to obtain the surface area according to the (BET) model. The pore volume and pore size distribution of the pores within the monoliths were measured from the isotherms using the BJH (Barett-Joyner-Halenda) model. The total

porosity of the fabricated materials was measured using the following equation (Alzahrani and Welham 2011):

$$\phi_t = \frac{W_M - W_T}{dLR_2\pi}$$

where W_M and W_T are the weights of the monolith when dried and when filled with water respectively, d is the density of water (at 23 ºC = 0.9975 g cm^{-3}) and L and R are the whole length and radius of the cylindrical monolith, respectively. The measurement was repeated five times and the average was taken.

Extraction of drugs

KEP and IBP were prepared individually at a concentration of 1 mg mL^{-1} in methanol and kept at 4 ºC in the dark. All the standards were prepared in 0.02 M phosphate buffer solution (pH 7). The monolithic silica rod was cut (1 cm) and placed inside the plastic syringe, which was used as a mould. The monolithic material was cleaned with 200 µL of methanol, then it was conditioned with 200 µL of 0.02 M phosphate buffer solution (pH 7). The sample solution (500 µL) was then added. After washing the column with 100 µL of 0.02 M phosphate buffer solution (pH 7), the sample was eluted from the monolithic rod using 100 µL of acetonitrile and then dispensed into an Eppendorf tube. The performance of the fabricated octyl-silica monolith was assessed using an HPLC-UV instrument in order to study the peak areas obtained for the standard drug and then comparing them with the peak areas of the non-processed drug standard solutions in order to calculate the extraction efficiency. The mobile phase was methanol and sodium acetate buffer solution (25 mM, pH 5) (50:50) and the flow rate was 0.5 mL min^{-1}. The UV detection was set at 223 nm and the sample injection volume was 20 µL.

The extraction recovery (R) was calculated using the following equation:

$$R = \left(\frac{V_a C_a}{V_s C_s}\right) \times 100\ \%$$ (Yazdi and Es'haghi 2005)

where V_a and V_s are the volume of the acceptor phase and the volume of the sample, respectively, while C_a and C_s are the final concentration of the analyte in the acceptor phase and the initial concentration of the analyte within the sample, respectively.

The analyte enrichment factor (EF) was calculated using the following equation:

$$EF = \left(\frac{C_a}{C_s}\right)$$ Montagna, Stramesi et al. 2000, Ho, Pedersen-Bjergaard et al. 2002(

RESULTS AND DISCUSSION

Formation of a sol-gel silica monolith

In this study, an inorganic silica-based monolith was fabricated, followed by derivatisation of the surface of the monolithic materials with octyl groups in order to use the monolith material as a sorbent for the extraction of NSAIDs. The silica gel was formed using a sol-gel process involving two kinds of reactions: hydrolysis of the sol-gel precursor and polycondensation of the hydrolysed products (Kumar, Malik et al. 2008, Pierre 2013). Metal alkoxides (TMOS) were utilised as a precursor material to form the silica monolithic structure. The hydrolysis of TMOS occurred due to nucleophilic substitution of the methoxy groups by water through nucleophilic addition followed by proton transfer, resulting in the formation of silicon hydroxyl groups that then interact with each other to form the siloxane species and water. The condensation reaction then continues, resulting in the formation of a three-dimensional network (Folgar 2010, Gaweł, Gaweł et al. 2010, Lofgreen and Ozin 2014). The protonation of TMOS happened easily in the presence of acid; therefore, HNO_3 was utilised in this study, while PEO was utilised as a porogen to form the macropores in the gel, since PEO forms hydrogen bonds with the silanols to form silicate polymer (Nakanishi and Soga 1997, Núñez, Nakanishi et al. 2008, Alzahrani and Welham 2013).

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After the mixing step, the casting process took place, which involved pouring the partially polymerised solution into a mould, which in this case was the plastic syringe. During the gelation step, the condensation reaction formed particles, which subsequently formed clusters that linked together to form a solid wet gel material (Brinker and Scherer 2013). It was observed that after formation of the gel matrix, there was a shrinkage in the silica rod during ageing and drying and this helped the monolithic rod to be released easily from the plastic syringe. After formation of the macroporous network silica monolith, it was treated with 1 M aqueous ammonia solution to obtain a mesoporous structure by converting the micropores, which have a low surface area, to mesopores, which have a high surface area (Alzahrani 2014). The monolithic silica rod was calcined at 500 ºC for 2 h to remove all the organic compounds from the inorganic materials and to obtain more mechanically stable materials. After calcination, a bright white and crack-free monolith was formed, and after this step, the monolithic rod retained its porosity, size and appearance.

Modification with octyl groups

The silica-based monolith is polar because of the silanol groups on its surface. The concentration and activity of these moieties can vary from batch to batch. In addition, these groups are weak acids and their ionisation can be easily suppressed and subsequently, their use as an ion-exchange material will be quenched (Robards, Robards et al. 1994). Therefore, it is important to modify the surface of the silica monolith with different functional groups. The attachment of groups on the silica surface is easier than on an organic polymer support, since it has a high number of cross-linking bonds, which require hours to reach equilibrium for surface activation (Alzahrani 2015). In this study, the monolithic silica rod was chemically functionalised with octyl groups. The chemical modification on the monolithic silica rod was carried out with 10 mL of a solution of derivatisation reagent consisting of chloro(dimethyl)octylsilane in dried toluene, followed by washing with toluene to remove the unreacted materials.

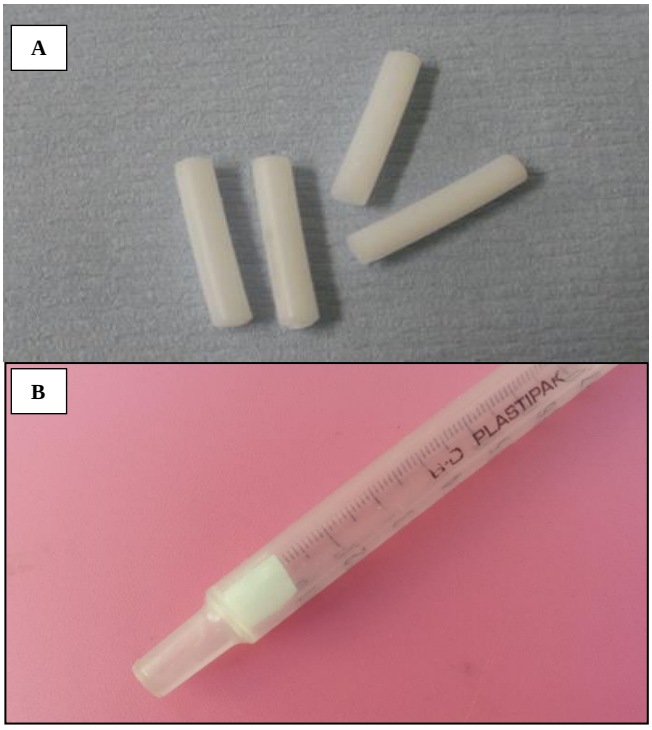

Fig. 1(A) photograph showing the monolithic silica rod monolith prepared using plastic syringe as a mould, (B) after cutting a piece (1 cm) of the monolithic silica rod and placing inside 1 mL plastic syringe in order to use it as a sorbent. The sol–gel precursor was 0.282 g PEO (MW = 10,000 Da), 2.537 mL of 1 M HNO_3 and 0.291 mL of distilled H_2O. The derivatisation reagent was 0.5 g chloro(dimethyl)octylsilane in 5 mL of dried toluene and 10 drops 2,6-lutidine, the end capping reagent was 0.5 g trimethylchlorosilane in 5 mL of dried toluene.

It is known that after derivatisation of the surface of the silica-based monolith with the octyl groups, these groups act as a barrier for free neighbouring silanol groups to be derivatised with the octyl groups; therefore, after derviatisation of the silica-based monolith with octyl groups, the groups were endcapped. For

this, small organic groups were used consisting of trimethylchlorosilane (TMCS) in dried toluene in order to block unreacted silanol moieties, since otherwise they could cause secondary interactions with the polar functional groups in the sample matrix and could hence decrease the extraction efficiency of the sorbent (Sanagi, Naim et al. 2001, Alzahrani and Welham 2012). The modification reaction was carried out in the presence of 2,6-lutidine as a catalyst in order to increase the reactivity of the derivatisation reagent (Wu and Fokin 2007).

Alzahrani and Welham (Alzahrani and Welham 2011) found that after modification of the silica-based monolith with octadecyl moieties (C_{18}) in order to use the fabricated materials for the preconcentation of proteins, the colour of the monolithic silica rod changed from bright white to translucent after modification with C_{18} groups. However, in this study it was found that the colour of the monolithic materials was not changed after derviatisation with C_8.

Figure 1 (A) shows the monolithic silica rod after fabrication. It was first cut and the width of the monolithic rod was adjusted using a special cutting blade and then the monolithic rod was placed (1 cm in length) inside a plastic syringe, which was then utilised for the extraction of the drugs of interest, Fig. 1 (B).

Characteristics of the fabricated materials

SEM-EDAX analysis

The prepared monolithic materials before and after coating with octyl groups was studied using SEM analysis in order to investigate the morphological structure of the prepared materials and to compare the morphological features of the two samples. Figure 2 shows the SEM micrographs of the bare silica-based monolith, Fig. 2 (A and C), and of the octyl-hybrid silica monolith, Fig. 2 (B and D). It was found that the domain size (macropores and skeleton) of the bare silica monolith decreased after modification with octyl groups, thus confirming the modification of the materials with octyl groups.

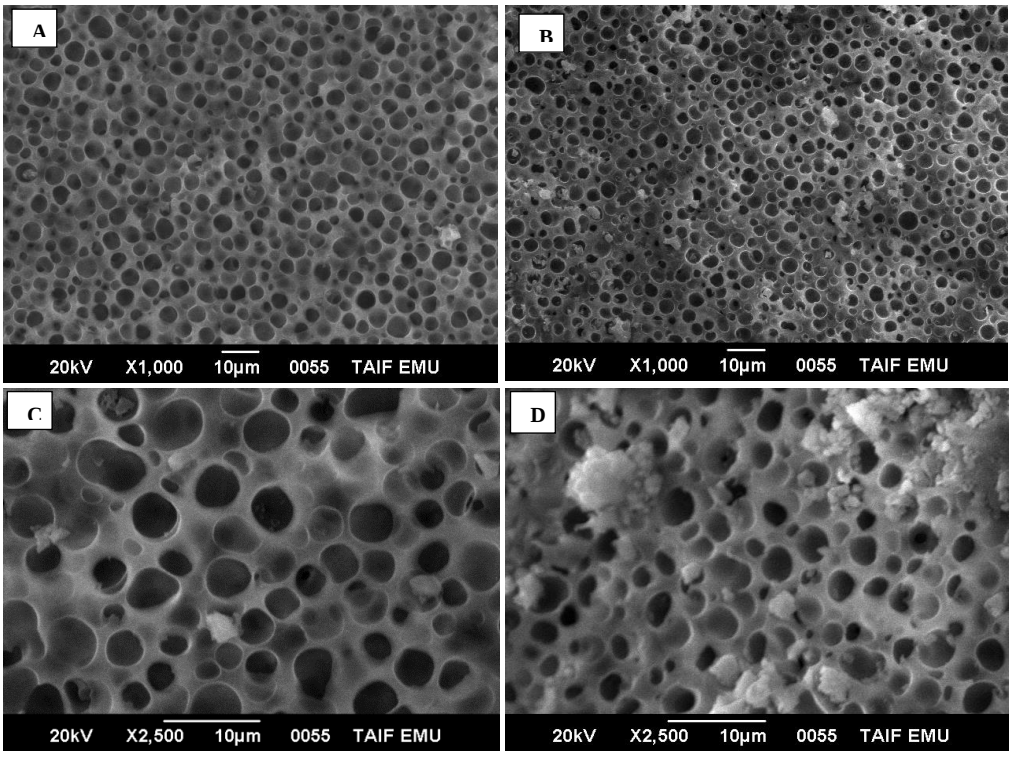

Fig. 2 SEM micrographs showing the main structure of the fabricated silica monolith before (A and C) and after modification with octyl groups (B and D).

The elemental characterisations of the bare silica-based monolith and octyl-hybrid silica monolith were obtained using EDAX analysis. Figure 3 shows the EDAX spectra of the non-modified silica monolith (A) and of the silica monolith modified with octyl groups. The result shows strong peaks for silicon (Si) at 1.739

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KeV and oxygen (O) at 0.525 KeV. The EDAX spectra shows that a new peak of carbon (C) at 0.277 KeV was observed after modification of the surface of silica monolith, thus confirming the modification of the silica monolith of the organic moieties. As can be seen in Table 1, the presence of C, O and Si in the octyl-hybrid silica monolith were determined by EDAX analysis to be 29.83%, 54.11% and 16.06%, respectively, indicating that the octyl moieties had been successfully anchored onto the monolith.

Table 1. Quantitative EDAX analysis for all the elements in the bare silica monolith and in the octyl-hybrid silica monolith

Sample	Element	KeV	Atom %	Total
Bare silica monolith	O	0.525	73.21	100.00
	Si	1.739	26.79	
Modified silica monolith with octyl groups	C	0.277	29.83	100.00
	O	0.525	54.11	
	Si	1.739	16.06	

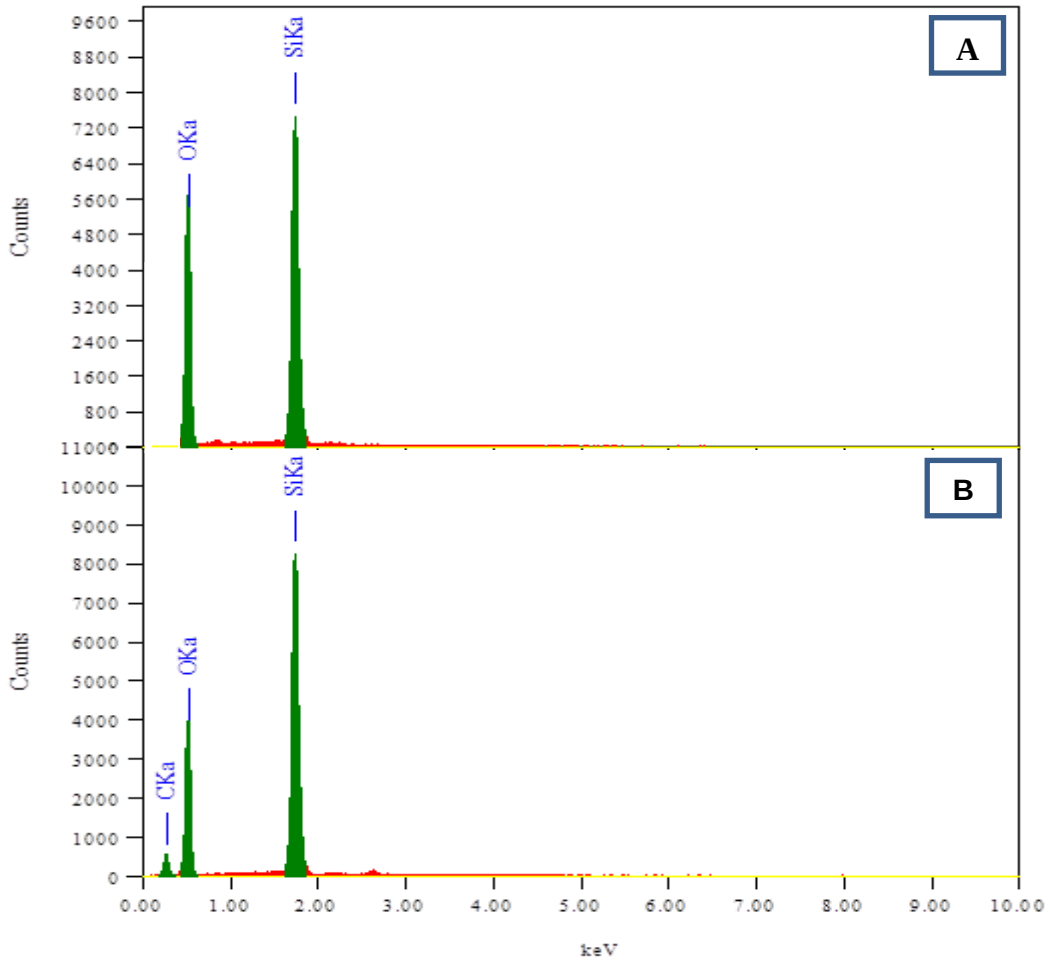

Fig. 3 EDAX spectra showing (A) bare silica-based monolith and (B) silica-based monolith after modification with octyl groups.

It was very important to make sure that the octyl groups were not only in the outer surface of the silica-based monolith but also in the inner surface of the monolithic rod; therefore, three cross-sections from different parts of the monolithic rods (upper, middle and lower) were assessed by checking the morphology of the fabricated monolithic materials before and after derivatisation with the alkyl groups using SEM analysis, and it was found that there was no difference in the morphology of the fabricated materials. In addition, the percentage of C in each cross-section was investigated using EDAX analysis, as can be seen in Table 2. From the

EDAX results, it was found that the internal surface of all the cross-sections of the silica-based monolith were derivatised with octyl groups, and the percentage of C in all sections of the monolithic rod were similar.

Table 2. Quantitative EDAX analysis for all the elements in all cross-sections of the octyl-hybrid silica monolith

Spectrum	C%	O%	Si%	Total
Upper-section	29.83	54.11	16.06	100.00
Middle	28.04	54.53	17.43	100.00
Lower-section	25.49	57.79	16.72	100.00

Physical properties

The physical properties of the bare silica-based monolith and the octyl-hybrid silica monolith, such as the surface area, pore size and pore volume, were studied through a physisorption technique using BET analysis, and the relative standard deviation was calculated for three different samples. It was found that the BET surface area of bare silica-based monolith in this study (173±3.7 $m^2 g^{-1}$) was reduced after anchoring of the organic groups on the inner surface of the mesopores (162±5.4 $m^2 g^{-1}$). In addition, the porosity of the fabricated materials was calculated, and it was found that the porosity was reduced from 0.51±3.9 to 0.36±2.4 after derivatisation with alkyl chains (C_8).

The effect of the octyl surface modification on the average pore size and pore volume was investigated, as seen in Fig. 4, which shows the pore size distribution of the silica-based monolith before and after modification with octyl groups. It was found that the average pore size of the octyl-silica monolith was in the mesoporous range (11.78 nm), which was a little smaller than the average pore size of the bare silica monolith (14.12 nm). Moreover, the total pore volume of the silica-based monolith was also reduced from 0.627 $cm^3 g^{-1}$ to 0.568 $m^2 g^{-1}$ after modification with octyl groups. The reduction in the physical properties of the fabricated silica monolith after modification with octyl groups was expected. The reason for the decrease in the surface area, porosity, pore volume and average pore diameter was due to the replacement of surface silanol groups on the surface of silica monolith by larger chemical moieties as well as due to blocking of the micropores in the monolithic materials by the bonded phase.

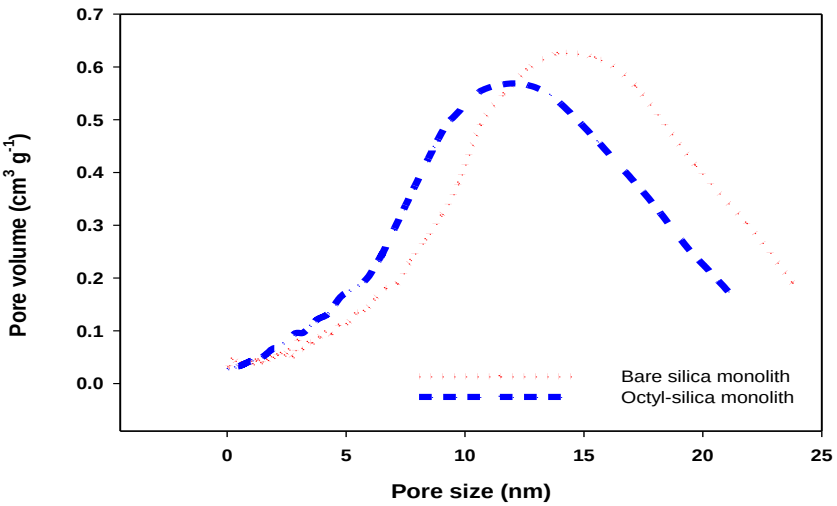

Fig. 4. Pore size distribution profile of the silica-based monolith before and after modification with octyl groups using the BJH method.

Extraction of drugs

The fabricated octyl-hybrid silica monolith was utilised as a sorbent for the extraction of NSAIDs. In this study, KEP and IBP were selected as the test analytes to be used to check the performance of the fabricated monolith. After placing the monolithic column inside the plastic syringe, the column was activated

using 200 µL of methanol solution and then equilibrated with 200 µL of 0.02 M phosphate buffer solution (pH 7). After applying the sample solution (500 µL), the monolithic column was washed and the elution with the target drugs was collected and injected into an HPLC-UV instrument. The enrichment factors of the preconcentrated drugs were calculated by comparing the peak area obtained by the preconcentrated drugs using the sorbent with the peak area of the direct HPLC analysis. As can be seen in Table 3, the enrichment factors of KEP and IBP were 23.54 and 22.72, respectively. Moreover, it was found that the extraction recoveries of the drugs were more that 95% for both NSAIDs.

Table 3. Measurements of the enrichment factor and extraction efficiency

Analyte	Enrichment factor (EF)	The extraction recovery (R) %
KEP	21.54	96.88
IBP	22.72	97.34

The calibration curves were constructed by plotting the peak areas of the drugs versus the drugs' concentrations, in order to evaluate the linearity of the method, and the linear dynamic range was found to be 40-800 µg mL^{-1} for KEP and IBP. As can be seen in Table 4, good linearities of the preconcentrated KEP and IBP using the octyl-hybrid silica monolith were obtained based on the linear coefficient (R^2) values being greater than 0.9974, thus showing a high degree of correlation between the concentration and peak area.

Table 4. The concentration range and regression data for KEP and IBP in an aqueous sample

Analyte	Concentration range (µg mL^{-1})	Regression line		
		Slope	Intercept	R^2 value
KEP	40-800	673.6	- 14665.2	0.9978
IBP	40-800	414.1	7745.5	0.9974

The reproducibility of the performance of the fabricated monoliths was evaluated by intra- and inter-column precision, and the intra- and inter-column standard deviations (RSDs) were determined. The results obtained from this investigation showed that the fabricated monoliths made to preconcentrate the test NSAIDs drugs (KEP and IBP) was reproducible, since a good run-to-run reproducibility (n=3) was achieved, with RSD values in the range between 3.0 and 5.9% for KEP and 4.8 and 5.6% for IBP, while the inter-column precision (n=3) varied from 4.9 to 6.8% for KEP and between 6.3 and 7.6% for IBP.

Table 5. Column precisions at three different concentrations for the extraction of NSAIDs

Analyte	Intra-column precision (RSD%, n=3)			Inter-column precision (RSD%, n=3)		
	Low 40 µg mL^{-1}	Medium 400 µg mL^{-1}	High 800 µg mL^{-1}	Low 40 µg mL^{-1}	Medium 400 µg mL^{-1}	High 800 µg mL^{-1}
KEP	3.0	4.6	5.9	4.9	5.1	6.8
IBP	4.8	3.4	5.6	6.7	6.3	7.6

CONCLUSION

In this study, a silica-based monolith was fabricated and modified with octyl (C_8) groups. This fabricated monolith was evaluated as an extraction medium for the extraction of NSAIDs, namely KEP and IBP. The fabricated materials were studied using different analytical techniques. Further study indicated the good fabrication reproducibility and extraction stability of the monolithic material. Work is currently in progress to extract NSAIDs from different media.

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