Review article

Optimising factors affecting solid phase extraction performances of molecular imprinted polymer as recent sample preparation technique

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ABSTRACT

Molecular imprinted solid-phase extraction is the technique that uses molecular imprinted polymer as the sorbent in solid phase extraction. Molecular imprinted solid-phase extraction is effective and efficient for the extraction process and cleaning as compared with solid phase extraction (SPE) without molecular imprinted polymer. The complexity of variables in molecular imprinted solid-phase extraction arise as problems in the analysis, therefore it is necessary to optimize the extraction conditions of molecular imprinted solid-phase extraction. To achieve the sorption equilibrium and achieve the shortest time, certain parameters such as contact time, ion strength of sample, pH of sample, amount of sorbent, sample flow rate, addition of salt and buffer solution, washing solvent, elution solvent, and loading solvent need to be optimized. The selection of suitable properties and quantities of each factor greatly affect the formation of appropriate interactions between the sorbent and analytes. Percentage recovery is also influenced by formation of the appropriate bonds, sample flow rates, extraction time, salt addition, and sorbent mass. Therefore, in the future, molecular imprinted solid-phase extraction optimization has to consider and adjust various factors reviewed in this paper to form appropriate interactions between the absorbent and target molecules which have an impact on the optimal results.

1. Introduction

Solid phase extraction has been extensively developed as a routine technique in sample preparation processes from liquid or solid matrices because this technique is relatively easy, provides great recovery, only requires a small amount of solvents, flexible, and can be automated [1, 2]. To improve the extraction efficiency and selectivity of solid phase extraction, molecular imprinted polymers are used in combination with solid phase extraction, namely molecularl imprinted solid phase extraction [2, 3, 4]. Molecularl imprinted polymers are man-made polymers characteristically prepared by the conformation of a complex composed of a template, monomers, and a cross-linker that formed in the three dimensional polymer network. This polymer has a selectivity and affinity towards the target molecule because the binding sites are complementary with the template in both size, shape, and in the position of the functional groups [5, 6, 7, 8, 9, 10, 11, 12] Molecularly imprinted polymers are also stable and relatively cheap, so this method have been harnessed for developing selective sample pre-treatment methods [11, 13]. Because of

that, molecularly imprinted solid phase extraction (MISPE) enables pre-concentration of the analytes and allows removal of the disruptive compounds from the sample matrix [14].

Molecularly imprinted solid phase extraction optimization is a difficult task due to the high number of variables that exist, added to the circumstances that they are mutually dependent [15]. To obtain extracts that are free from matrix interference, available recognition elements must be improved to fulfill the requirements in the given application for general use of the molecularly imprinted solid phase extraction (MISPE) [15]. In addition, the conditioning step, loading step, washing step, and the elution step parameters possess a strong influence on the whole performance of molecular imprinted solid phase extraction (MISPE), regarding loading capacity, selectivity, and also affinity. Therefore, the appropriate preferences, both qualitatively and quantitatively, will guarantee that polymers with the desired characteristic have been produced [16]. Hence, optimization of the Molecular Imprinted Solid Phase Extraction method has to be based on the characteristics of molecular imprinted polymers, the

interaction among molecular imprinted polymers and analytes, and the appropriate solvents used in the extraction process [17]. The more selective the step of solid phase extraction process, the more sensitivity will be acquired, so it is very important to develop and optimize solid phase extraction (SPE) procedures [15].

To increase the effectiveness of the analyte extraction process in the sample, the extraction conditions, such as the loading, washing, and the elution of the solvents must be carefully optimized. The optimization process begins by packing molecularly imprinted polymers (MIP) particles into an empty solid phase extraction (SPE) cartridge, with frits placed at the top and bottom, which is used as the molecular imprinted solid-phase extraction (MISPE) column. Before use, the column is consecutively washed by the selected washing solvent until no more compound is detected, and then conditioned with the loading solvent. A standard solution of the optimal solvent is loaded into the column and passes through the molecular imprinted solid-phase extraction (MISPE) column at a certain flow rate. The column is then flushed with the washing solvent to remove any non-specifically bound molecules whilst retaining those binding specifically. Then, the analyte that remains in the column is eluted using an elution solvent. Several types of washing solvents and elution solvents were studied to find solvents with the maximum selectivity. All loading, washing and eluting fractions were collected, and directly analysed using high performance liquid chromatography (HPLC) [18].

Presently, there are no publications which discuss the related factors that must be considered in the optimization of extraction conditions of molecular imprinted solid-phase extraction (MISPE). Therefore, this paper will discuss these factors in order to produce a molecular imprinted solid-phase extraction (MISPE) method that meets the requirements for the sample preparation.

2. Molecular imprinted solid-phase extraction (MISPE) component

The molecular imprinted solid-phase extraction (MISPE) cartridge consists of frit, molecular imprinted polymer (MIP), and frit which is the packing procedure of molecular imprinted solid-phase extraction (MISPE) Cartridge. Figure 1 depicted the packing procedure of molecular imprinted polymer (MIP), conditioning of the molecular imprinted solid-phase extraction (MISPE) cartridge, sample loading, sample washing and sample elution [17] (see Figure 2).

3. Molecular imprinted solid-phase extraction (MISPE) modes

Molecular imprinted solid-phase extraction (MISPE) consists of several modes. The basic modes are the offline mode and the online mode [19, 20, 21, 22]. Generally, the offline mode is used in molecular imprinted solid-phase extraction (MISPE). The process includes conditioning of the molecular imprinted solid-phase extraction (MISPE) cartridge, loading of sample, washing of any interferences, and elution of the analyte. The eluate will be analysed in analytical instrument such as tandem mass spectrometry (MS/MS), liquid chromatography/mass spectrometry (LC/MS), high performance liquid chromatography (HPLC) and etc. The online mode presents an automatic process of loading of sample, washing of interference, elution of analyte, and the separation and detection of the analyte. In online mode, there are some loop of port injection valve to facilitate the separation process of analyte. The most crucial factors in the development of molecular imprinted solid-phase extraction (MISPE) protocol are the choice of loading of sample, washing solvent, and eluting solvent [21]. In offline and online modes, the parameters such as contact time [23], ion strength of sample [24], pH of sample [25], amount of sorbent [15], sample flow rate [24], addition of salt and buffer solution [26], washing solvent [2, 24], elution solvent [27], and loading solvent [28] need to be optimized. The parameters that must be optimized in both modes are the same, because in both modes consists of four stages (conditioning, loading, washing, eluting). But in online mode it can be used for untreated samples because there are some loop of port injection valve to facilitate the separation process of analyte.

3.1. Offline modes

Recently, the offline mode of molecular imprinted solid-phase extraction (MISPE) has been extensively used.

Off-line molecular imprinted solid-phase extraction (MISPE) protocols have no differences from other solid phase extraction (SPE) procedures. The operational process includes pre-conditioning, loading of the sample, washing of interferences and elution of the sample [29].

In a typical procedure, 15–500 mg of MIPs is packed into cartridges [30, 31, 32, 33, 34]. First, the cartridge is conditioned by a conditioning solvent. This aims to maximise the interactions between molecular imprinted polymer (MIP) and the analyte's target in the sample. The loading solvent is selected depending on the kind of monomer and porogen interaction during polymerisation. A solvent with low polarity is chosen for loading organic samples to protect the binding sites. After that, the next step is the sample washing. The aim of this step is to
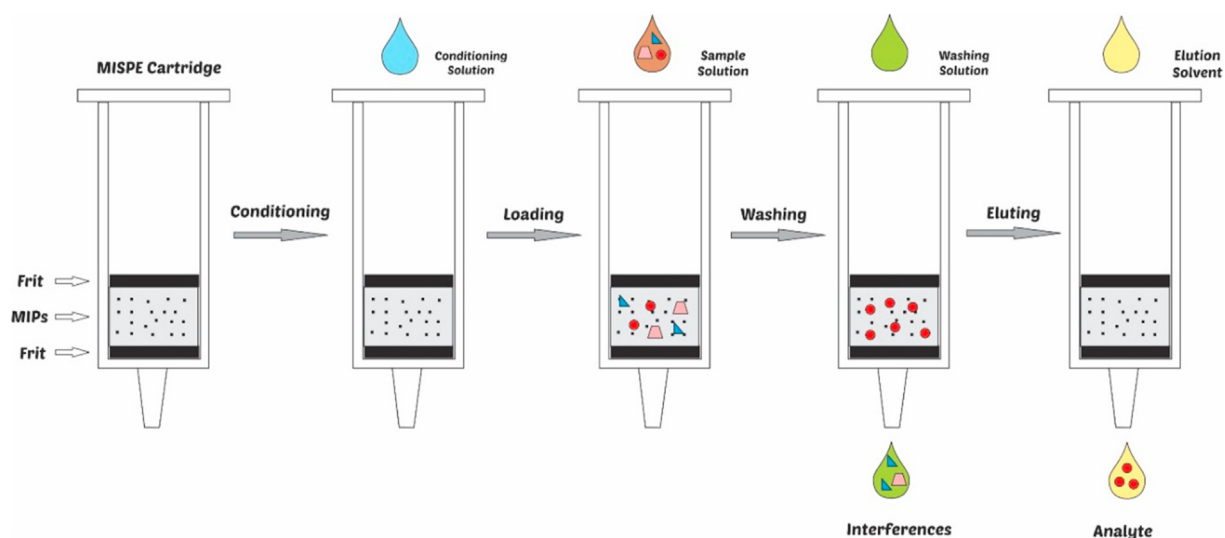

Figure 1. Molecular imprinted solid phase extraction (MISPE) procedure.
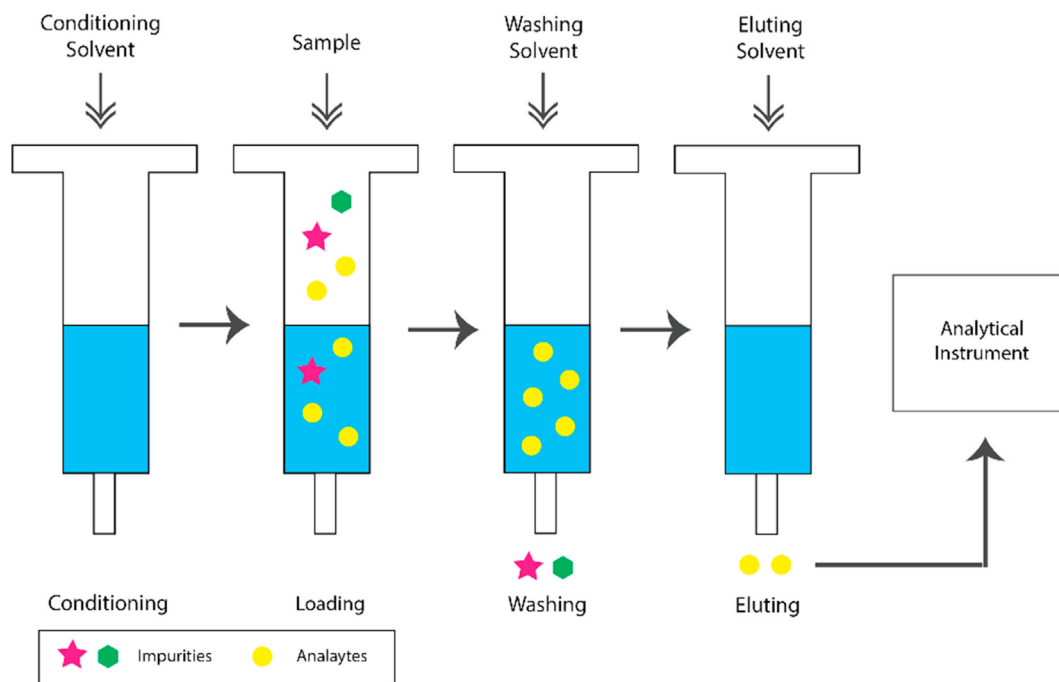
Figure 2. Steps in offline modes.

optimize the interaction between the molecular imprinted polymer (MIP) as sorbent and the analyte specifically, and also to synchronously elute the impurities. Usually in this step, an organic solvent with low polarity is chosen. Then, the final step in molecular imprinted solid-phase extraction (MISPE) is sample elution. To get high enrichment factors and good recovery, small amounts of solvent are needed. Usually, the polar solvents are used with small amount alkali or acid additives. After the elution process the eluate is dried and the residues are dissolved in the correct solvent. The analytes are analysed by analytical instrument such as MS/MS, LC/MS, high performance liquid chromatography (HPLC) and

etc. This mode is less efficient regarding time, at longer times the probability of error is increased [19].

An example of a compound analysed in an offline mode is atrazine. Atrazine is a herbicide that is widely used to kill weeds. Atrazine is also a selective herbicide that acts to inhibit photosynthesis in vulnerable plants. First, the molecular imprinted polymers were used to extract atrazine from extracts of beef liver. Then, chloroform was extracted from a tissue sample and loaded into the cartridge. The selective retention of Atrazine and interferences's elution were attained with chloroform as the washing solvent and with acetonitrile (10% v/v) as the elution solvent
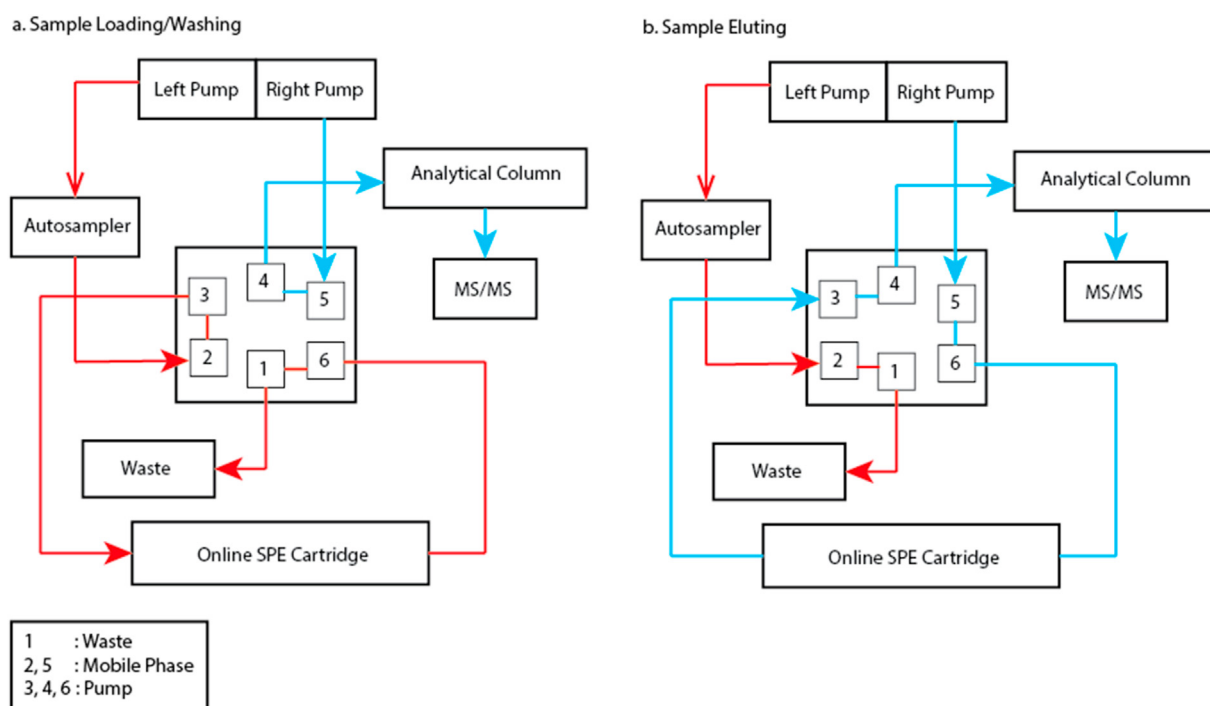

Figure 3. Steps in online mode.

[35]. Subsequently, the molecular imprinted polymers were used to extract simazine from the sample (aqueous solution). The sample loaded into the cartridge and was attended by passing an air, it's intended to dry the column. Accordingly, the selectivity of the simazine' retention and interferences' elution were achieved using the washing solvent (dichloromethane). Finally, the simazine was eluted by methanol. In an aqueous environment, hydrophobic interaction and ion exchange interaction as nonspecific binding play a role on the simazine's retention. Whereas, if simazine in an organic solvent (e.g dichloromethane), the electrostatic interactions and hydrogen bonding play a role in simazine's recognition. Consequently, the switch to dichloromethane becomes a prominent step for extraction based on the affinity of the target compound.

3.2. Online modes

In contrast to the offline mode, the online mode provides automatic sample loading, washing of interference, analyte elution, separation, and detection by the analytical system [29] as can be seen in Figure 3. In a typical procedure, a small pre-column packed with molecular imprinted polymers is placed and entered to the loop of a six-port injection valve. The column is loaded with the sample and the interferences are washed, the analytes are eluted by the eluting solvent, and separated in the analytical column to be analysed by the detector [19].

The left pump carries out the autosampler process, and the sample passes through the online cartridge and becomes waste. The right pump inflates the mobile phase into the analytical column and is analysed by the instrument. At the eluting step (Figure 3b), the left pump also works in conjunction with the right pump. However, the difference with the loading and washing step is that the sample from the left pump does not go through the online cartridge whereas the mobile phase of the right pump goes through an online cartridge.

In the loading step (Figure 3a) the left pump carries the mobile phase and the autosampler carries the sample, mobile phase and sample to the loop of port injection valve number 2 and 3, then enters the online solid phase extraction (SPE) cartridge (the analyte trapped in the online SPE cartridge), and the solvent enter the loop of port injection valve number 1, then stream diverted to waste. In the washing step (Figure 3a), the left pump carries the washing solvent to port numbers 2 and 3, then enters the online SPE cartridge, washing the sample in the online solid phase extraction (SPE) cartridge. The interferences stream is diverted to waste and the analyte is trapped in the online cartridge. The right pump (Figure 3a) illustrates the process that will occur in the eluting step. The right pump carries the eluting solvent through ports 5 and 4 and then through the analytical column to elute the analyte which will be analysed by tandem mass spectrometry (MS/MS).

In the eluting step (Figure 3b), the right pump carries the eluting solvent. The eluting solvent passes through port 5 to port 6 and enter the online solid phase extraction (SPE) cartridge to carry the analytes in online cartridge to ports 3 and 4, and then the analytes enter the analytical column and will be analysed by tandem mass spectrometry (MS/MS). Whereas the left pump (Figure 3b) illustrates the process that occurs earlier in the loading step where the analyte is trapped in the online solid phase extraction (SPE) cartridge and the stream is diverted to waste.

The examples of analytes studied using the online mode of solid phase extraction (SPE) include Sudan dyes [36], Para Red [37], riboflavin [38], fluoroquinolone [39], tetracycline [40], residues of triazine [41] and oestrogens [42] in food (chili sauce, egg, tomato sauce, and milk) and in the environmental samples (soil and water).

The Advantages and Disadvantages of Offline and Online Modes of Molecular Imprinted Solid Phase Extraction can be seen at Table 1 (see Table 2).

Table 1. Advantages and disadvantages of offline and online modes.

Mode of MISPE	Advantage	Disadvantage
Offline Mode	Overall operation has a lot of choices of solvents and additives [19, 20].	The disadvantages of offline mode is contamination of analytes and potential loss (It caused by the sample handling requirements include isolation, preconcentration and injection into instrument) [19, 20].
	The operation quite simple and easy. Hence, enrichment rate and selectivity in this mode are higher [19, 20]	This mode takes a long time for operation, so the error will be increased and use several organic solvents in washing [19, 20].
Online Mode	Directly connected with the chromatographic system [19, 43].	The disadvantages of this technique are the high pressure of the online system when the column is filled up with nano-sized materials and the addition of an SPE column that is easily damaged. A strategy has been proposed to control the drawbacks of column-based SPE by performing bead injection [19, 43].
	Analysis time and analyte loss will be reduced by using online mode as well as sensitivity, accuracy, and precision will be increased by eliminating personal errors [19, 43].	
	The required amount of solvent is also lower and online mode allows partial or total automation of analytical steps [19, 43].	
	In this mode, the enrichment steps and sample cleaning are automated cause it can allow the direct injection of untreated samples. So the online mode has better limits of detection and reproducibility as compared to the offline mode [19, 43].	

Table 2. Application of molecular imprinted solid phase extraction.

Template	Sample	Target Analyte	Mode	Reference
4,4′Methylenebisphenol	River organic matter	Bisphenol A	Off-line	[55]
β-Agonists	Calf urine	β-Agonists	Off-line	[56, 57]
Bisphenol A	Spiked tap water and lake water	Bisphenol A	On-line	[58, 59]
Brombuterol	Human and calf urine	Clenbuterol	Off-line	[60]
Bromoclenbuterol	Liver samples	Clenbuterol	Off-line	[61]
Caffeine	Aqueous test samples, natural water, and human urine	Methylxanthines	Off-line	[62]
Catechol	Effluent river water	Catechol	Off-line	[63]
Cephalexin	Human serum	Cephalexin	On-line	[64]
Cyanide	Waste water	Cyanide	Off-line	[65]
Cotinine	Human urine	Cotinine	Off-line	[66]
Dopamine hydrochloride	Urine	Adrenergic drugs	Off-line	[66]
Ibuprofen	River water	Anti-inflammatory drugs	Off-line	[52]
Monosulfuron	Soil samples	Monosulfuron	Off-line	[67]
Monocrotophos	Water and soil	Organophophorus	Off-line	[68]
Naproxen	Urine samples	Naproxen	Off-line	[50]
Organotin	Environmental samples	Organotin	Off-line	[69]
p-tert-butyl-phenol	Environmental water, purified water	Bisphenol A	On-line	[70]
Pentachloro-phenol	Lake water, river water, and waste water	Pentachlorophenol	On-line	[71]
Phenytoin	Plasma	Phenytoin	Off-line	[72]
Pirimicarb	Tap water, spring water, river water, and sea water	Pirimicarb	On-line	[73]
Propazine	River water	Triazines and their metabolites	Off-line	[74]
Quercetin	Plasma	Quercetin	Off-line	[51]
Terbuthylazine	River water	Triazines	On-line	[75]
Verapamil	Urine and plasma and cell culture	Verapamil and gallopamil	On-line	[76]

4. Selectivity study of Molecular Imprinted Solid Phase Extraction

Molecular imprinted polymers are widely used for selective extraction process in complex matrix because of their molecular recognition ability and receptor-like properties, beside of that, this technique relatively simple, fast, and cost effective [44, 45, 46]. Specific binding sites on the polymer surface provide more accessible binding sites which have high specificity and selectivity for target molecules [47].

Zhu et al. studied the molecular imprinted polymers solid-phase extraction method for selective extraction and enrichment process of double substituted sulfonylurea herbicides. Molecular imprinted polymera have been made using metsulfuronmethyl as the template molecule, divinylbenzene as cross-linker and 2-(trifluoromethyl)acrylic acid as the functional monomer. In the study, the molecular imprinted polymers selectivity was compared with non-imprinted polymers, and can be seen that the adsorption of metsulfuronmethyl on the non-imprinted polymers was considerably lower when compared to imprinted polymers under the same experimental conditions, which indicates that the imprinted polymer cam binds the template effectively with very small non-specific adsorption. When the experiments was carried out to confirm the selectivity of the molecular imprinted polymera, can be seen that the molecular imprinted polymer have low nonspecific binding of dissimilar sulfonylurea herbicides on the polymer. It means that the imprinted polymers are a good tool for binding assays, affinity extraction, and affinity separation.

Dong et al. synthesizing and applying monosulfuron-imprinted polymer to solid-phase extraction which used to determine monosulfuron residues in soil. Monosulfuron, methacrylic acid as the functional monomer, ethylene dimethacrylate as the cross-linker and 2,2′-azobis(2-methylpropionitrile) as the initiating agent were dissolved in dimethylformamide as the porogen. The binding affinity of the imprinted polymer was evaluated through equilibrium adsorption experiment and the results showed that the monosulfuron imprinted polymers have higher affinity than non-imprinted polymer. The scatchard analysis also showed that monosulfuron imprinted polymers have higher binding

association constants and have a clearer binding sites than the non-imprinted polymer. The selectivity of the monosulfuron imprinted polymers ware also evaluated by measuring its capability to resolve structural analogs using the High Performance Liquid Chromatography process and the result showed that the imprinted polymer has selectivity for the monosulfuron and has potention as a separation material in solid phase extraction.

5. Application of Molecular Imprinted Solid Phase Extraction

In the last few years, one of the most promising molecular imprinted polymers applications is molecular imprinted solid-phase extraction (MISPE). Most of the research conducted focuses on the extraction of compounds from biological samples, mainly biofluids [48], however there is also some papers reporting about extraction of compounds from tissue samples [35]. Several analytes have been isolated from urine as a sample, some of them are diphenyl phosphate [49], and naproxen [50]. Quercetin [51]have also been isolated from plasma sample. Other drugs, like propranolol [4] and enrofloxacine [52] have also been extracted from several matrices, like urine, bile, plasma, and also from animal tissue. Molecular imprinted solid-phase extraction (MISPE) has also been applied in extraction of compounds from another matrices, such as environmental samples [53], food and plants [54].

6. Factors for optimization of extraction conditions of Molecular Imprinted Solid Phase Extraction

6.1. Effect of pH

In the molecular imprinted solid-phase extraction (MISPE), the optimization process of pH value has a particularly important influence to enable satisfactory results to be gained from the extraction process. The occurrence of appropriate interactions among the absorbent in the column and targeted molecules in the liquid medium, and the retention in the solid phase extraction (SPE) cartridges depends on the pH of the medium [25].

The pH of the sample to be extracted plays a very necessary role in the Solid Phase Extraction procedure since it will influence the specific intermolecular interactions that occur, including ionic interactions, hydrogen bonding, and hydrophobic interactions which occur amongst the analytes in the sample and molecular imprinted polymer [77]. The bond that occurs will determine the effective absorption of an analyte onto the sorbent [32] and thus, the efficiency of the extraction process can be influenced by pH. As in the study by Djozan, et al. [78] about the optimum conditions for the pre-concentration and extraction process of methamphetamine and ecstasy by molecular imprinted solid-phase extraction (MISPE), different pH values have an impact on the bonds formed. In this study, when the pH value was lower than 7, methamphetamine, ecstasy, and methacrylic acid are in their protonated forms [79]. Hence, it is likely that MAA's carboxylic groups are only able to interact with the hydronium ions rather than interact with the amino groups' hydrogen atoms of methamphetamine and ecstasy, which renders a low efficiency to the extraction process. At pH values higher than 9, methamphetamine and ecstasy are in their molecular forms, but methacrylic acid is in anionic form. Because of that, only hydrogen bonding can happen among the analytes and methacrylic acid. Therefore, the optimal conditions in which comparatively robust ionic interactions can occur among the protonated analytes and the molecular imprinted polymer (MIP)'s anionic carboxylate groups are at pH 8 [78]. In another study, Tabandeh et al. [25] explained that the binding character of allopurinol was not supremely affected at pH higher than 7. However, at more acidic pH values, the recovery of allopurinol decreases significantly due to the protonation process of this molecule and the subsequent breakdown of the hydrogen bonds. The charged molecules cannot place themselves at the polymer binding sites, therefore their recovery will be reduced.

Recovery of analytes also varies with the different pH values of the sample, which occur due to changes in the strength of the specific intermolecular interactions, mainly ionic interactions among the prepared molecular imprinted polymers and analytes, as was reported in the study conducted by Du et al. [77] As in the study by Du et al [77] the recovery of cytokine is very dependent on the pH value of the sample. At pH around 6.0 and 8.0, the neutral form of cytokine dominates, but the molecules will be protonated due to a decrease in pH value. In addition, the carboxyl group of poly (MAA-co-EGDMA) monolith with a pKa value of 5 will be partially deprotonated at pH higher than 6.0 resulting in a decrease of the extraction efficiency due to lower absorption capability of carboxyl groups at the imprinted sites. A decrease in terms of extraction efficiency is also caused by the deprotonation of imprinted sites together with the increase of the pH [80]. When the value of pH is lower than 5, the protonation process of the amine group of K was obtrusive, whilst the protonated charged molecules could not "match" the binding sites, including hydrogen bonding interactions and electrostatic interactions in imprinted cavities. Hence, the K molecules were not retained effectively by the monolith. Therefore, 5 was selected as the optimum pH value because the interaction between the analytes and molecular imprinted polymer, especially the electrostatic interaction, may be reach the strongest. Besides that, the available cavities and specific binding sites in the molecular imprinted polymer are optimal, which results in a higher recovery [77].

In addition, the pH value of the sample solution directly affects the stability and turn-out of several compounds in divergent matrices. Chen et al. explained that catechins have a higher stability in solutions with pH smaller than 4. Martins et al. [23], also showed that the stability of catechins decreases progressively in an alkaline solution (pH > 7). Thus, the optimized pH that was used in the extraction process of molecular imprinted solid-phase extraction (MISPE) was 4, because a higher efficiency of the extraction process was achieved. In studies by Koohpaei, et al. and Sorouraddin et al. about optimization of the extraction conditions of molecular imprinted solid-phase extraction (MISPE) for the herbicide triazine with MAA as monomers, it can be seen that atrazine is comparatively stable in neutral media, weakly acidic media, and also

weakly alkaline media, but will quickly hydrolyse into derivatives of hydroxyl in strong alkalis and acids [81]. Therefore in this study, a pH of around 7.0 was chosen [16].

Based on the above results, it can be concluded that the sample's pH must be adjusted with the properties of the analyte and sorbent, such as pKa value. In addition, in the molecular form of the analyte and sorbent, the occurrence of ionisation, and the stability and presence of several compounds at a certain pH, must be considered to be able to form appropriate interactions among the targeted molecules and the absorbent. The proper interaction among the targeted molecule and the absorbent molecules in the water media and also the retention of the analytes in the solid phase extraction (SPE) cartridge will determine the effectiveness of adsorption of the analyte to the sorbent, and thus, the extraction efficiency.

6.2. Effect of sorbent mass

To see the influence of the sorbent mass against the % recovery, the molecular imprinted polymer (different amounts) will be packed into the solid phase extraction (SPE) cartridge. Based on research by Sadeghi and Jahani [34], the increase of the weight of polymer caused by adsorption (florfenicol) increased up to 120 mg and became constant. This condition is related to the active sites of the sorbent's saturation. Different ranges of sorbent mass (50–250 mg) were chosen. Based on the results, the optimal extraction conditions did not increase significantly when the sorbent mass used was above 150 mg. The results showed that the optimal conditions for the amount of sorbent mass was 125 mg [16]. The correlation of sorbent mass with the efficiency of (molecular imprinted solid-phase extraction (MISPE) was examined at different mass ranges of sorbent from 100 to 500mg for sotalol. Sotalol is an ethanolamine derivative with antiarrhythmic and antihypertensive properties. To see the impact of the sorbent mass on % recovery, the cartridge was filled with different quantities of the sorbent. The ER (Extraction Recovery) % of sotalol is dependent on the sorbent mass. So, the effect of the sorbent mass can increase the extraction recovery %. The highest extraction recovery % of molecular imprinted polymer (97%) was obtained at 300 mg (mid amount of sorbent), this condition depends on the ratio of sotalol on the vacant sites in molecular imprinted polymer. The extraction recovery % did not increase significantly when the sorbent was in excessive amounts, cause a certain amount of analtye have interacted with a certain amount of sorbent too. So, the results suggest that the optimum sorbent mass was 300mg (mid amount) [82].

Based on research by Koohpaei et al. [15] about the optimization of solid phase extraction (SPE) using developed modern sorbent for trace determination of ametryn in environmental matrices, the optimization of ametryn as a sorbent mass was carried out. Ametryn was chosen with the mass range 50–250 mg to examine the impact of sorbent mass on % recovery and the cartridges of solid phase extraction (SPE) were packed with polymer (different amounts). Based on the results, the extraction recoveries did not increase significantly when the amount of sorbent was >200 mg. In this study, the optimal extraction recovery % result was with the mid amount of sorbent mass. This happened because analytes with a certain amount will bind with molecular imprinted polymer (sorbent mass) with a certain amount as well, and will produce maximum results if the analyte has been completely bound to the sorbent mass in a certain amount. If there is too much sorbent mass, then no analytes interact with the sorbent mass, so the further addition of sorbent mass is useless. An increased of sorbent mass can cause difficulties for the sample to pass through the system. The problems between polymer and non-specific adsorption can be reduced by the use of small amounts of molecular imprinted polymer [83]. So, the surface area of the polymer for non-specific adsorption can be reduced. In order to determine the correct sorbent mass to be filled in the solid phase extraction (SPE) cartridge, a series of different sorbent mass conditions should be used, and the recovery percentage from each sorbent must be recorded. From studies already carried out, the mass of the sorbent must not be too much

because the analyte will have difficulty passing through the system. The amount of sorbent mass must be optimized in advance to match amount of analytes. When the analyte interacts entirely with the sorbent, no cavity is formed so the bond becomes specific. If there is too much sorbent mass, there are concerns that other substances will interact with the molecular imprinted polymer.

6.3. Effect of loading solvent and volume

Sample volume is one of the primary factors to be evaluated for the extraction capability of sorbents for analytes at low concentrations [28]. Low loading volumes of samples are actually beneficial regarding potential matrix effects and extraction times [84], but extraction efficiency and pre-concentration factors usually increase when the sample volume is increased [78]. This happens because an increase in the sample volume can improve the amount of the target compound that is adsorbed into the molecular imprinted solid-phase extraction (MISPE) sorbent and also increases the sensitivity of the method [24]. Even so, it should be noted that occasionally too much volume can reduce the recovery, as in a study conducted by Sanagi, et al. [27]. In this study it was found that the recovery of analytes increased from volumes of 5 mL up to 10 mL, beyond which the value of recovery decreased drastically. The analyte's recovery with a loading volume of 5 mL was smaller due to lack of interaction among the analytes and the extracting material's binding sites. Best recoveries for Solid Phase Extraction sorbents were determined at a loading volume of 10 mL, denoting that the analyte was fully bound towards the active sites. Upon loading a volume greater than 10 mL, the recovery of analyte declined, perhaps since the sorbent's active sites were over-saturated, and thus excessive analyte could not be bound towards the active sites. . Even in a study by Koohpaei, et al. [16], a significant reduction regarding recovery was discovered for volumes of sample from 5 up to 15 mL per minute. This phenomenon can be described by the polymer's heterogeneous surface that entangles the existence of cavities with different levels of energy. Use of a small amount of sample enables the interaction between the analytes and a larger amount of binding sites than when greater volumes of sample are applied. Seemingly, in the matter of application of a higher sample volume, a partial breakthrough volume for several binding sites has been achieved. In addition, this shows that the volume of eluent influenced the binding capacity of the molecular imprinted polymer monolith, and the analytes that attached to the molecular imprinted polymer were partially eluted at a larger volume elution [77].

Besides the amount of the solvent, the concentration of the loading solvent is also a matter that must be considered. Ideally, recovery of extraction should not depend on the concentration of the sample. In other words, there ought to be no prominent difference in recovery at all ranges of concentrations that are analysed. However, research by Koohpaei, et al. [16] showed that selectivity and affinity of the template were preferable at greater concentrations. At greater concentrations, the capability of atrazine to produce atrazine-atrazine complexes, both on the surface of the polymer and in the solution increased and brought an increased selectivity of atrazine.

Besides the concentration and volume of the loading solvent, the properties of the solvent used is also a matter that must be considered. In research conducted by Bakas et al. [85] about the selective extraction of dimethoate using molecular imprinted polymers, it can be seen that the bonding of dimethoate using methanol and acetonitrile, which are polar solvents, was low (less than 90%). The best result was reached when small volumes of dichloromethane and hexane were used as loading solvents. In other studies, conducted by Jiang, et al. about [45] selective determination of 17β-estradiol (E2) use molecular imprinted solid-phase extraction (MISPE) with high performance liquid chromatography, different loading solvents were explored. The best result was obtained when acetonitrile was employed as a loading solvent because all of the E2 that was loaded was restrained by the cartridges. This is thought to occur because acetonitrile is a porogen solvent which, when used in

polymerisation, can sway the polymer chain solvation level and also adjust the microenvironment solvation of the binding sites alike, within the developing polymer [86]. Besides acetonitrile, methylene chloride could fully load E2 onto molecular imprinted polymer cartridges, but the specific interaction which occurs among the molecules of the template and the molecular imprinted polymers was disrupted. While, the use of polar media allowed a lineal disruption towards the recognition ability of the MIPs, which carries a significant loss in the loading process for molecular imprinted polymer cartridges, thus, acetonitrile was selected. In other studies conducted by Dong, et al. [87], MeCN which is a porogen in the synthesis of molecular imprinted polymer, and chloroform, which is a solvent for herbal extraction, were considered as solvents for solid phase extraction (SPE) samples. Both of these solvents have also been used as the porogen in the synthesis of ephedrine imprinted polymers [15] and can stabilise the interactions among the molecular imprinted polymer and the template. The use of $CHCl_3$ as an solid phase extraction (SPE) sample solvent made it possible to directly load Chinese Ephedra extract in the solid phase extraction (SPE) column, but it was found that it would result in a reduced loading capacity of the column after a few experiments. However, the structure of the molecular imprinted polymer can experience changes [87]. Therefore, MeCN was chosen since a stable column capacity was achieved. It can be seen that the choice of loading solvent has a significant effect on the results, therefore the loading solvent has to be selected based on the type of interaction that happens among the porogen and the monomer throughout polymerisation [88] and adjusted with the properties of the analyte in the sample. Based on the explanation above the type of solvent used is able to influence the interactions that occur, the properties of the bonds formed, the strength of the bonds formed, and thus, affecting the obtained recovery.

Furthermore, the higher the loading volume, the higher the recovery, but in excess conditions, in other words when the sorbent is over saturated, a high volume will be useless because a number of the analytes will be wasted so the recovery value decreases. In addition, the properties of the loading solvent, such as polarity, must be adjusted. Therefore, determination of the exact volume of loading the solvent must be done with caution because it is a crucial factor affecting the obtained recovery.

6.4. Effect of washing solvent and volume

The washing process is an important step in molecular imprinted solid-phase extraction (MISPE) which is critical for MIP-SPE clean up [89, 90] and to get the best molecular imprinted solid-phase extraction (MISPE) results [2, 24]. The aim of the washing process is to reduce the occurrence of specific interactions among the analytes and molecular imprinted polymer, and concurrently, elute the contaminants that may interfere the results obtained [85]. The washing step is expected to be able to reduce the nonspecific interaction at the binding sites or interfering adsorption [19, 27, 91], and is useful for selective extraction of target analytes [85]. Hence, the interaction between the analyte and binding site can be maximally maintained [27]. Therefore, to promoted a successful molecular imprinted solid-phase extraction (MISPE) procedure, optimizing the washing step is important to improve the extraction efficiency, improve the purification effect [92] and to obtain maximum recovery of the analytes [89]. There are several important parameters that need to be optimized, such as composition, ratio, and amount of the washing solvent [92]. Polarity, pH value and the ionic concentration of the washing solution are potential factors that can affect the recovery of molecular imprinted solid-phase extraction (MISPE) [2, 24].

There are a lot of washing solvents that can be used, either as a single substance or as mixtures with certain ratios, such as acetonitrile, methanol, acetone, tetrahydrofuran, dimethyl formamide (DMF), and dichloromethane (DCM) [89]. Generally, washing solvents that provide good recovery and high specific retention rates will be chosen [25]. The choice of washing solvents also considers the suitability with the properties of impurities in the sample, so the washing solvent is able to bind the impurity and take it out of the cartridge [93]. In research conducted

by Du et al. [77], washing step was an important process to increase the binding selectivity of cytokinin and to synchronously decrease non-specific interactions. It can be seen that when the amount of methanol was lower than 5%, recovery of cytokinin was barely different in the molecular imprinted polymer monolith. When the amount of methanol in the washing solution was higher than 10%, recovery of cytokinin decrease with the increase of methanol concentration. The results showed that if the cytokinin retention capability on the molecular imprinted polymer was higher, the specificity and hydrophobic interaction of molecular imprinted polymer monoliths would increase.

Significant losses of target analytes must be considered in the selection of washing solvents. Demeestere, et al. [94] explained that the washing process using acidified acetonitrile with up to 1% of acetic acid for the extraction of antidepressants with methacrylic acid as the monomers, led to significant losses of target analytes. This may be due to an increase in the capacity of hydrogen bonding of the washing solvent in the presence of acid, encouraging rivalry with the analytes that were selectively retained for hydrogen bonding at the sites of the imprinted polymer. In addition, non-selective electrostatically retained analytes are also supposed to be removed more efficiently from the cartridge in the presence of acetic acid which is due to the transformation of methacrylic acid and carboxylic acid groups into non-ionised forms [94]. There are also molecules that are able to eliminate all the non-specific bonds that occur to the polymer, but the analytes are also removed from the imprinted polymer as in research conducted by Bakas, et al. [85] In this research promising results were obtained by using dichloromethane as a washing solvent, but 65% of dimethoate was also removed. In research by Shi, et al. [2] about detection of 17β-estradiol (E2) trace using molecular imprinted solid-phase extraction (MISPE) combined with high performance liquid chromatography (HPLC), a diverse concentration of phosphate buffer was applied in the washing procedure. Greater binding selectivity was obtained with the higher concentration of the phosphate buffer [45]. When the amount of cations in the washing solvent increased, ion exchange among the functional groups of the polymer's proton and cations erased the hydrogen bond donor groups. Despite this, the groups were necessary for selective retention and also non-selective retention of molecular imprinted polymer [53]. This deletion effect was more meaningful towards non-selective retention than toward selective retention. This happens since the high selectivity of hydrogen bonding among the monomer and template was firmer than that of the nonselective hydrophobic interaction. Several binding sites were removed after analogues that absorbed non-selectively were washed, hence this enabled more 17β-estradiol to selectively bind into the exempt binding sites, which increased the selectivity of the washing process by decreasing the 17β-estradiol's washing recovery, however escalating other analogues's washing recoveries [2].

The form and properties recognition are ordinarily better when porogen is used as the solvent for the polymerisation process of the molecular imprinted polymer. For that reason, Sanagi, et al. [27] used acetonitrile in combination with water as a washing solvent. The result showed that with approximately 30% of acetonitrile as the component of the washing solvent, the quinalphos's recovery by the molecular imprinted polymer cartridges was unchanged at 92.3%. This indicates that there are specific interactions that occur on binding sites. Nevertheless, a greater percentage of acetonitrile in mixed solvents, which is more than 40%, causes a large reduction in quinalphos recovery in molecular imprinted polymer cartridges as a consequence of interference of specific interactions among the binding sites and analytes. Accordingly, an alloy of acetonitrile (30%) and water (70%) was selected [27]. The washing step also has a considerable influence on the efficiency of absorption. Sadegi and Jahani [32], optimized molecular imprinted polymer for the selective solid phase extraction (SPE) of florfenicol or FF which used 4-vinyl pyridine as a functional monomer and florfenicol as the template. In this study, the process of washing used a weak acid solvent which could interfere with the non-specific interactions which happen on the absorbents. The addition of approximately 1% of acetic

acid in the washing solution increased the absorption efficiency, but the concentration of acetic acid further reduces the absorption efficiency of florfenicol on the molecular imprinted polymer.

Based on the explanation above, it can be concluded that the volume, the concentration, and the type of washing solvent used must be adjusted to the molecular properties of the analyte and the impurity. The washing solvent must be able to reduce the occurrence of specific interactions among analytes and molecular imprinted polymer, elute the contaminants that may interfere, and reduce the non-specific interaction at binding sites, or interfering adsorption, in order to produce a molecular imprinted solid-phase extraction (MISPE) method that meets the requirements for the sample preparation.

6.5. Effect of elution solvent type and volume

The type of elution solvent and its volume affect the efficiency of extraction shown by the % recovery. The greater the % recovery, the more efficient the extraction process. In this study, 20% of methanol/acetic acid (v/v) presented the highest recovery and then the addition of 2 mL of 20% methanol/acetic acid (v/v) gave the highest efficiency of elution Methanol was chosen as an elution solvent because the hydrogen bond is strong and it has a high permeability (analytes), so can induce the efficient elution. The addition of acetic acid (1%–15%) into the mixture helped to surmount the strong interactions between molecular imprinted polymer and the analyte and to increase the enrichment factor. Methanol with acetic acid (0%) was tested to ensure that acetic acid was effective in the desorption of quinalphos. The results indicated the addition of acetic acid could increase the % recovery of the analyte. However, the solvents with acetic acid (10% and 15%) can decrease the recovery of the analyte. Therefore, methanol with acetic acid (5%) was selected as the best elution solvent. To optimize the volume of elution solvent, different volumes of elution solvent were selected. The volumes were 3 mL, 6 mL, 10 mL, and 15 mL. The results showed that the increase of the volume (solvent) from 3 mL - 6 mL increased the recovery of quinalphos from 82% - 98%. But, if the elution solvent volume was increased (10 mL–15 mL), the quinalphos' recovery decreased from 71% - 53% [27].

Quinalphos is acidic, so it requires the addition of acids where the concentration is not too high. The greater of the percentage of acetic acid in methanol that interacts with the analyte, causing a decrease of percent recovery because the addition of too much acid can interfere with its interaction with protonation. Protonation is the addition of protons (hydrogen ions) to atoms, molecules or ions producing conjugate acids. Protonation can cause the chemical species charge to change. A study was carried out that presented the influence of the composition of the elution solvent on the analyte's recovery. This study used 9 solvents with different contents of acetic acid and methanol. Acetic acid and methanol were eluted to see the capability to elute atrazine optimally from the molecular imprinted polymer column. Those solvent were 2 mL methanol with 1, 2, 3, 4 and 5% of acetic acid and 3 mL methanol with 0, 1, 2 and 3% of acetic acid. The volume of elution solvent (3 × 1 mL methanol +1% acetic acid) gave the highest % recovery compared to the others [16].

Atrazine has pKa 1.6 (strong acid) and when added to a high concentration of acid it produces a non-optimal result, so it is only added to 1% acid (the lowest concentration). If the acid is added with a concentration that is too high, it will cause protonation and a steric effect so that the interaction of the elution solvent and analytes will not be optimal.

To optimize the type of elution solvent, 1 mL (1 g) of enrofloxacin dissolved in 0.1M HEPES was filtered in the cartridges and was eluted by 1 mL methanol with trifluoro acetic acid (TFA) v/v (1%–10%). Each fraction of the enrofloxacin's concentration was measured by high performance liquid chromatography-fluoresence detector (HPLC–FLD). The addition of TFA interferes with the interactions between the template and polymer on the carboxylic acid group's protonation, with TFMAA and MAA as the functional monomers. An eluting solvent of 1 mL of methanol/trifluoro acetic acid (95:5) resulted in a 97 % recovery of

enrofloxacin with 4% of RSD. Hence, this mixture was chosen for development of the method [95]. Enrofloxacin is a weak acid, so the optimal results had the addition of acid with a mid-amount (5%). If the acid is added with the highest concentration, protonation will occur so that the interaction is less optimal because of the conjugate acid formation.

Hydrogen bonds have non-covalent interactions that responsible for maintaining the molecule's target on molecular imprinted polymer. Hydrogen bonds can be destroyed with high polar solvents. To find the right eluting solvent, different solvents was used. The chosen solvents were MeCN, methanol, acetic acid (10%) + methanol, acetic acid (6%) + methanol, and acetic acid (3%) + methanol. The highest % recoveries were shown by methanol + acetic acid (10%). Accordingly, 2×1 mL of (90:10 v/v) methanol and acetic acid was chosen [25].

Allopurinol as an analyte has pKa 9.31 (alkaline) so the optimal results are with the addition of acids with the highest concentration of 6%. Because of the high polarity of the solvent, there is a large electronegativity difference and the bond between solvent and analyte will be stronger than the hydrogen bond. Methanol is preferred as an elution solvent because it has aprotic properties. Apolar solvents (n-hexane, chloroform, and toluene) didn't impact the binding of molecular imprinted polymer and so could not supress any non-specific interactions between the blank polymer and the template [85]. So, the selection of the elution the solvent and its volume must be based on the electronegativity of the analyte. The elution solvent must have the same polarity as the analyte so that the analyte can be eluted properly. If the volume of elution is too much, excess solvent will don't have an effect because the analyte has eluted with a certain amount of solvent. The addition of acid to the mixture was applied to surmount strong interactions between the analyte and the molecular imprinted polymer and to increase the enrichment factor. The addition of acid depends on the properties of the analyte. If the analyte is acidic, only a small addition of acid is required, whereas if the analyte is alkaline, increasing the concentration of the acid addition will cause an increase in the analyte recovery [16, 85].

6.6. Optimization of sample flow rate

Flow rate of the solution sample can influence the % recoveries of the analytes and set the analysis's time. Flow rate of the sample illustrates how the optimal flow rate of a sample is needed to produce the highest % recovery. The aim is to optimize the time and achieve satisfactory results [24]. If the sample flow rate is high, it can be advantageous for high enrichment factors but the sorption kinetics can lessen the sorption effectiveness.

The correlation between the flow rate of florfenicol and the sorption efficiency showed that the sorption efficiency of florfenicol was lowered if the flow rates were >2 mL/min. This is because of the short time interaction of florfenicol with the molecular imprinted polymer, especially in recognition sites. If the flow rate was low, accordingly the efficiency of sorption was decreased and may be concerned to desorption of adsorbed species from the sorbent [32]. Based on research by Rodríguez et al. [39] the flow rate of the sample should be kept low to support the selective interactions of antimicrobial with the binding sites, thereby can increasing retention in the column of molecular imprinted polymer. The higher flow rates can caused an increase of system pressure, that can influence the system improvements (long-term). The impact of flow rate of florfenicol was assessed by loading 1 mL of ENRO's solution (0.5 mg/L in 0.1M of HEPES) into cartridges with different flow rates (0.25–2.0 mL/min). The extraction recoveries were 96% at flow rates <0.75 mL/min. If the loading flow rate was high, it will lower the % recovery caused by a decrease of the interaction time between the polymer binding site and the analyte [95].

So, for determination of the sample flow rate in molecular imprinted solid-phase extraction (MISPE) optimization, the flow rate with the highest % recovery should be selected. To get the highest % recovery, the flow rate shouldn't be too fast, because it can cause the shorten contact time between the analyte and the recognition site on the molecular imprinted polymer.

6.7. Contact time

The optimization of contact time's aim is to find the optimum contact time to give the highest extraction efficiency and recovery. Contact time describes the time taken by the sample to dissolve in the extraction phase. Based on research by Martins et al. [23] about the optimum extraction conditions of a catechin molecule as a template, an increase of contact time between the extraction phase and sample resulted in a higher percentage of extraction recovery. In this study, the contact time of five min with methanol was chosen because it showed the highest recovery and extraction efficiency compared to the other times (ten min and two min), and presented the highest peak in the chromatograms. If the contact time is too long, it is possible that the drug molecules dissolved in the elution of the solvent may evaporate simultaneously with the solvent, and if the contact time is too short, it is possible that the drug molecule has not been fully absorbed with the sorbent.

6.8. Salt addition

In the research conducted by Panamgama [26], the addition of $NaHSO_3$ or sodium bisulfite salts and Na_2CO_3 or sodium carbonate salts in the tannin's extraction process increased the yield in the extraction process and also could reduce the extracted sample's viscosity [26]. In a study by Martins et al. [23] the addition of approximately 5% NaCl showed a preferable extraction capability, reflected by the greater chromatographic peak area. This allegedly happened because the salt addition magnified the mass transfer in the extraction procedure. Actually, the salt addition can lead to an increase or decrease in the amount of analyte that is extracted, reliant on the salt concentration and the compound. When the salt is supplemented, molecules of water will solvate around the salt [96] which causes bad solubility of polar elements. This increases the liquidation of the elements in the membrane sac. Because the diffusion of analytes into the membrane sac to acceptor solvents was the rate limiting step, this indicates that the addition of salt accelerates this process. For more non-polar compounds, the addition of salt slightly reduced the amount extracted. This could be due to increased movement to the water sample surface for these non-polar compounds, also called the "oil effect" [97, 98]. Based on the explanation above, it can be concluded, the process of adding salt must be adjusted according to the properties of the compound, such as polarity.

6.9. Effect of ionic strength

Addition of a salt to the aqueous solution can decrease the quantity of solvent (water) to dissolve the analyte. This happens because of the formation of hydration spheres over ions which formed from the salt molecules. Based on research by Sorouraddin and Mohammad, the influence of salt addition to the sample has been evaluated at different concentrations. The results showed that addition of salt (NaCl) into the sample did not have a significant impact on extraction recovery [24]. Ionic species in the aqueous rebinding media affected the binding of propanolol and penicillin G. In aqueous media, the effect of salt ions followed the Hofmeister series with the kosmotropic ions. If the kosmotropic ions is high, the results will show the higher of binding augmentation. The hydrogen bonds play a prominent role in the binding between penicillin G to molecular imprinted polymer-1 cause the addition of water (small amount) gave a negative effect to binding capacity. molecular imprinted polymer-2 was less sensitive to water and maintained the template even occurred at the high amounts of water in rebinding solution. If the salt ions are added in media with water-poor, the binding to molecular imprinted polymer-1 will be follow the Hofmeister series of ions, whereas molecular imprinted polymer-2 will showed a mechanism of ion exchange. The results of that research

support the theory that the kosmotropic salts ions give their effect through modification of the hydrating environment alteration of hydrating environment can cause the exert effect of kosmotropic salts ions [99].

When hydrogen bonding is important for recognition (molecular imprinted polymer-1), the kosmotropic ions will appear to support the stable formation of molecular imprinted polymers–template interactions [100]. S-triazine has a low pKa, so it means that this compound exists entirely in anionic form. There is not a significant effect on the extraction recovery can be explained by an increase of the ionic competition between the anions and Na$^+$. So, in this case, the addition of salt does not affect the ionic competition. Whereas, according to Djozan et al. [78], the results showed that an increased salt addition caused a decrease of extraction efficiency (around 10%). This condition was due to the increase of ionic competition between HMAMP$^+$ and Na$^+$ to form the ionic's interaction with the carboxylate ion group. This interaction occurred in the molecular imprinted polymer matrix. This happens because the pKa of d-methamphetamine is 9.87, so it means that this compound exists entirely in cationic form [78]. So, the addition of salt can increase the % extraction recovery because Na + ions can increase the ionic strength if the sample molecules are neutral. Increased ionic strength will increase the % extraction recovery.

7. Conclusion

Optimization of the molecular imprinted solid-phase extraction (MISPE) is very important because the more selective the step of the Solid Phase Extraction process, the more sensitivity will be acquired. There are several factors that should be considered in the optimization of extraction conditions of molecular imprinted solid-phase extraction (MISPE), such as pH, sorbent mass, loading solvent, washing solvent, elution solvent, sample flow rate, extraction time, salt addition and ionic strength. The selection of suitable properties and quantities of washing solvent, loading solvent, elution solvent, ionic strength and also the right pH value greatly affect the formation of the appropriate interactions among the target molecules and the absorbent. Percentage recovery is also influenced by the formation of appropriate bonds, sample flow rates, extraction time, salt addition, and sorbent mass. Knowing the various factors that influence molecular imprinted solid-phase extraction (MISPE) optimization is very important. Through this article, it is hoped that the readers will be able to know these various factors. In carrying out molecular solid-phase extraction (MISPE), these factors can be taken into consideration in choosing the right optimal conditions at each stage. Through factors optimization, effective and efficient molecular imprinted solid-phase extraction (MISPE) process can be carried out. Therefore, in the future, molecular imprinted solid-phase extraction (MISPE) optimization has to consider and adjust the various factors mentioned above, to be able to form appropriate interactions between the absorbent and target molecules such that the results obtained are optimal.

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