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Review

Matrix solid-phase dispersion

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Abstract

Matrix solid-phase dispersion (MSPD) is a patented process, first reported in 1989, for conducting simultaneous disruption and extraction of solid and semi-solid samples. MSPD permits complete fractionation of the sample matrix components as well as the ability to selectively elute a single compound or several classes of compounds from the same sample. The method has been applied to the isolation of drugs in food animal tissues but has also found wide application in the analysis of herbicides, pesticides and pollutants from animal tissues, fruits, vegetables and other matrices. The present article provides a review of MSPD applications in these and related fields and discusses the factors known to affect MSPD methods. Both the practical and theoretical aspects of MSPD are also presented.

Keywords: Matrix solid-phase dispersion; Reviews; Solid-phase extraction

Contents

1. Introduction

The use of solid-phase extraction (SPE) in an analytical protocol requires that a sample first be in a homogeneous, liquid state prior to addition to a SPE column or disc device. A major complication to the use of SPE is the presence of particulates. These particulates can impede and block flow as they occupy the spaces between the solid-phase support materials or disc fibers. Thus, liquid samples that are relatively non-viscous and free of particulate can often be applied directly to SPE, although the analyst may seek to alter pH or ionic strength, or may

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choose to conduct a preliminary fractionation or modification of the sample by other techniques. Removal of particulate can usually be accomplished by centrifugation or by filtration through a more coarse or open-pore size material. This is important not only for the effect on flow-rate but also because of the potential to alter results. Variability in the particulate content for a number of samples within a batch to be extracted by SPE can lead to variability in recoveries, with the particulate actually acting as a discontinuous phase at the head of the column. Thus, the rendering of viscous or particulate-containing samples as suitable for SPE may require a number of procedural steps. The situation becomes even more complicated when we wish to separate components of a solid sample by SPE.

2. Preparation of solid samples for solid-phase extraction

Solid samples, such as animal tissues, vegetables and fruits, may be prepared for SPE by a stepwise process that begins with disruption of the gross architecture of the sample. The process of sample disruption is intended to divide the sample into smaller and smaller pieces, providing an overall greater surface area that may subsequently be exposed to extraction. This may involve mincing or dicing of the sample, followed by homogenization in the presence of water or organic solvents of various compositions. Similarly, samples may be frozen in liquid nitrogen or by exposure to dry-ice or they may be freeze–dried to produce a material that can be mechanically pulverized. These processes produce a finely divided powder that may then be extracted as described above.

In order to obtain complete sample disruption, particularly rupture of cellular membranes in biological samples, one may add detergents such as sodium dodecyl sulfate or triton to the process. These detergents assist in dissolving the lipohilic components but also greatly complete sample extraction and clean-up.

The procedures offered for disruption and extraction ideally isolate the target analytes with high efficiency and a degree of chemical specificity. However, many efforts to isolate the compound(s) of interest require repeated extractions of the homogenized matrix, replacing the solvent with fresh each time, remixing, centrifuging and pooling the supernatant fractions in the end, in order to obtain adequate recovery. This approach can require the use of large volumes of solvent and the subsequent need to evaporate and dispose of the solvent so employed. In many cases, the sample and solvent combination lead to the formation of emulsions, which further complicates the efficiency of extraction and adds greatly to the time required for the analyst to complete the protocol.

Another approach involves the use of abrasives, such as sand, blended with the sample by means of a mortar and pestle or by a related mechanical device. The shearing forces generated by the blending process disrupt the sample architecture and provide a more finely divided material for extraction. The material can either be mixed directly with solvents or packed into a column to perform a more classical chromatographic elution. Some procedures use abrasives that also possess the properties of a drying agent, such as sodium sulfate or silica, producing a material that is finely divided but also quite dry for subsequent extraction as described. Such sample preparation also permits extraction by continuous solvent reflux techniques (Sohxlet devices). Blending samples with a drying agent is also commonly used today in supercritical fluid extraction (SFE) protocols, wherein the presence of water otherwise compromises the extraction results.

3. The development of matrix solid-phase dispersion

In 1989 [1], a new process for the disruption and extraction of solid samples was introduced. This process, matrix solid-phase dispersion (MSPD), combines aspects of several techniques for sample disruption while also generating a material that possesses unique chromatographic character for the extraction of compounds from a given sample (see Refs. [2–9] for reviews). MSPD involves blending a viscous, solid or semi-solid sample with a solid

support, such as silica, that has been derivatized to produce a bound organic phase, such as octadecylsilyl (C_{18}), on its surface. These materials are, of course, the same materials used as packing for SPE columns. For MSPD they are simply being used in a different manner than originally intended. In this manner, the solid support serves the same purpose as the use of sand as an abrasive: the shearing forces of blending with a mortar and pestle or other mechanical device disrupt the gross architecture of the sample, breaking the material into smaller pieces. However, the presence of the bound organic phase provides a further dimension to the process: sample components dissolve and disperse into the bound organic phase on the surface of the particle, leading to the complete disruption of the sample and its dispersion over the surface. Sample components distribute over the surface based on their relative polarities: non-polar components disperse into the non-polar organic phase based on their distribution coefficients with the phase and the dynamic changes that occur as this process proceeds; smaller, highly polar molecules (water) are envisioned to associate with silanols on the surface of the silica particle and inside the pores of the silica solid support as well as with matrix components capable of hydrogen bonding; larger, less polar molecules distributing across the surface of the now-biphasic, bonded-phase/dispersed-sample-lipid structure.

The degree to which sample disruption and dispersion is accomplished by MSPD is perhaps best demonstrated in the accompanying scanning-electron micrographs (SEMs; Fig. 1a–d). Fig. 1a illustrates the physical characteristics of the bonded-phase solid support particles. The sharp edges and rough surface serve to provide shearing during mechanical blending of a sample. Fig. 1b is a SEM of underivatized silica particles after blending with liver tissue. Disruption of the sample architecture is accomplished, as noted by the clumps of cells distributed about the landscape. However, the component cells are not themselves disrupted, as is the case shown in Fig. 1c and d where C_{18}-derivatized materials were used. Fig. 1c illustrates the complete sample disruption and dispersion of the sample matrix. This is further supported by Fig. 1d where two particles are seen to have broken away from one another, revealing the layer of material that has become dispersed over the surface.

4. Performing a matrix solid-phase dispersion extraction

Thus, a highly viscous, semi-solid or solid sample can be placed in a mortar containing a bonded-phase solid support material and mechanically blended to perform a complete disruption and dispersal of the sample. This resulting MSPD blend is sufficiently dry, in part due to the absorption of water into the pores of the silica, to transfer and pack into a column for more classical application of SPE to the isolation of sample components. The processes of blending and preparing a column for MSPD extraction have proven to be quite generic, with the same general approach proving to be applicable to a wide range of matrices and analytes (Table 1) [10–89]. This process is diagrammatically displayed in Fig. 2.

MSPD has been most frequently applied to the isolation of drugs, herbicides, pesticides and other pollutants from animal tissues, fruits and vegetables. These applications of the method usually employ a relatively small sample (approximately 0.5 g) blended in a mortar and pestle using 2.0 g of a bonded-phase solid support (a four-to-one ratio of support to sample), usually a C_8 or C_{18} material. The mortar and pestle used should be glass or agate, as porcelain and other porous materials have been shown to lead to analyte and sample loss. The blending process does not require vigorous effort to accomplish but is dependent on the degree of connective tissue or other more rigid biopolymer content of the sample. It has been noted for some animal tissues that simply covering the sample with solid support material and waiting for an hour leads to dissolution of the sample into the bonded phase. This is not highly recommended, however, as concerns over sample/analyte stability become an issue. Different analysts may apply differing amounts of pressure or attain different degrees of dispersion of the sample. This may be reflected in different levels of recovery in analyst-to-analyst comparisons during method validation studies. However, excellent agreement is still usually attained in the final result, with

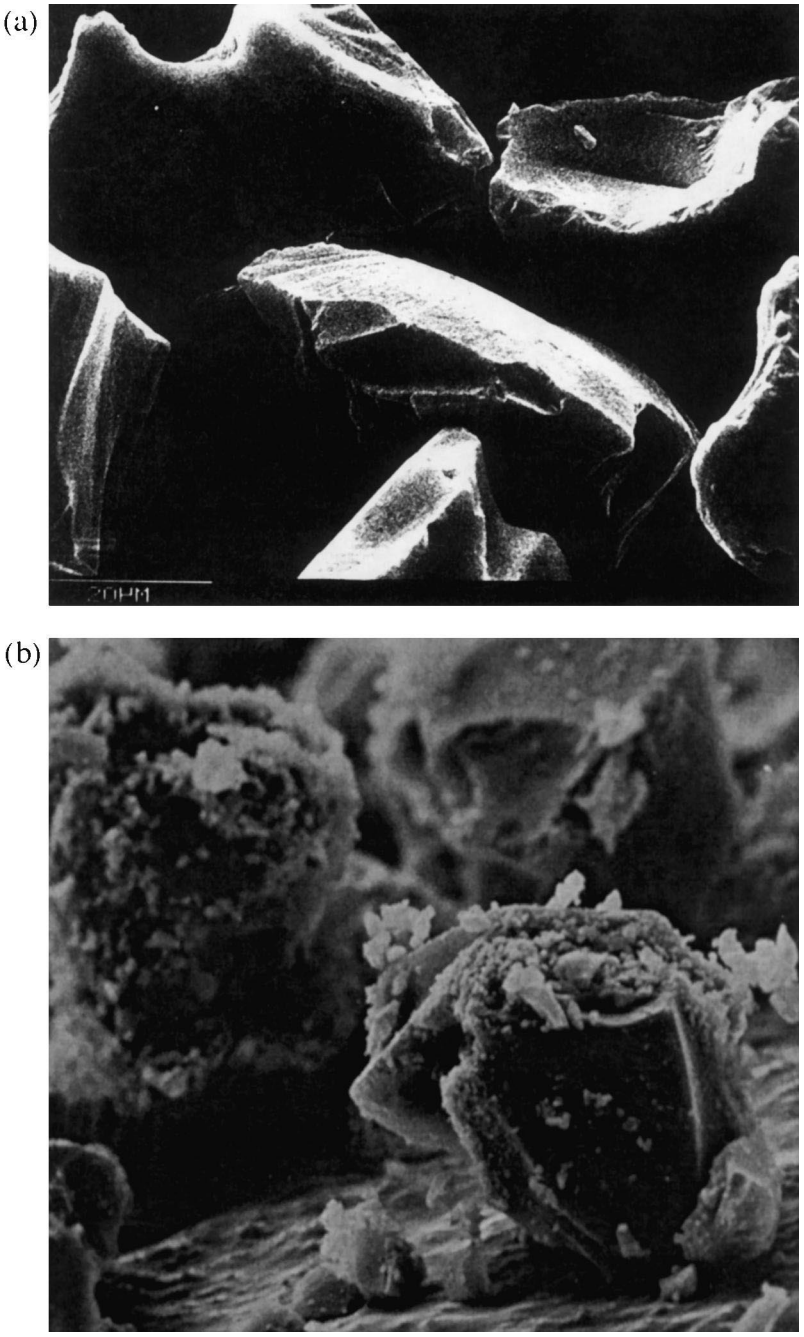

Fig. 1. (a) Shows a scanning electron micrograph (SEM: 20 micron resolution) of C_{18}-derivatized silica particles. (b) Is a SEM (20 micron resolution) of underivatized silica particles after blending with bovine liver tissue. Note the clumps of tissue and fragmented silica. (c) Shows the same process using C_{18}-derivatized materials. The sample is completely disrupted and evenly dispersed over the material (20 micron resolution). (d) Shows a closer view of the material (2 micron resolution) illustrating the layer of sample that is formed using the C_{18}-derivatized material.

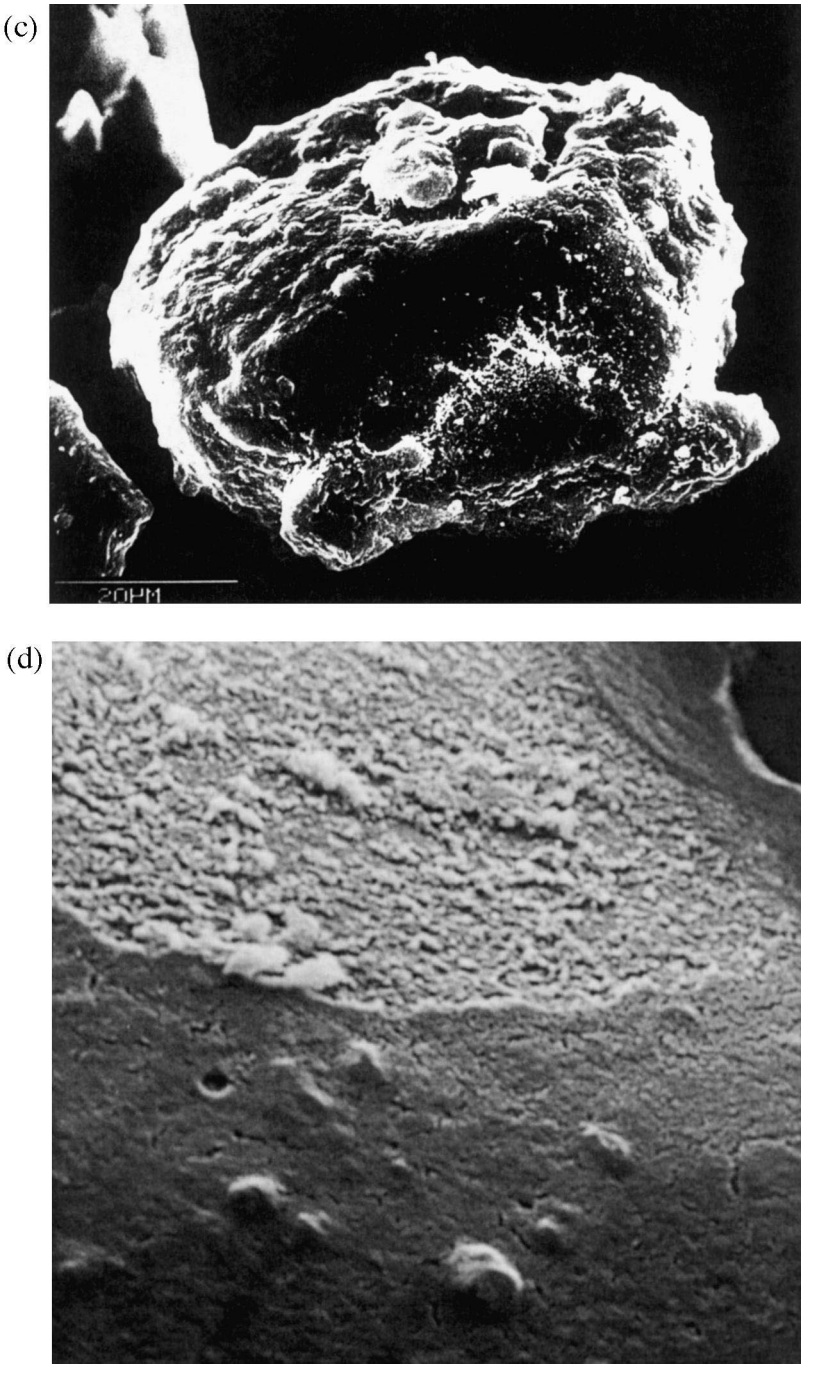

Fig. 1. (*continued*).

Table 1
Applications of MSPD to the analysis of residues

Analyte(s)	Matrix	Ref.	Analyte(s)	Matrix	Ref.
Alkylphenol ethoxylates	Tissues	[10]	Penicillin	Porcine tissues	[48]
	Fish	[11]	Pesticides	Beef fat	[49]
	Fish	[12]		Catfish muscle	[50]
Aminoglycosides	Bovine kidney	[13]		Crayfish	[51]
Antibacterials	Foods, review	[14]		Fish	[52]
Benzimidazoles	Animal tissues	[15]		Fruit, vegetables	[53]
	Bovine liver	[16]		Milk	[54]
	Swine muscle	[17]		Oranges	[55]
	Bovine milk	[18]		Oysters	[56]
	Calve tissues	[19]		Vegetables	[57]
	Bovine milk	[20]		Fish	[58]
β-Agonists	Bovine liver	[21]		Plant materials	[59]
	Bovine liver	[22]		Fruits and vegetables	[60]
β-Carotene	Medical foods	[23]		Citrus fruits	[61]
Carbofuran	Corn	[24]		Human serum	[62]
Chloramphenicol	Milk	[25]		Citrus fruits	[63]
Chlorsulfuron	Milk	[26]		Foods and soils	[64]
Chlorsulon	Milk	[27]	Pollutants	Aquatic species	[65]
	Milk	[28]	Pyrethroidss	Vegetables	[66]
Clenbuterol	Bovine liver	[29]	Sulfa drugs	Chicken tissues	[67]
	Liver	[30]	Sulfadimethoxine	Catfish	[68]
Coal-tar dyes	Confectioneries	[31]		Catfish	[69]
Drug residues	Animal tissues	[1]		Catfish muscle	[70]
	Animal tissues	[2]		Catfish, plasma	[71]
	Animal tissues	[7]	Sulfamethazine	Animal tissues	[72]
	Animal tissues	[6]		Swine tissues	[73]
	Foods	[3]		Swine tissues	[74]
	Milk	[32]	Sulfonamides	Animal tissues	[75]
	Animal tissues	[33]		Infant formula	[76]
Drugs, pollutants	Aquatic species	[34]		Meat, milk	[77]
Furazolidone	Chicken muscle	[35]		Milk	[78]
	Milk	[36]		Salmon muscle	[79]
	Swine muscle	[37]		Salmon muscle	[80]
Ivermectin	Fish muscle	[38]		Swine muscle	[81]
	Milk	[39]		Tissues, milk, eggs	[82]
	Liver	[40]		Bovine, swine tissues	[83]
Moxidectin	Bovine tissues	[41]	Tetracyclines	Foods	[84]
Nicarbazin	Animal tissues	[42]		Milk	[85]
Oxamyl, methomyl		[43]		Milk, meat, cheese	[86]
Oxolinic acid	Catfish	[44]	Vitamins	Medical foods	[87]
Oxytetracycline	Catfish muscle	[45]		Infant formula	[88]
PCBs	Fish	[46]		Infant formula	[89]
PCBs, pesticides	Fish	[47]			

good overall accuracy and precision and low variability [1–9].

Milk and more viscous samples, such as blood, can be blended by placing the sample in a test tube or a syringe barrel that will subsequently serve as a column and mixing the sample and solid support with a spatula or related device. Solid samples previously processed through a blender or some other homogenizing step may similarly be prepared.

Once the MSPD blending process is complete, the material is transferred to a column constructed from a syringe barrel, or some other appropriate device, containing a frit that retains the entire sample. The sample is then compressed to form a column packing

by using a modified syringe plunger. A second frit may be placed on top of the material before compression. The principles of performing good chromatography always apply: one should avoid channels in the column and not over-compress or compact the material.

Addition of eluting solvent to the column may be preceded by use of some or all of the solvent to backwash the mortar and pestle. Most applications have utilized 8 ml of solvent to perform an elution. Evidence from some studies indicates that most target analytes are eluted in the first 4 ml [1,2,4,5,90–92].

Since the entire sample is present in the column it is also possible to perform multiple or, particularly, sequential elutions of the sample [1]. This property permits isolation of a single compound, a class of compounds or even several classes of compounds from a single MSPD sample. Data have been presented that show that one can actually fractionate the

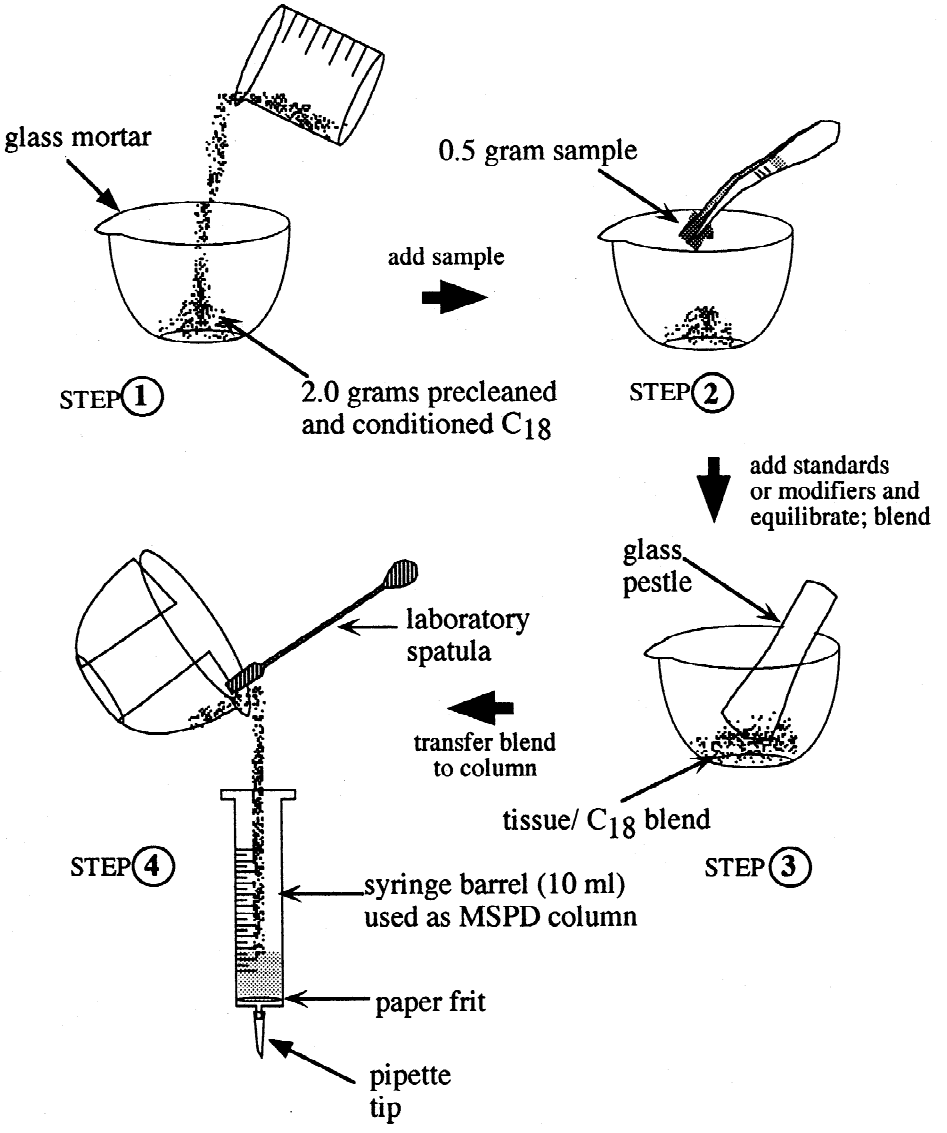

Fig. 2. A schematic representation of the MSPD process.

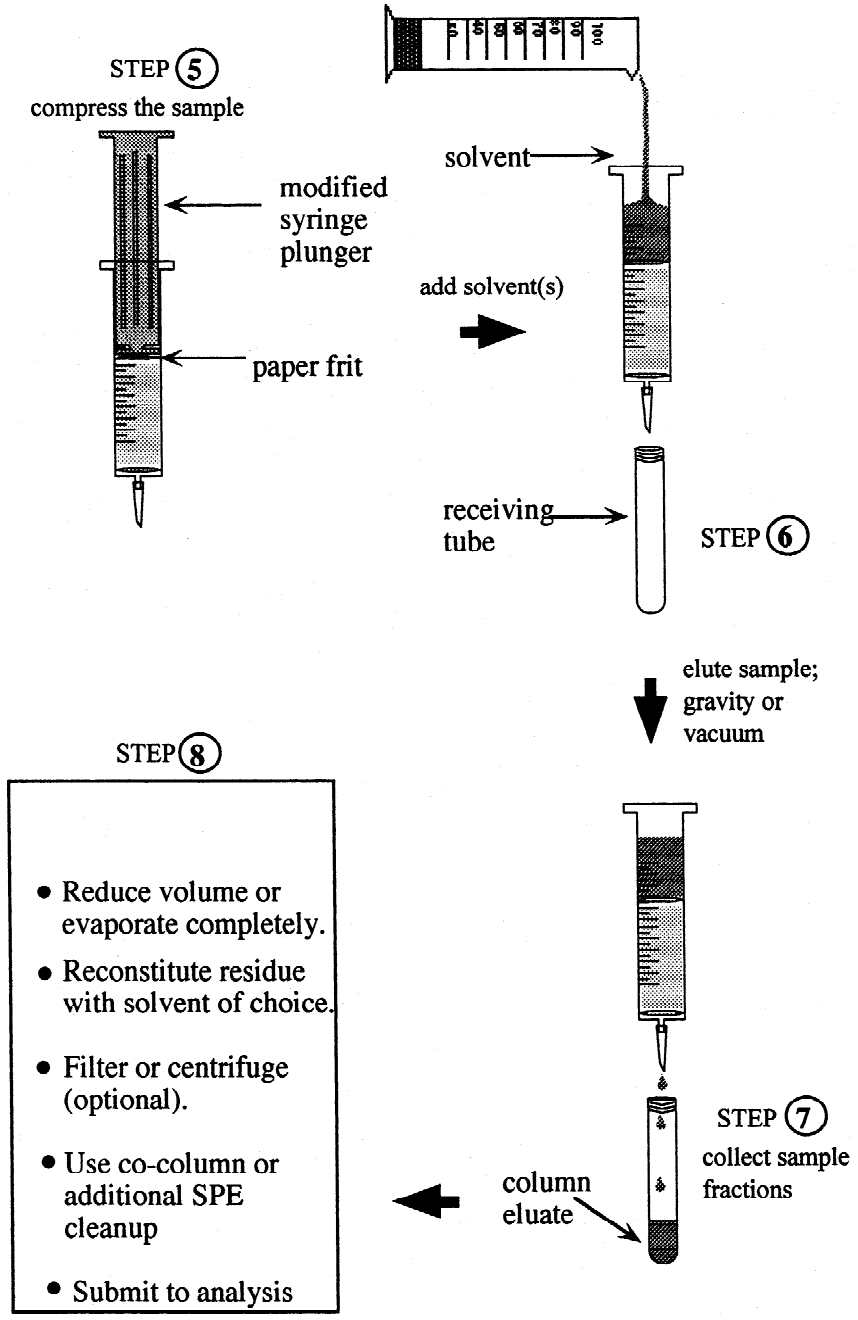

Fig. 2. (*continued*).

contents of the entire sample, including macromolecular components of the sample matrix itself. This property has proven useful in isolating and identifying endogenous components [90–92].

For these purposes, MSPD columns prepared with C_{18} supports have been most frequently eluted with a sequence of solvents beginning with the least polar (hexane) and increasing the polarity (ethyl acetate,

acetonitrile, methanol) up to water. This may be followed by acid, base or salt to alter the ionic state of the column components. Typical elutions for single compounds have reflected the desire to perform a degree of selective fractionation, using solvents of moderate polarity or solvents modified by the addition of acid, base, salts or varying percentages of other solvents.

Most MSPD elutions have been conducted by gravity flow. In some instances it is stated that flow was initiated by the application of pressure to the head of the column or by placing the columns on a vacuum box and briefly applying suction. Similarly, other methods have employed the use of vacuum boxes to control the flow of the various elution solvents.

Many MSPD procedures also employ the use of co-columns to obtain a further degree of fractionation and sample clean-up. The co-column material (Florisil or silica, for example) may be packed into the bottom of the same column as the MSPD material or may be used as an external column stacked so as to collect and further fractionate the sample as it elutes from the MSPD column [2–9].

5. Factors affecting matrix solid-phase dispersion analyses

MSPD is, as with SPE, a form of chromatography and the general principles of the science apply. However, MSPD is different from SPE and possesses characteristics that are somewhat more complex than standard chromatographic procedures. MSPD is, as opposed to all other forms of chromatography, designed to expeditiously disrupt and disperse the components of solid samples into a bound organic phase on a solid support that can subsequently be used as a column packing material from which sample components may be eluted. In this manner, the sample becomes dispersed throughout the column and is part of the overall chromatographic character of the system: interactions involve the stationary phase, the solid support, the mobile or eluting phase and all of the sample matrix components as well. This type of interaction is observed in some SPE methods wherein sample components accumulate on the head of a column and act as a discontinuous phase that may affect recoveries and results. Indeed, this phenomenon is also observed in performing high-performance liquid chromatography (HPLC) and gas chromatography (GC) when repeated injections lead to the accumulation of an immobile or non-volatile, discontinuous phase, respectively, at the head of a column. The accumulation of these materials is often indicated by the presence of peak tailing, peak splitting, shoulders and, on some occasions, the complete loss of certain sample components to the analysis. MSPD, in essence, takes advantage of this phenomenon, dispersing the entire sample throughout the entire column, creating a unique chromatographic phase.

The dynamic interactions that are developed are not completely understood. However, we can address the factors that have been shown to effect performance. For the most part, these are the same factors that are recognized as influencing the performance of an SPE procedure.

5.1. The nature of the solid support

All reports to date concerning the use of MSPD have employed silica-based solid supports. While polymeric supports derivatized with an organic phase would be expected to work as well, there is currently insufficient data to make that claim. One positive aspect of the use of silica-based supports may be the presence of underivatized silanols on the surface and in the pores of the support material. These silanols may serve an important role in providing a drier sample than would otherwise be obtained if a material lacking functional groups capable of hydrogen bonding small molecules were to be used. This can be an important factor in MSPD since the entire sample is added to the column: if the sample is too wet, packing and eluting the sample may prove difficult. Indeed, non-end-capped materials have been found to be quite suitable in several MSPD applications [2,4–9].

Pore size in the solid support has also been examined [4]. It was reported that there was no discernible difference in MSPD performance between several different pore-size materials.

Particle size is relatively important, however. The use of particles of 3–20 μm diameter lead to low or non-existent flow-rates. Most MSPD applications

have used a 40 μm diameter particle. It has also been reported that a mixed particle size material, ranging from 40 to 100 μm, also works quite well for MSPD and is less expensive in bulk [2–9].

5.2. The nature of the bonded phase

Most applications of MSPD have utilized a reversed-phase material, particularly C_{18} and C_8. There are some reports of the use of cyanopropyl (CNPr) and related normal-phase materials. The latter cases have employed more polar phases in an effort to isolate more polar analytes, whereas the applications using reversed-phase materials have been to isolate more lipophilic entities.

There is little doubt that the presence and nature of the bonded phase plays a significant role in MSPD. A lipophilic bonded-phase is believed to be essential to the properties of both sample disruption and dispersion. This lipophilic phase is also believed to lead to the formation of a new phase that resembles a cell membrane bilayer assembly, giving the MSPD material its unique chromatographic characteristics.

Similarly, end-capping has been examined and found not to be of significant influence on the results for a given analyte. Likewise, the percent carbon load did not appear to have an appreciable effect on the analytical outcome [2–9].

Two items that have been noted to be essential to SPE are also essential in MSPD: the solid support materials should be pre-washed to remove potential interferences and the solid support should be preconditioned with a solvent, ''fluffing-up'' the phase, prior to blending with a sample.

5.3. The nature of the sample matrix

Since the sample matrix actually becomes part of the chromatographic phase, it is anticipated that the results and recovery would change for a given analyte in going from one matrix to another, say fish tissue to tomatoes. This may well be the case but little data exist upon which to state this as fact. Nonetheless, the theoretical aspects of lipid content, total protein, etc., and their distribution are reflected in how an MSPD elution performs.

While the bonded-phase on the solid support is immobile, the dispersed matrix components are not. What is observed in MSPD applications is the fractionation of the entire sample, as demonstrated by mass-balance experiments. Thus, certain matrix components are eluted as compound-classes in certain fractions, depending on the eluting solvent and the dynamic interactions between dispersed matrix and solid-phase components. In this manner, certain target analytes tend to be eluted in fractions that are not readily predictable by their relative distributions into a solid-phase or the applied eluting solvent. This is explained by the fact that certain chemical classes of analytes are consistently co-eluted with the matrix components in a given fraction. In many cases, however, the relative polarities of the analytes and co-elutants are quite different and these potential interferences can often be removed by the use of a standard SPE technique or by simple solvent suspension.

Thus, the matrix interactions with the solid-phase and the mobile phase also have a pronounced effect on the elution order of compounds from an MSPD column [1–9].

5.4. Matrix modification

As with liquid samples to be applied to SPE columns, it is sometimes necessary to alter the ionization state of the sample components to assure that certain interactions occur between the solid support bonded-phase and/or the eluting solvent in MSPD. This may be accomplished by adding acids, bases, salts, chelating or de-chelating agents, antioxidants, etc., at the time of sample blending and/or as an additive to the eluting solvent.

5.5. The nature of the eluting solvent and the sequence of addition

As with SPE, the relative polarity of the eluting solvent to that of the solid support bonded-phase play a significant role in determining what remains on the column and what is eluted. In MSPD, we must also consider retention and elution of the second phase of sample matrix components. As noted above, many target analytes are observed to elute with matrix components under polarity conditions that are not readily predictable. Nonetheless,

the sequence and design of an elution profile should strive to retain as much of the sample on the column as possible while removing the target analyte(s) with a high degree of specificity. This cannot always be accomplished and the use of co-columns or other clean-up techniques must be applied. For some applications, however, the eluate may be sufficiently clean to take directly to final analysis. A few reports have illustrated the use of the eluate in an immunoassay, with organic solvent being removed and replaced with assay buffer.

6. Conclusion

MSPD is a distinct analytical technique that possesses many of the characteristics of other chromatographic methods. However, its ability to directly handle solid, semi-solid and viscous samples, to provide a mechanism to simultaneously disrupt and disperse a sample over a bonded-phase solid support that may subsequently be used as a column packing and the generation of a unique chromatographic phase that provides a new dimension of sample fractionation, make MSPD unique. The application of MSPD to difficult analytical problems has shown that it can greatly reduce analyst time, increase sample throughput and shorten turn-around time, reduce solvent use and the attendant expense of solvent purchase and disposal, as well as provide analytical results that are equal to or better than classical or ''official'' methods. Initial concerns about the use of small sample size and the corresponding losses in sensitivity and homogeneity have been overcome. Sensitivity has been greatly increased by the development of new analytical instrument technologies that permit the use of much smaller sample sizes. Indeed, the recognition that working from 5 g of sample that is extracted and dissolved in a final volume of 100 μl is equivalent to extracting 0.5 g of sample and dissolving it in 10 μl for analysis helps address this issue. Homogeneity can also be reconciled by previous homogenization of an entire sample. Taking sub-samples of the homogenate for MSPD analysis is simply a smaller scale version of the more classical approach to the problem.

Development of techniques such as MSPD that use smaller sample size, that minimize solvent use and that are amenable to automation is a positive direction for analytical science. The interfacing of such sample preparation and fractionation techniques to immunoassay-based technologies, to micro-devices and enhanced analytical instruments with greater specificity and sensitivity will, in all of its scientific complexity, greatly simplify and speed the task of obtaining essential data.

References

[1] S.A. Barker, A.R. Long, C.R. Short, J. Chromatogr. 475 (1989) 353.
[2] S.A. Barker, A.R. Long, J. Liq. Chromatogr. 15 (1992) 2071.
[3] S.A. Barker, R. Hawley, Int. Lab. 46 (1992) 16.
[4] S.A. Barker, A.R. Long, in: V.K. Agarwal (Ed.), Analysis of Antibiotic Drug Residues in Food Products of Animal Origin, Plenum Press, New York, 1992, p. 119.
[5] S.A. Barker, A.R. Long, M.E. Hines, J. Chromatogr. 629 (1993) 23.
[6] S.A. Barker, Chemtech 23 (1993) 42.
[7] S.A. Barker, Z.E. Floyd, in: J. Pesek, M. Matyska, R. Abuelafiya (Eds.), Chemically Modified Surfaces: Recent Developments, Royal Society of Chemistry, 1996, p. 66.
[8] S.A. Barker, LC·GC Int. 11 (1998) 719.
[9] S.A. Barker, LC·GC Int. May (Supplement) (1998) 37.
[10] M. Zhao, F. van der Wielen, P. de Voogt, J. Chromatogr. A 837 (1999) 129.
[11] J. Tolls, M. Haller, D.T. Sijm, Anal. Chem. 71 (1999) 5242.
[12] J. Tolls, M. Haller, D.T. Sijm, J. Chromatogr. A 839 (1999) 109.
[13] L.G. McLaughlin, J.D. Henion, P.J. Kijak, Biol. Mass Spectrom. 23 (1994) 417.
[14] B. Shaikh, W.A. Moats, J. Chromatogr. 643 (1993) 369.
[15] S.A. Barker, T. McDowell, B. Charkhian, L.C. Hsieh, J. Assoc. Offic. Anal. Chem. 73 (1990) 22.
[16] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Assoc. Offic. Anal. Chem. 73 (1990) 860.
[17] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Food Comp. Anal. 3 (1990) 20.
[18] L.C. Kappel, S.A. Barker, J. Vet. Pharmacol. Ther. 19 (1996) 416.
[19] S.A. Barker, M. Claxton, L.C. Kappel, J. Vet. Pharmacol. Ther. 20 (1997) 163.
[20] S.A. Barker, L.C. Kappel, J. Vet. Pharmacol. Ther. 20 (1997) 160.
[21] D. Boyd, M. O'Keeffe, M. R Smyth, Analyst 119 (1994) 1467.
[22] D. Boyd, M. O'Keeffe, M.R. Smyth, Anal. Proc. 32 (1995) 301.

[23] G.W. Chase, R.R. Eitenmiller, A.R. Long, J. AOAC Int. 82 (1999) 663.
[24] R. Yang, C. Fu, Fenxi Ceshi Xuebao 13 (1994) 72.
[25] A.R. Long, L.C. Hsieh, A.C. Bello, M.S. Malbrough, C.R. Short, S.A. Barker, J. AOAC 38 (1990) 427.
[26] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Assoc. Offic. Anal. Chem. 72 (1989) 813.
[27] F.J. Schenck, S.A. Barker, A.R. Long, Laboratory Information Bulletin, FDA. 5 (1989) 3381-1.
[28] F.J. Schenck, R. Wagner, W. Bargo, J. Liq. Chromatogr. 16 (1993) 513.
[29] D. Boyd, P. Shearan, J.P. Hopkins, M. O'Keeffe, M.R. Smyth, Anal. Proc. 30 (1993) 156.
[30] D. Boyd, P. Shearan, J.P. Hopkins, M. O'Keeffe, M.R. Smyth, Anal. Chim. Acta 275 (1991) 221.
[31] S. Kai, T. Nikkawa, A. Takahashi, A. Koizumi, Y. Hyoudou, S. Suzuki, H. Nakazawa, J. Food Hyg. Soc. Japan 37 (1996) 146.
[32] S.A. Barker, A.R. Long, J. AOAC Int. 77 (1994) 848.
[33] S. LeBoulaire, J.C. Bauduret, F. Andre, J. Agric. Food Chem. 45 (1997) 2134.
[34] C.C. Walker, H.M. Lott, S.A. Barker, J. Chromatogr. 642 (1993) 225.
[35] M.M. Soliman, A.R. Long, S.A. Barker, J. Liq. Chromatogr. 13 (1991) 3327.
[36] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Agric. Food Chem. 38 (1990) 430.
[37] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Assoc. Offic. Anal. Chem. 73 (1990) 93.
[38] E. Iosifidou, P. Shearan, M. O'Keeffe, Analyst 119 (1994) 2227.
[39] F.J. Schenck, J. Liq. Chromatogr. 18 (1995) 349.
[40] F.J. Schenck, S.A. Barker, A.R. Long, Lab. Information Bull., FDA 6 (1990) 3425.
[41] M. Alvinerie, J.F. Sutra, D. Capela, P. Galtier, A. Fernandez-Saurez, E. Horne, M. O'Keeffe, Analyst 121 (1996) 1469.
[42] F.J. Schenck, S.A. Barker, A.R. Long, J. Matusik, Lab. Information Bull., FDA 5 (1989) 3354.
[43] S.C. Stafford, W. Lin, J. Agric. Food Chem. 40 (1992) 1026.
[44] H.H. Jarboe, K.M. Kleinow, J. AOAC Int. 75 (1992) 428.
[45] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. AOAC 73 (1990) 864.
[46] Y.-C. Ling, M.-Y. Chang, I.-P. Huang, J. Chromatogr. A 669 (1994) 119.
[47] Y.-C. Ling, I.-P. Huang, Chromatographia 40 (1995) 259.
[48] M. McGrane, M. O'Keeffe, M.R. Smyth, Analyst 123 (1998) 2779.
[49] A.R. Long, L.C. Hsieh, C.R. Short, S.A. Barker, J. AOAC 74 (1991) 493.
[50] A.R. Long, L.C. Hsieh, C.R. Short, S.A. Barker, J. AOAC 74 (1991) 667.
[51] H.M. Lott, S.A. Barker, J. AOAC Int. 76 (1993) 663.
[52] H.M. Lott, S.A. Barker, Environ. Monit. Assess. 28 (1993) 109.
[53] C.M. Torres, Y. Pico, J. Manes, Chromatographia 41 (1995) 685.
[54] F.J. Schenck, R. Wagner, Food Addit. Contam. 12 (1995) 535.
[55] C.M. Torres, Y. Pico, M.J. Redondo, J. Manes, J. Chromatogr. 719 (1996) 95.
[56] H.M. Lott, S.A. Barker, J. AOAC Int. 76 (1993) 67.
[57] E. Viana, J.C. Molt, G. Font, J. Chromatogr. 754 (1996) 437.
[58] R. Yang, C. Fu, Hebei Daxue Xuebao, Ziran Kexueban 14 (1994) 29.
[59] J. Tekel, S. Hatrik, J. Chromatogr. A 754 (1996) 397.
[60] C.M. Torres, Y. Pico, J. Manes, J. Chromatogr. A 778 (1997) 127.
[61] C.M. Torres, Y. Pico, J. Manes, J. AOAC Int. 80 (1997) 1122.
[62] C.M. Lino, C.B. Azzolini, D.S. Nunes, J.M. Silva, M.I. da Silveira, J. Chromatogr. B 16 (1998) 147.
[63] A.I. Valenzuela, R. Lorenzini, M.J. Redondo, G. Font, J. Chromatogr. A 839 (1999) 101.
[64] Y. Pico, J.C. Molto, J. Manes, G. Font, J. Microcol. Sep. 6 (1994) 331.
[65] M.D. Crouch, S.A. Barker, J. Chromatogr. A 774 (1997) 287.
[66] Y.-C. Ling, I.-P. Huang, J. Chromatogr. 695 (1995) 75.
[67] S. Fukushima, S. Taguchi, T. Nishumune, K. Sueki, Osaka-furitsu Koshu Eisei Kenkyusho Kenkyu Hokoku, Shokuhin Eisei 12 (1993) 59.
[68] C.C. Walker, S.A. Barker, J. AOAC Int. 77 (1994) 1460.
[69] C.C. Walker, R.L. Thune, S.A. Barker, J. Vet. Pharmacol. Ther. 18 (1995) 1.
[70] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. AOAC 73 (1990) 868.
[71] C.C. Walker, S.A. Barker, J. AOAC Int. 77 (1994) 908.
[72] C. Renson, G. Degand, G. Maghuin-Rogister, P. Delahaut, Anal. Chim. Acta 275 (1993) 323.
[73] P. Shearan, M. O'Keeffe, M.R. Smyth, Food Addit. Contam. 11 (1994) 7.
[74] P. Shearan, M. O'Keeffe, Analyst 119 (1994) 2761.
[75] H. Tamura, M. Yotoriyama, K. Kurosaki, N. Shinohara, Shokuhin Eiseigaku Zasshi 35 (1994) 271.
[76] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Liq. Chromatogr. 12 (1989) 1601.
[77] L.S.G. Van Poucke, G.C.I. Depourcq, C.H. Van Peteghem, J. Chromatogr. Sci. 29 (1991) 423.
[78] A.R. Long, C.R. Short, S.A. Barker, J. Chromatogr. 502 (1990) 87.
[79] G.J. Reimer, A. Suarez, J. Chromatogr. 555 (1991) 315.
[80] G.J. Reimer, A. Suarez, J. AOAC Int. 75 (1992) 979.
[81] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Agric. Food Chem. 38 (1990) 423.
[82] V.K. Agarwal, J. Chromatogr. 624 (1992) 411.
[83] L.V. Walker, J.R. Walsh, J.J. Webber, J. Chromatogr. 595 (1992) 179.
[84] S.A. Barker, C.C. Walker, J. Chromatogr. 624 (1992) 411.
[85] A.R. Long, L.C. Hsieh, M.S. Malbrough, C.R. Short, S.A. Barker, J. Assoc. Offic. Anal. Chem. 73 (1990) 379.
[86] E. Brandsteterova, P. Kubalec, L. Bovanova, P. Simko, A. Bednarikova, L. Machackova, Zeitschr. Lebensmitt.-Unters.-Forsch. A – Food Res. Technol. 205 (1997) 311.

[87] G.W. Chase, R.R. Eitenmiller, A.R. Long, J. AOAC Int. 82 (1999) 107.
[88] G.W. Chase, A.R. Long, J. AOAC Int. 81 (1998) 582.
[89] G.W. Chase, R.R. Eitenmiller, A.R. Long, J. AOAC Int. 82 (1999) 1140.
[90] M.E. Hines, A.R. Long, T.G. Snider, S.A. Barker, Anal. Biochem. 195 (1991) 197.
[91] M.E. Hines, J.M. Jaynes, S.A. Barker, J.C. Newton, F.M. Enright, T.G. Snider, Infect. Immun. 61 (1993) 1.
[92] M.E. Hines, K.S. Frazier, J. Clin. Microbiol. 31 (1993) 610.