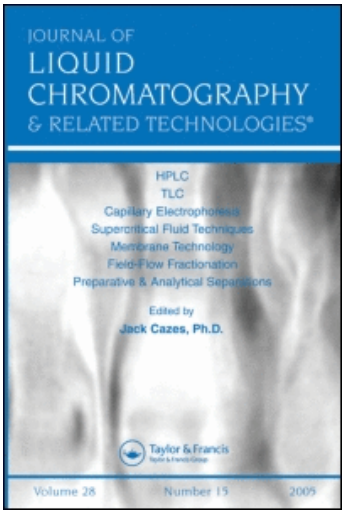

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An Alternative Method for Determination of Additives in Polypropylene Using Supercritical Fluid Extraction and Enhanced Solvent Extraction

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Abstract: The extraction of Irganox 1076, Irgafos 168, and Irganox 1010 from polypropylene (PP) by supercritical fluid extraction (SFE) and enhanced fluid extraction (ESE) was investigated to find an alternative method to the dissolution extraction required by regulators for polymers used for the packaging of liquid pharmaceutical formulations. The maximum recovery with SFE was obtained at a CO_2 pressure of 680 bar at a temperature of 100°C, with 10% methanol as modifier and static and dynamic extraction times of 30 and 40 minutes, respectively. This gave a recovery of ≥95% for Irganox 1076 and Irgafos 168 compared to the pharmacopoeial method, and a recovery of 62% for Irganox 1010. With ESE, the maximum extraction was obtained at a temperature of 100°C, a restrictor flow rate of 5 mL/min, a static extraction time of 90 minutes, and a solvent mixture of 2-propanol-cyclohexane (75:25 v/v). The recoveries for Irganox 1076 and Irgafos 168 were 109% and 121%, respectively, compared to the pharmacopoeial method, while the recovery for Irganox 1010 was 86%. When a higher temperature was used with ESE, the recoveries of Irganox 1076 and Irgafos 168 were unchanged but that of Irganox 1010 increased to 96%. Unfortunately, at the higher temperature, the PP partly melted and caused a system blockage. A better recovery than 86% of

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Irganox 1010 is required for a method to be an alternative to the dissolution extraction method.

Keywords: Supercritical fluid extraction, Enhanced fluid extraction, Polypropylene, Irganox 1076, Irganox 1010, Irgafos 168

INTRODUCTION

Polymers are, in many instances, the preferred packaging material for liquid pharmaceutical formulations. To give the polymeric material the desired properties, it usually contains low molar mass additives (antioxidants, plasticisers, anti-block agents, lubricants, etc.). Unfortunately, the additives may interact with the content in an undesirable way. When the packaging is used for a pharmaceutical formulation, regulators require identification of the additives in the polymer by use of a dissolution extraction method.[1] Other techniques to extract additives from polymers also exist, which have been described by Vandenburg et al.[2] Some of them offer the advantage of automation of the extraction process. With supercritical fluid extraction (SFE), additives from polymers can be extracted rapidly and accurately without dissolving the matrix.[3–8] Another similar extraction method is enhanced solvent extraction (ESE). When this was compared to Soxhlet extraction using chloroform to extract Irganox 1010 from polypropylene (PP), ESE was three times as fast.[9] Microwave assisted extraction (MAE) has also been used for the extraction of additives from polyolefins. The extraction was much faster compared to Soxhlet extraction.[10] Cano et al. showed that the efficiency of MAE of adipate plasticisers from poly(vinyl chloride) (PVC) depended on the kind of solvent, the temperature achieved, and the heating time.[11] Ultrasonic extraction has also been used to extract additives from polyolefins in a fast and efficient way.[12,13]

Both SFE and ESE should preferably extract the additives without dissolving the polymer. SFE uses a supercritical fluid (SF), which exhibits physicochemical properties intermediate between those of a liquid and a gas. The most commonly used gas for SFE is CO_2, which becomes supercritical above 31°C and 73.8 bar. The solvating power of CO_2 is a function of the density of the SF and the density depends on the pressure and temperature. CO_2 is a non-polar solvent, although it has some affinity for slightly polar molecules. If polar molecules are to be extracted, the polarity of the solvent can be increased by adding a polar modifier. ESE is a liquid extraction technique that works under pressure. By performing the extraction under pressure, it is possible to increase the temperature to above the boiling point of the solvent, which will have a positive effect on analyte diffusion and solubility. The solvent should provide swelling of the matrix, which enhances the diffusion, and be a good solvent for the analyte. This can be achieved by mixing a non-polar with a more polar solvent.

The previously mentioned method in the European Pharmacopoeia involves a dissolution extraction method that is quite laborious.[1] In view of developments in extraction techniques, alternative ways of extracting Irganox 1076, Irgafos 168, and Irganox 1010 (Figure 1) from PP were investigated. SFE and ESE methods were investigated by means of chemometric software, and the optimum extraction recoveries of the three additives from the PP material were compared to the recoveries obtained with the pharmacopoeial method.

EXPERIMENTAL

Materials

The antioxidants Irganox 1010, Irganox 1076, and Irgafos 168 were obtained from Ciba Speciality Chemicals, Västra Frölunda, Sweden. Two batches of commercial grade polypropylene (PP), having the same degree of crystallinity and containing the same amount of antioxidants, were used in the experiments. The PP granules were freeze ground in a Retsch ultracentrifugal mill before extraction. The ground particles were sieved and those with a size of 0.43 to 0.80 mm were used.

Extraction Techniques

SFE and ESE were performed on the ISCO SFX 3560 automated supercritical fluid extraction system (ISCO, Lincoln, Nev., USA). It was equipped

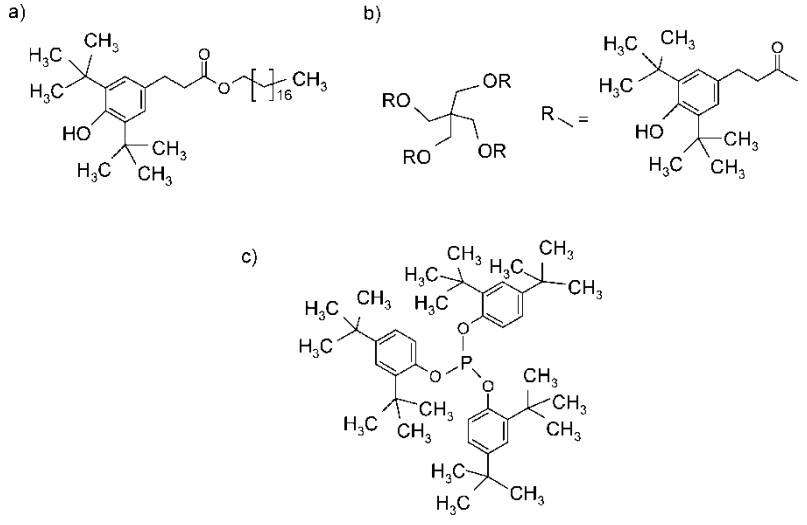

Figure 1. Molecular structure of a) Irganox 1076, b) Irganox 1010, and c) Irgafos 168.

with dual pump fluid delivery with a modifier addition and an automated restrictor. The extraction chambers had a volume of 10 mL and were made of PEEK.

Reference Method

The extraction results were compared to the results obtained with the method described in the European Pharmacopoeia.[1] According to the EP method, 2 g of the sample is boiled during reflux in toluene for 1.5 h. The solution is then allowed to cool to 60°C, after which methanol is added to precipitate the polymer. The solution is then filtered over a glass filter and the filtrate is kept for further analysis.

Liquid Chromatography (LC)

The LC analyses were performed on an Agilent 1100 HPLC system (Agilent, Kista, Sweden) using acetonitrile-ultrapure water (95:5, v/v) as eluent. The flow-rate was 1.0 mL/min and 20 μL was injected on a 3.9 × 50 mm, 5 μm Waters Symmetry C18 column (Waters Corporation, Milford, Mass., USA) operating at 50°C. The analytes and standards were dissolved in pure acetonitrile after ultrasonication for 1 h. A typical chromatogram from the LC analysis is shown in Figure 2.

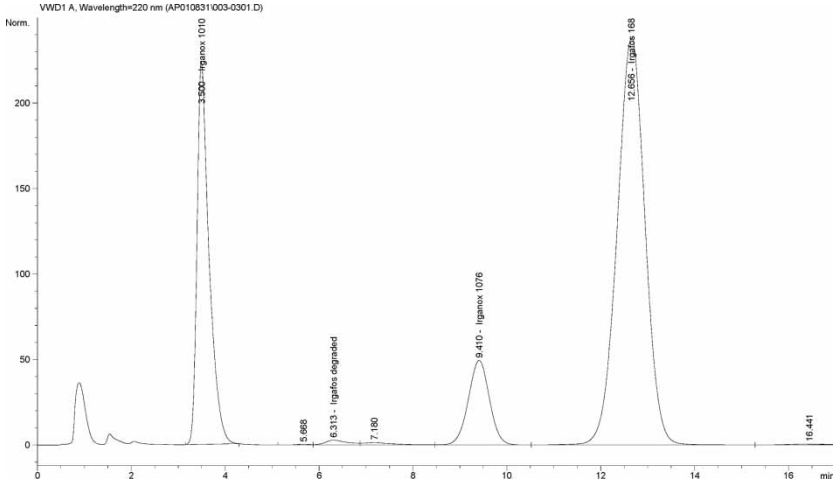

Figure 2. A typical chromatogram from an LC analysis of an extract. Column C_{18}, 5 μm particle diameter, 3.9 × 50 mm; column temperature 50°C; mobile phase acetonitrile-ultrapure water (95:5); flow rate 1 mL/min; UV detection 220 nm; injection volume 20 μL.

Chemometrics

The chemometric design and evaluation were carried out using the software package Modde 6.0 (Umetri, Umeå, Sweden).

RESULTS

Supercritical Fluid Extraction

The optimisation of the SFE parameters was divided into two separate parts: collection parameters and extraction parameters.

Optimisation of the Collection Parameters

Of the collection parameters, three were identified as most influential on the collection efficiencies. They were the collection temperature, restrictor flow rate (the flow rate with which the SF depressurises into the collection vial), and pressurised collection (slight pressurisation of the collection vial to reduce 'violent' depressurisation of the SF). A simplified extraction procedure was devised in order to reduce any influence on the extraction recoveries from the polymer matrix. Under this procedure, the additives as pure materials were added to a sand matrix and then extracted at 60°C at a pressure of 400 bar. Initial experiments had shown that using dichloromethane as collection solvent and using non-pressurised collection gave good recoveries. The results from optimising the collection parameters indicated that higher flow rates seem beneficial to the extraction efficiency of Irganox 1010. One reason for this result could be that this experiment is solubility limited, hence higher flow rates will reduce saturation of the SF. The other reason could be that Irganox 1010 needs higher flow rates to be transferred out of the extraction chambers since it is the most bulky antioxidant of the three. The latter explanation seems more viable since the other antioxidants (Irganox 1076 and Irgafos 168) display lower recoveries at higher flow rates, suggesting that the process is not solubility limited. Some of the results obtained from the experiment described above are summarised in Table 1. From the results, the higher restrictor flow rate and temperature were chosen.

Optimisation of the Extraction Parameters

The optimal SFE parameters were investigated by studying the influence of five different extraction parameters on the recovery. The parameters were pressure, temperature, percentage modifier, dynamic extraction time, and static extraction time. These are further described in Table 2. A set of experiments was performed where the parameters were varied between the maximum and minimum values shown in Table 2.

Table 1. Supercritical fluid extraction recoveries from three antioxidants added to a sand matrix. Extraction pressure and temperature were 400 bar and 60°C respectively. The values are an average of three extractions

Collection temperature	Restrictor flow rate	Average recovery (%)		
		Irganox 1010	Irganox 1076	Irgafos 168
2	1.5	78 ± 5	93 ± 1	97 ± 1
2	2	87 ± 1	91 ± 1	91 ± 3
30	2	86 ± 9	92 ± 3	91 ± 1

Toluene was chosen as the collection solvent since it displayed excellent solubility for all three antioxidants and has a reasonably high boiling point so that enough solvent remains in the collection vial, even at high restriction temperatures.

From the first set of experiments, the extraction temperature and pressure were identified as the most important parameters with optimum recoveries attainable when these parameters were set to maximum values. A further six experiments were performed and all data were fitted by partial least squares projections to latent structures (PLS) by the chemometric software. Figure 3 shows the coefficient plot for the three additives. The higher blocks in Figure 3 indicate greater influence of that parameter, while the negative heights mean a negative influence of that parameter. The plots are

Table 2. Maximum and minimum values of the SFE parameters

Parameter	Maximum value	Minimum value	Function
Extraction pressure	680 bar	160 bar	Pressure at which the extraction occurs
Extraction temperature	100°C	60°C	Temperature at which the extraction occurs
Modifier volume MeOH	10%	1%	Changing the concentration of modifier in the SF will vary the polarity of the SF and hence the solubility of the analytes
Dynamic extraction time	40 min	15 min	Time during which a continuous flow of SF passes through the extraction chamber
Static extraction time	30 min	15 min	Time during which the extraction chamber is filled with stationary SF

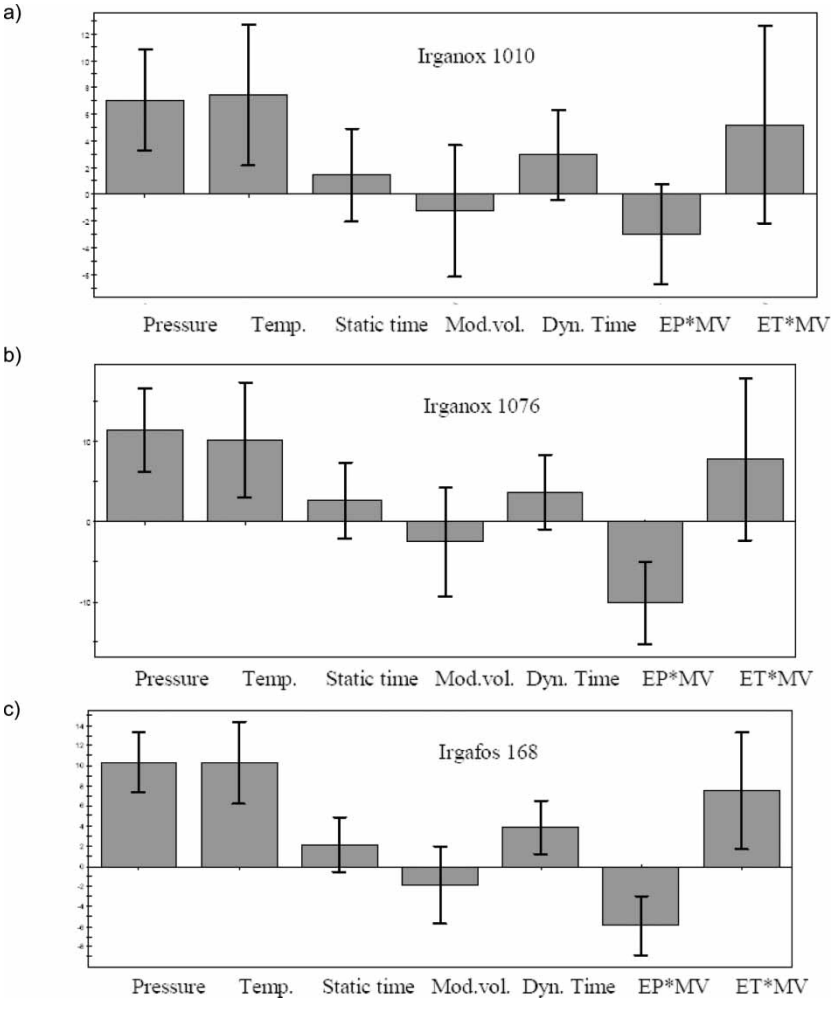

Figure 3. The effect of the SFE parameters on the recovery of a) Irganox 1010, b) Irganox 1076, and c) Irgafos 168. The two last variables are combinations of two separate variables: extraction pressure and modifier volume, and extraction temperature and modifier volume.

very similar for all three additives with the exception of Irganox 1010, which displayed poor reproducibility for the interaction terms. For all three additives, the extraction pressure and temperature are the most important parameters. Increasing both of these variables will result in higher recoveries. The evaluation shows that the same effect is also obtained by increasing the dynamic and static extractions, although their influence is less pronounced. The influence of the modifier volume does not seem to be significant. Performing

an extraction at the maximum values displayed in Table 3, which were an extraction pressure of 680 bar, extraction temperature of 100°C, modifier volume of 10%, dynamic extraction time of 40 min, and static extraction time of 30 min, gave the maximum obtained result with SFE. Figure 4 shows the extraction results compared to the pharmacopoeial method. At the maximum obtained recoveries, Irganox 1076 and Irgafos 168 are comparable with the recoveries from the pharmacopoeial method, but the recoveries for Irganox 1010 are slightly lower than obtained with the pharmacopoeial method.

Enhanced Solvent Extraction

In ESE there are fewer parameters to be optimised than in the SFE experiment. The variables that can be optimised are extraction solvent, extraction temperature, static extraction time, dynamic extraction time, restrictor flow rate, and maximum extracted volume. The instrumental setup used for these experiments allows a maximum volume of 15 mL to be extracted, therefore, the three last variables are interdependent. The restrictor flow rate depends on the dynamic extraction time and the maximum extractable volume. The dynamic extraction time and the restrictor flow rate should, therefore, be chosen in such a way that this maximum volume is not exceeded. It is thought that the restrictor flow rate and maximum extracted volume are not important variables since this process is not expected to be solubility limited (because of the low concentration of the additives). For this reason, varying the dynamic extraction time should not be critical. This leaves the extraction solvent, extraction temperature, and static extraction time as the most important ones. This is consistent with Lou et al. who found that

Table 3. Optimum SFE parameters

Parameter	Value	
Extraction pressure	680	bar
Extraction temperature	100	°C
Restrictor temperature	100	°C
Collection temperature	30	°C
Static extraction time	30	min
Restrictor flow rate	2.5	mL/min
Modifier volume	10	%
Dynamic extraction time	40	min
Solvent rinse	2	mL
Sample chamber wash time	60	s
Collection solvent	Toluene	
Modifier	Methanol	

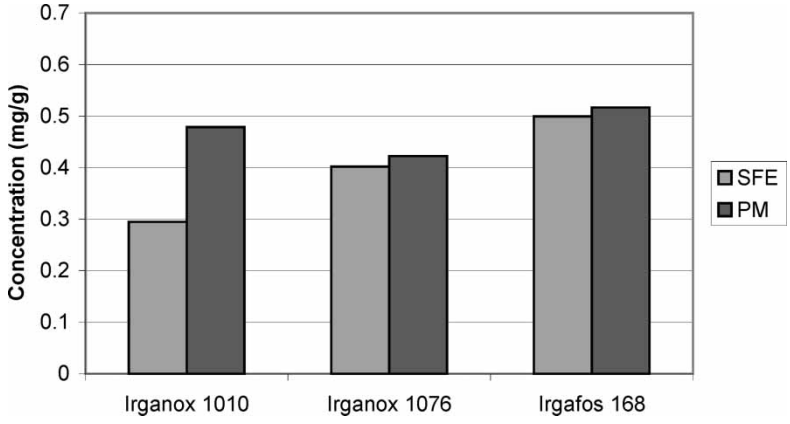

Figure 4. Obtained results from SFE at optimum conditions compared to results obtained with pharmacopoeial method (PM).

extraction solvent and temperature were the most important parameters.[14] An experimental design was used to identify the most important variables that would allow us to find the optimum extraction conditions. Table 4 displays the maximum and minimum values of the parameters that were optimised. A fractional factorial design, where the factors were varied at two levels with one centre point, was set up. All experiments were replicated three times. In the design, nine types of experiments had to be performed. As extraction solvent, a mixture of 2-propanol and cyclohexane was chosen. The choice of solvents was based on a paper by Vandenburg and coworkers in which a solvent selection procedure is described using Hildebrand solubility parameters.[9] A solvent mixture offers the advantage of having one solvent for the additives (2-propanol) and one swelling agent for the polymer (cyclohexane).

The experiments were evaluated by means of a multiple linear regression (MLR) model. The importance of the extraction parameters for the recoveries of the three additives is shown in Figure 5. From this figure, it is clear that the percentage of swelling agent is the most important parameter. The extraction

Table 4. Maximum and minimum values for the ESE parameters

Parameter	Maximum value	Minimum value
Extraction temperature (°C)	100	80
Restrictor flow rate (mL/min)	5	0.5
Static extraction time (min)	90	40
Amount of swelling agent in extraction solvent (%)	25	2.5

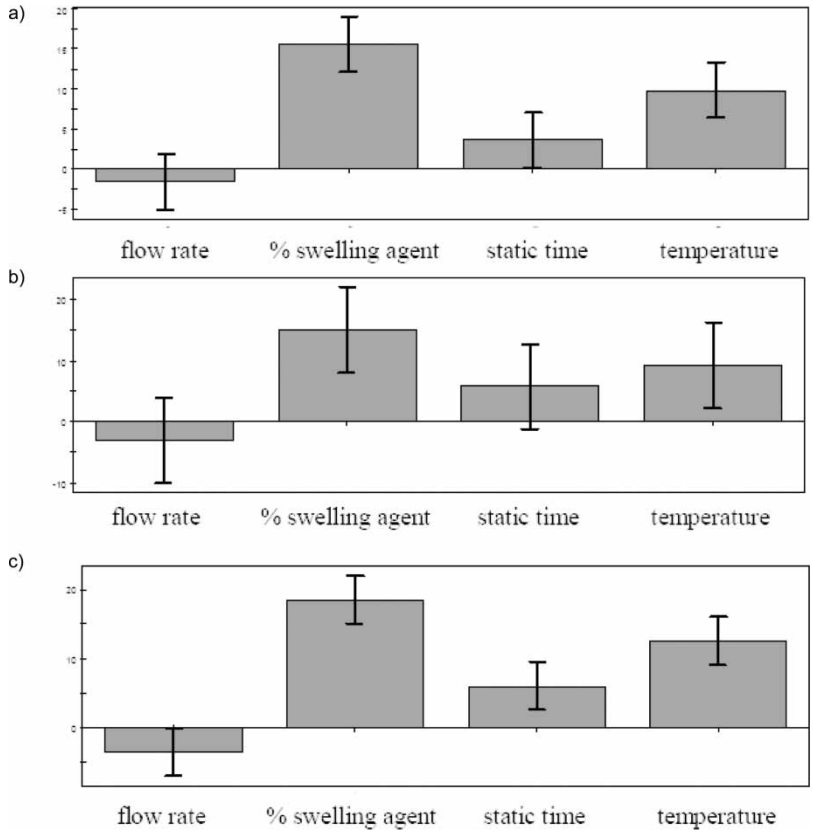

Figure 5. The effect of the ESE parameters on the recovery of a) Irganox 1010, b) Irganox 1076 and c) Irgafos 168.

temperature is also an important parameter, while the flow rate and static time only have a minor effect on the extraction recoveries. Figure 6 shows the response plot for the temperature and modifier volume for the three additives. This indicates that the optimum recoveries should be obtained at the highest temperature and modifier volume. The response plots for temperature vs. flow rate and static extraction time, respectively, are similar for all additives, and the plots for Irganox 1010 have been chosen to illustrate this (Figure 7 and Figure 8).

When the set of experiments was evaluated, we could see that a model containing interaction terms between flow rate and static extraction time, and between static extraction time and modifier volume would give a better model. The model also gave an indication of curvature, although this gave an overfitted model. However, when the obtained models were verified with another set of experiments, the best predictions were obtained with a

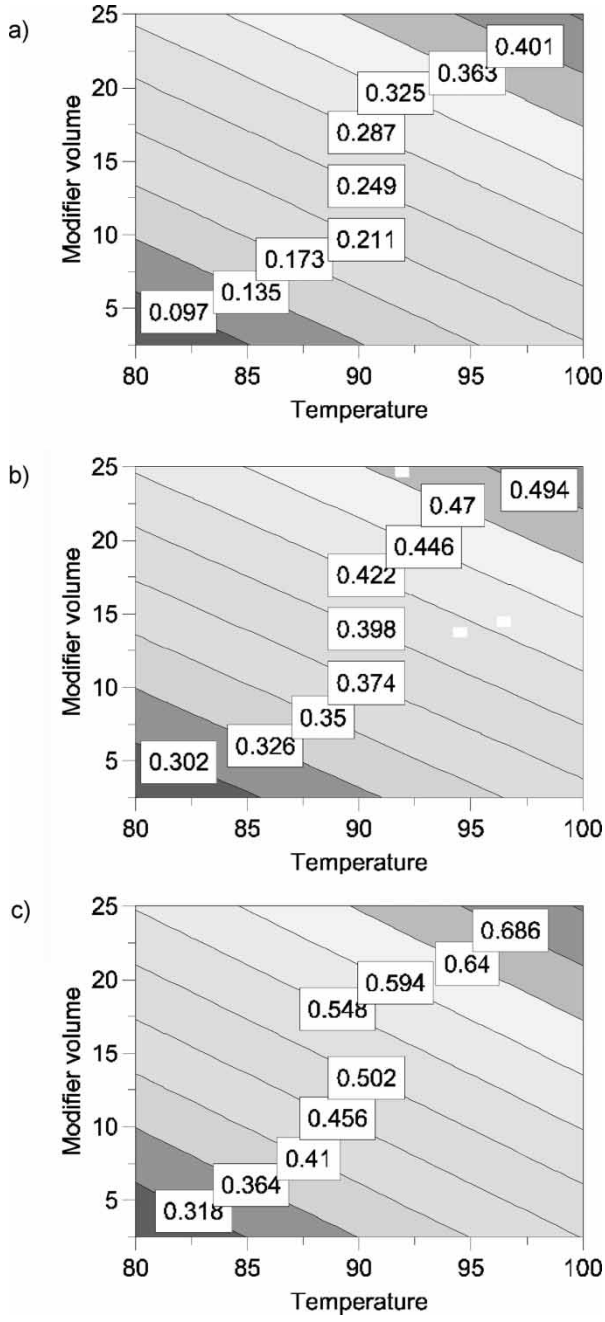

Figure 6. The response plot for temperature and modifier volume for a) Irganox 1010, b) Irganox 1076, and c) Irgafos 168. Flow rate is 0.5 mL/min and static extraction time is 90 min.

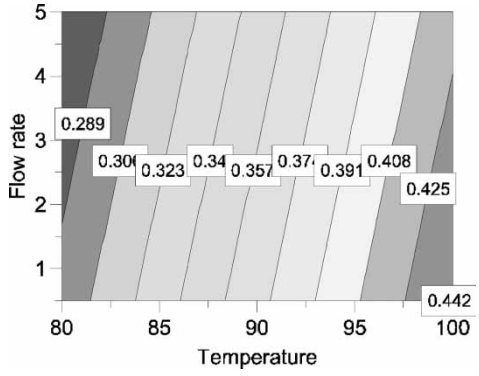

Figure 7. The response plot for temperature and flow rate for Irganox 1010. Static extraction time is 90 min and modifier volume is 25%.

model without interaction terms (Table 5). The result obtained also showed that the best recoveries were found when the factors were tested at their maximum values in the experimental design, i.e., a solvent mixture of 2-propanol–cyclohexane (75:25 v/v), an extraction temperature of 100°C, a flow rate of 5 mL/min, and a static extraction time of 90 min (Table 6). According to Figure 7, the maximum recovery should be obtained at a lower flow rate, although a slightly higher result was obtained at the highest flow rate than at the lowest. Figure 9 shows the result obtained for ESE at the best conditions compared to the pharmacopoeial method for extraction of the additives. The amounts of Irganox 1076 and Irgafos 168 extracted exceeded the amounts found with the pharmacopoeial method, although the recovery of Irganox 1010 was still a little bit lower than the amount found with the pharmacopoeial method. At and near the optimum

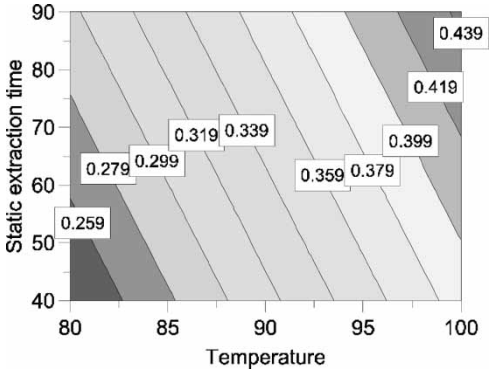

Figure 8. The response plot for temperature and static extraction time for Irganox 1010. Flow rate is 0.5 mL/min and modifier volume is 25%.

Table 5. Verification of ESE model by comparing obtained result with predicted. "Temp" is the temperature, "Flow" is the flow rate, "Stat time" is the static extraction time, "%CH" is the modifier volume, "exp." is the experimental value, "pred." the predicted value, "%" is the prediction error

				Irganox 1010			Irganox 1076			Irgafos 168		
Temp	Flow	Stat time	%CH	Exp.	Pred.	%	Exp.	Pred.	%	Exp.	Pred.	%
100	1	30	2.5	0.133	0.138	3.4	0.324	0.297	−8.5	0.342	0.342	0.1
100	0.5	60	2.5	0.191	0.174	−9.3	0.399	0.333	−16.7	0.445	0.403	−9.6
100	3	60	2.5	0.227	0.161	−29.1	0.401	0.315	−21.4	0.477	0.374	−21.6
100	3	60	25	0.326	0.397	21.6	0.364	0.462	27.2	0.509	0.653	28.2
100	0.5	90	25	0.435	0.443	1.9	0.445	0.513	12.7	0.630	0.736	16.8

Table 6. Optimum ESE conditions. IPA: 2-propanol, CH: cyclohexane

Parameter	Value	
Extraction pressure	140	bar
Extraction temperature	100	°C
Restrictor temperature	100	°C
Collection temperature	20	°C
Static extraction time	90	min
Restrictor flow rate	5	mL/min
Max. extr. volume	15	mL
Dynamic extraction time	3	min
Collection solvent	75/25	IPA/CH

extraction conditions, the reproducibility for Irganox 1076 and Irgafos 168 varied by less than 2% relative standard deviation (RSD), and for Irganox 1010 by 5% or less.

As the best conditions were found at the maximum ESE parameters tested, an extraction was performed at a higher temperature, 120°C, using the other maximum parameters as given in Table 4. At the higher temperature, a higher amount of Irganox 1010 was extracted than at 100°C, while the amounts of Irganox 1076 and Irgafos 168 were unchanged (Table 7). Unfortunately, at the higher temperature, the polymer sample partly melted and caused a system blockage. This means that it is difficult to achieve a higher recovery by performing extractions at a temperature higher than 100°C.

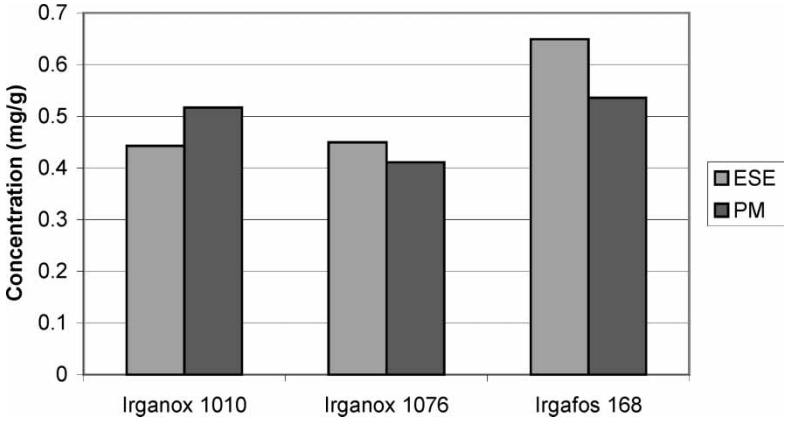

Figure 9. Obtained results from ESE at optimum conditions compared to results obtained with the pharmacopoeial method (PM).

Table 7. Comparison of extraction recoveries with ESE at 100°C and 120°C relative to the pharmacopoeial method

	Irganox 1010	Irganox 1076	Irgafos 168
100°C	86%	110%	123%
120°C	96%	109%	123%

DISCUSSION

Supercritical Fluid Extraction

For SFE, the recoveries for Irganox 1076 and Irgafos 168 almost reached the recoveries of the pharmacopoeial method (Figure 4). For Irganox 1010, the result obtained with SFE was a little lower than with the pharmacopoeial method. The poor recovery of Irganox 1010 has been noted by several authors.[15,16] It could be explained either by limited solubility of the additive or by limited diffusion. Figure 3 shows that the most influential parameters for reaching the optimum extraction were temperature and pressure. The temperature and pressure will influence the physical properties of the supercritical fluid, and the temperature will also influence the diffusion of the additives through the polymer matrix. Lou et al. studied the extraction of the same three additives from polyethylene (whether this was low- or high-density polyethylene was not specified) with SFE. They also found that Irganox 1010 was the most difficult to extract. They stated that such large molecules as Irganox 1010 are generally less soluble in supercritical carbon dioxide than smaller molecules, and that a temperature increase would more likely be a problem for the heavier solutes, as a temperature increase would give a supercritical fluid with poorer solubility.[17] As our recovery for Irganox 1010 had its maximum value at 100°C instead of at 60°C, the higher pressure that was used in our study (680 bar) gave better solubility than the highest pressure that was used in Lou's study (300 bar), which means that the solubility does not seem to be the limiting factor in our case. This is also consistent with the solubility of naphthalene referred to by Taylor, who says that the solubility decreased with increasing temperature at a pressure of 100 bar, but increased with temperature at pressures above 150 bar.[18] As in the present study, Baner found that the extraction of Irganox 1076 and Irganox 1010 from PP gave lower recoveries for Irganox 1010. This was explained by the lower solubility for high molecular mass species in supercritical fluids, or by the fact that the PP was not sufficiently swollen by the supercritical CO_2.[15] In our study, we used methanol as a modifier to the supercritical CO_2. This would give a solvent with more polarity and, thereby, result in better solubility of the additives, although according to Figure 3, the modifier volume added had a very small influence on the extraction recovery. Therefore, it is likely that the material is not sufficiently swollen to allow complete extraction

of the additives.[19,20] Clifford et al. studied the extraction of Irgafos 168 and Irganox 1010 from PP with SFE. In this study the maximum pressure and temperature used were lower than in our study, although at the higher pressures the two additives seemed comparable in their ease of extraction, as opposed to the results presented in our study. They reached almost a 100% recovery, but their extraction took place over a longer time period.[21]

Enhanced Solvent Extraction

The parameters that had the most effect on the extraction recovery when the extraction was performed with ESE were the amount of swelling agent and temperature for all three additives (Figure 5). The response plots indicate that the optimum recovery should be obtained at the lower flow rate (Figure 7), although the optimum condition was obtained at the maximum values tested. For Irganox 1076 and Irgafos 168, the recoveries were even higher than with the pharmacopoeial method (Figure 9). When Irganox 1076 was extracted with ESE from LLDPE using a mixture of ethyl acetate and hexane, the maximum extraction yield was obtained at 100°C and 45% hexane. At higher temperatures the polymer started to melt, similar to what was described for the present study.[22] Figure 9 shows that the maximum recovery obtained for Irganox 1010 was 86%, using a solvent mixture of 2-propanol–cyclohexane (75:25 v/v) at an extraction temperature of 100°C. When Vandenburg et al. extracted Irganox 1010 from PP, a recovery at 100% was achieved when they used 2-propanol at 120°C.[23] Mixing two different solvents can give a faster extraction. When the effect of adding cyclohexane to 2-propanol was studied, it was found that the fastest extraction was achieved using 2-propanol–cyclohexane (97.5:2.5 v/v) at 140°C.[24] In the present study, the highest recovery was achieved using 75% 2-propanol and 25% cyclohexane, although this was done at a lower temperature. When Marcato and Vianello investigated the extraction of PP using microwave assisted extraction, they managed to extract almost 100% of Irganox 1010 at 125°C with ethyl acetate–n-hexane (75:25 v/v). They concluded that extraction from polymers with a crystalline structure, such as PP, is the most difficult and that Irganox 1010 is a compound that shows quite slow extraction.[25] In spite of the difficulties of extraction from PP, Freitag and Johan achieved almost complete extraction of Irganox 1010 from PP, HDPE, and LDPE within 3 to 6 minutes, using either 1,1,1-trichloroethane or a mixture of acetone–n-heptane at 420 W microwave power.[26]

As an alternative to the pharmacopoeial method, both SFE and ESE can be used to extract Irganox 1076 and Irgafos 168 from PP, although ESE is simpler to use, and it even gave a higher recovery than the pharmacopoeial method. For Irganox 1010, the pharmacopoeial method gave a better recovery than both SFE and ESE. The best recovery of Irganox 1010 was obtained with ESE. Extracting a very bulky analyte such as Irganox 1010

from a semi-crystalline polymer like PP is indeed a challenge, and the best conditions are likely to be very close to the temperature of partial melting of the lower molar mass fractions of the polymer. Small variations in the polymer samples could, therefore, cause problems when working on the edge. Consequently, flow extraction techniques such as ESE and SFE are less robust and system blockage could easily occur.

CONCLUSION

SFE and ESE were optimised to extract Irganox 1076, Irgafos 168, and Irganox 1010 from PP. The best recovery with SFE was obtained with a pressure of 680 bar, at 100°C, 10% methanol as modifier, and dynamic and static extraction times of 40 and 30 min, respectively. The optimum of ESE was obtained at an extraction temperature of 100°C, with a restrictor flow rate of 5 mL/min, and static extraction time of 90 min, using a solvent mixture of 2-propanol–cyclohexane (75:25 v/v). The best result for the extraction of Irganox 1076 and Irgafos 168 were comparable to the pharmacopoeial method, and even better for ESE. Irganox 1010 was more difficult to extract and the best recovery (86%) was obtained with ESE. The need to operate at fairly high temperatures is a drawback of both methods as it increases the risk of melting the sample, thereby causing a system blockage. This is an obstacle that needs to be considered carefully for use of either of the methods as a routine control.

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