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Microwave-assisted extraction of felodipine tablets☆

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Abstract

A microwave-assisted extraction (MAE) method was developed to determine felodipine and its degradation product H152/37 in tablets. These substances were present at different concentration levels, differing with a factor of ca 600. The choice of extraction solvent was found to be of great importance. The optimized solvent consisted of 5% methanol in acetonitrile. Methanol was capable of dissolving the outer covering layer. Acetonitrile made the inner matrix swell, fragmenting the tablet into small pieces releasing the analytes. Temperature was also of great importance and 80°C was needed to get a method with acceptable precision. At lower temperatures tablet cracking was incomplete for some units. Another advantage using a higher temperature was that shorter extraction times could be used. For instance, at 80°C, an extraction time of 10 min was sufficient. With the final method 99.0%, and 99.2% was extracted of felodipine and H152/37, respectively, compared to values obtained with a validated ultrasonication method. The developed method involves a minimum of manual operations, since whole tablets can be directly used for the extraction. The method can be used for single tablets as well as for ten tablets. This enables use of the method for determining individual tablet variation, while also giving an average value of the drug amount in a tablet batch.

Keywords: Extraction methods; Microwave-assisted extraction; Pharmaceutical analysis; Felodipine; H152/37

1. Introduction

In microwave technology, destructive sample preparation methods, such as digestion and mineralization are the most widely used and these methods are well documented in the literature [1,2]. During the last 4–5 years there has been an increased interest in microwave-assisted extraction (MAE) as a replacement for Soxhlet extraction, or as an alternative to modern extraction techniques, like supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE; Dionex trade name, Accelerated Solvent Extraction). In several recent papers the merits of this new techniques are compared [3–5]. Some of the basic characteristics of MAE has been presented by Renoe [6,7] and Paré et al. [8]. One of the fastest growing areas with respect to the use of MAE, is for the analysis of environmental samples [7], reflected by extraction of phenols [9,10], imidazolinone herbicides [11,12], polycyclic aromatic

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hydrocarbons [3,13–15], polychlorinated biphenyls [14,15], organochlorine pesticides [14,15] and methylmercury [16] from matrices like soils, sediments and plant tissue. Other areas where MAE has been utilized is for the extraction of growth promotors in swine tissue [17], ergosterol and fatty acids in fungi [18], oligomers from PET [19], drug metabolites in rat faeces [20] and oils and greases in waste water [21].

A major field in analytical chemistry dealing with sample preparation on a routine basis is the pharmaceutical industry, but so far relatively few papers have been published in this area using MAE. Bouhsain et al. recently presented a system for on-line determination of paracetamol in different pharmaceuticals by microwave-assisted hydrolysis [22], and Lozak and Fijalek have used microwave digestion and flameless ASA to determine selenium in tablets [23].

The aim of this work was to develop a robust method for the determination of drugs in a solid tablet matrix based on microwave-assisted extraction, and to compare the developed method with previous methods based on SFE [24] or PLE [25]. The developed method should be free from artifacts, i.e. no degradation should occur during the extraction and the recovery should be high also for the possible degradation products.

Felodipine and its degradation product H152/37 were used as model substances. Delivered tablets, previously exposed for stability tests, contained felodipine and H152/37 in widely differing concentrations (ca. 600:1).

2. Experimental

2.1. Equipment

A microwave-assisted extraction unit, (MSP 1000; CEM, Matthews, NC, USA) was used for extraction of analytes from tablets. Maximum oven power for this system is 1000 W. For ultrasonication experiments a Branson 3200 ultrasonication bath (Kebo Lab, Spånga, Sweden) was used. All extracts were centrifuged at room temperature with a Wifug X-1 (Tillquist Analys, Kista, Sweden) and analyzed by a LC system consisting of a Waters 501 LC pump (Waters Associates, Milford, MA, USA), a Kontron MSI 660 autosampler (Kontron Instruments, Milan, Italy) equipped with a 10-μl injection loop, and a LDC Spectromonitor III (Division of Milton Roy, Riviera Beach, FL, USA) with the wavelength set to 240 nm. A reversed-phase ODS column (Nova-Pak C_{18} 60 Å, 4 μm, 150×3.9 mm, Waters) was used in the analysis. Chromatographic data were collected with Borwin chromatographic data system software, version 1.21 (JMBS Developments, Le Fontanil, France) on a personal computer (Hewlett-Packard 486/50 VL). Excel 97 (Microsoft, Redmond, WA, USA) was used for calculations and KaleidaGraph version 3.08 (Synergy Software, Reading, PA, USA) for graphic presentation.

2.2. Chemicals

Tablets containing felodipine and its degradation product H152/37 were obtained from Astra Hässle (Mölndal, Sweden). Felodipine and H152/37 standards were received from the same source. Carbazole (internal standard, I.S.) was purchased from Sigma (St. Louis, MO, USA). The chemical structures of felodipine, H152/37 and carbazole are presented in Fig. 1. Methanol (HPLC grade) and acetonitrile (HPLC grade) were delivered by Lab Scan (Dublin, Ireland). All water used was of analytical-reagent quality or better. Ethanol (95%) was delivered from Kemetyl (Stockholm, Sweden). Ortho-phosphoric acid (85%, analytical-reagent quality), sodium dihydrogenphosphate monohydrate (analytical-reagent quality) and sodium hydroxide (analytical-reagent quality) were obtained from Merck (Darmstadt, Germany).

Stock standard solution of felodipine was prepared by dissolving 1.0 mg/ml in ethanol and for carbazole (IS) by dissolving 3.0 mg/ml in methanol. All solutions were stored in darkness at 8°C to prevent degradation.

The mobile phase for LC was prepared by mixing acetonitrile–methanol buffer (4:2:4, v/v/v) (routine LC method) or alternatively (2:4:4, v/v/v) (developed LC method) run at a flow rate of 1 ml/min. The latter mobile phase had to be used to separate H152/37 from a carbazole impurity which coeluted using the former mobile phase, which was not designed to be used with carbazole as internal

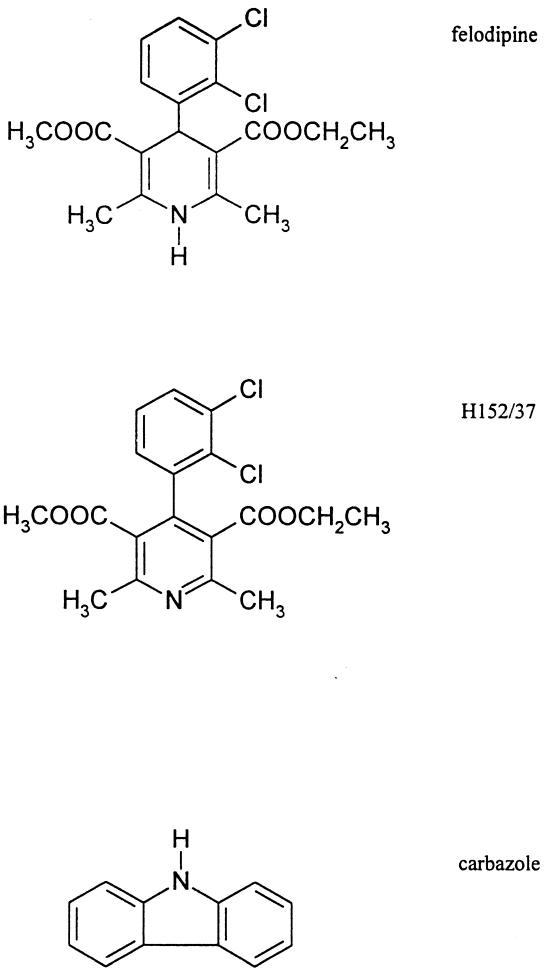

Fig. 1. Chemical structure of felodipine, the degradation product H 152/37, and carbazole (internal standard).

standard. The buffer was made by mixing 100 ml of sodium dihydrogenphosphate (1 *M*) with 15 ml of phosphoric acid (1 *M*), and diluting the mixture to 2 l with water. The pH value was checked to be in the interval 3.0±0.1, and if necessary adjusted with sodium hydroxide or phosphoric acid. The mobile phase was degassed for 10 min in an ultrasonic bath prior to use. The routine LC mobile phase is used, throughout, except in experiments performed to include the determination of H152/37. In neither case does the composition of the mobile phase affect the quantitation of felodipine. A comparison of chromatograms obtained using these two mobile phases is made in Fig. 2.

2.3. Procedures

With the MSP 1000 system, organic solvent extractions can be performed safely and conveniently. The system has a solvent detector to turn off microwave energy in the presence of residues of flammable organic solvents. During a run the current pressure and temperature conditions versus time is visualized. A graph showing the conditions during the entire procedure can be recalled and printed upon completion of a run. The MAE unit is capable of running a maximum of 12 sample vessels simultaneously, one of them being a reference vessel controlling heat and pressure. In all experiments 100 ml lined extraction vessels (LEVs) of PTFE (CEM) were used, certified for pressure up to 200 p.s.i. and temperature up to 200°C (1 p.s.i.=6894.76 Pa).

The development work was performed on single tablets in extraction vessels with 10 ml of solvent. After placing a new rupture membrane, the extraction vessel was closed and the operating steps started at 100 W microwave oven power for three and five vessels present in the oven or 300 W power for 12 vessels. The different power settings oven chosen to give similar heat up times when having different number of vessels present in the oven. In all cases the heat up time represented a minor proportion of the total extraction time. When extraction time was completed the extracts were allowed to cool below 35°C before the vessels were opened. 1.0 ml of internal standard solution (carbazole concentration 3.0 mg/ml) was added and after stirring, the extracts were quantitatively transferred to 20-ml centrifuge tubes. The extracts were centrifuged at 4000 rpm for 10 min. The supernatant was diluted with mobile phase in the proportions 1:5 (v/v) prior to LC analysis. At a later stage of the development work, ten tablets were used for the extraction with a final solvent volume of 15 ml. When extracting ten tablets per vessel, oven power was increased to 500 W and the supernatant was diluted 1:33 (v/v).

A reference solution containing 0.20 mg/ml felodipine and 0.055 mg/ml carbazole was prepared from the two stock standard solutions of felodipine and carbazole by diluting them with mobile phase.

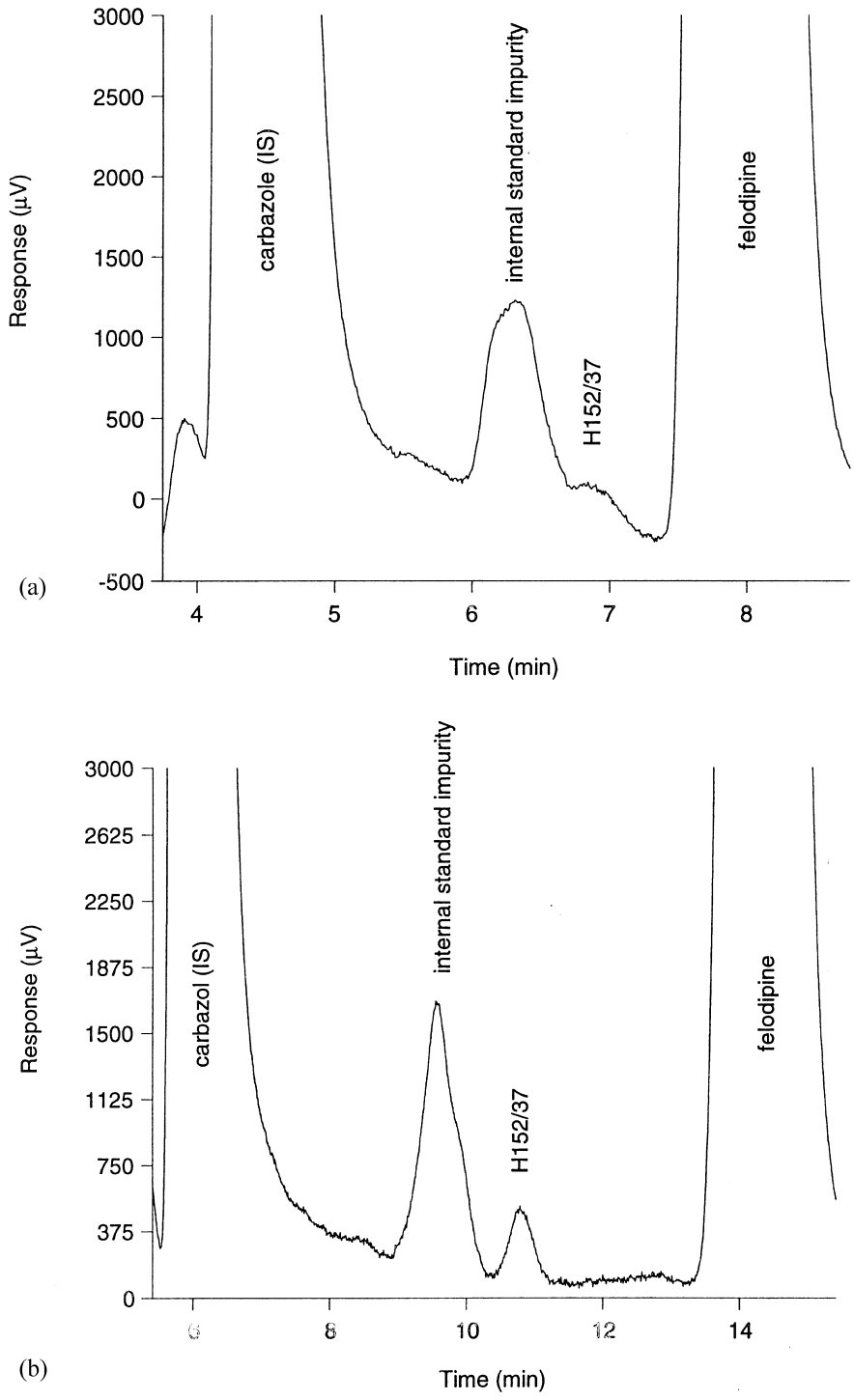

Fig. 2. Comparison of chromatograms using two different mobile phases; acetonitrile–methanol buffer in different proportions; (a) (4:2:4, v/v/v); (b) (2:4:4, v/v/v).

The reference solution was analyzed in duplicate before and after each series of extracts to calculate the value of the response factor (F_x). The contents of felodipine in the extract could then be quantified by multiplying the F_x value with mass of I.S. and ratio of peak area$_{\text{felodipine}}$/peak area$_{\text{I.S.}}$. The detection of felodipine and carbazole was linear in the range of 0.020–0.40 and 0.010–0.15 mg/ml with R^2 values of 0.997 and 0.996, respectively.

Validation was done against a routine method based on ultrasonication. Here ten tablets are pulverized in a mortar and an aliquot of 0.2 g tablet powder is transferred to a 50 ml volumetric flask. After adding 20.0 ml of acetonitrile and 10.0 ml methanol the flask is placed in a ultrasonic bath for 5 min. A total of 15.0 ml of a buffer (pH 3) is added to each flask and the flask is ultrasonicated for another 30 min. After completion the volume is adjusted to 50 ml with buffer. Internal standard is added and the extract is filtered using Millex-SR 0.5-μm filters (Millipore, Molsheim, France) prior to final LC analysis. In this work ten subsamples from the pulverized tablets was used for the assay, while the normal procedure only includes determination in duplicate.

3. Results and discussion

3.1. Comparison of different extraction solvents and temperatures

The first step in the method development was a comparison of different solvents and temperatures. Since the routine ultrasonication method utilizes a mixture of acetonitrile (ACN) and methanol (MeOH) these solvents were here investigated separately as well as in a mixture with the proportions 2:1 (v/v). In these experiments the temperature was set to 30, 40, 60 or 80°C. Four different extraction times were examined, 10, 20, 40 and 60 min. The results are presented in Table 1.

The data in Table 1 reveals several interesting characteristics regarding the extraction. In some cases (marked in bold Characters) it was possible to get close to 100% recovery.

3.1.1. Methanol

A visual inspection of the samples showed that when extracting with methanol at higher temperatures (60–80°C), a part of the inner matrix of the tablet was found on the bottom of the extraction

Table 1
The recovery and relative standard deviation (R.S.D.) of felodipine from tablets using microwave extraction with different solvents and temperatures (n=3): conditions giving approximately 100% recovery are marked in bold characters

Solvent	Extraction time (min)	Temperature (°C)							
		30		40		60		80	
		Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)
MeOH	10	91	6	90	3	50	41	55	14
	20	**96**	**2**	**97**	**2**	74	7	66	10
	40	**99**	**3**	**97**	**1**	81	16	81	7
	60	93	2	93	2	80	9	88	4
ACN	10	65	43	29	6	36	5	**102**	**3**
	20	55	59	44	3	66	35	**96**	**1**
	40	64	45	68	36	83	19	88	10
	60	83	30	75	5	80	14	94	1
ACN–MeOH (2:1)	10	20	9	28	7	37	13	75	8
	20	60	27	59	29	70	30	**96**	**1**
	40	90	18	86	23	81	4	93	3
	60	91	6	90	7	88	3	95	2

vessel as a highly viscous residue and another fraction was floating in the methanol phase. This can probably explain why recoveries never exceeded 90% even at extraction times up to 60 min, as felodipine probably is trapped inside the viscous residue, giving long diffusion times out to the bulk solvent. A striking result is that methanol at low temperature (30°C) was capable of extracting 96% of the felodipine in 20 min. This is probably explained by the fact that in these extractions the temperature was too low to substantially change the interior of the polymer matrix. The matrix instead appeared in a solid state as small flakes, thereby releasing the analyte. It should be pointed out that methanol was capable of dissolving the outer covering layer of the tablet at all temperatures investigated. A slight decrease in recovery could be seen when using pure methanol with an extraction time of 60 min at 40°C. This is explained by increased solvation of the polymer matrix at longer extraction times, causing an increase in viscosity. This was tested by running an extraction for 120 min. The recovery then remained on a similar level (91%, R.S.D. 4%, $n=3$).

3.1.2. Acetonitrile

In the case of acetonitrile, the outer layer could not be dissolved, but acetonitrile made the tablet interior swell (doubling the tablet size), and in most cases the outer covering layer cracked releasing the inner matrix and the analyte. In some samples the cracking was incomplete and the analyte had to diffuse through both the internal matrix and the uncracked covering layer, leading to lower recoveries for the chosen extraction time. This is reflected by the high R.S.D. values in some of the columns in Table 1 (especially at 30–60°C), which by visual inspection in all cases could be tracked back to incomplete cracking in some of the three subsamples. In these cases a nearly intact tablet was seen with the only difference being the enlargement of the tablet. In the cases when the tablet was cracked by the swelling of the inner matrix, the tablet inner matrix was released in a solid state leaving the solvent totally clear even at high temperatures.

ACN and ACN–MeOH mixture at 30 and 40°C showed low recoveries and high R.S.D. values which can be explained by the tablet behavior discussed above. The only recoveries comparable to low temperature methanol extraction are those obtained for pure ACN and ACN–MeOH mixture at 80°C. However pure ACN still suffers from uncertainties regarding the cracking of the outer covering layer. The low value (88%) after 40 min, extraction is due to the fact that one of three tablets was not cracked, giving a recovery of this subsample of only 78%. Good recoveries were obtained with the ACN–MeOH mixture at the high temperature, at least for the 20-min run.

3.2. Solvent optimization

Findings regarding the solvating process using the two different solvents (methanol dissolving outer layer and acetonitrile swelling inner matrix) as well as the fact that a mixture of them in some cases gave high recoveries, lead to a closer investigation of such mixtures. The goal was to find a concentration of methanol capable of dissolving the outer layer, but still not dissolving the tablet core to a highly viscous form at the high temperatures that might be needed to speed up the extraction process. The recovery of felodipine using different concentrations of methanol in acetonitrile can be seen in Fig. 3. Extraction time was set to 60 min, and extraction temperature to 60°C, with three replicates at each concentration.

It can be seen that the recovery increases when the amount methanol is decreased from 50% down to 5%, where 94% of the felodipine is recovered. Slightly lower recovery at 10 and 1% indicated that there might be a maximum in the recovery in the concentration range of 1–10% of methanol in acetonitrile. The results of a more detailed investigation in this concentration range are shown in Fig. 4. In these experiments the extraction time was decreased to 20 min, since preliminary experiments had shown that this would be sufficient.

From Fig. 4a it can be seen that about 96% recovery was achieved in the entire interval 4–10%, with low R.S.D. values (1–2%). In all these cases the tablet outer layer had been dissolved, and the inner matrix released by a swelling process. These low methanol concentrations did not dissolve the polymer matrix, which probably explains the high recoveries. Also in subsamples with low concentrations (below 4%) of methanol in acetonitrile one

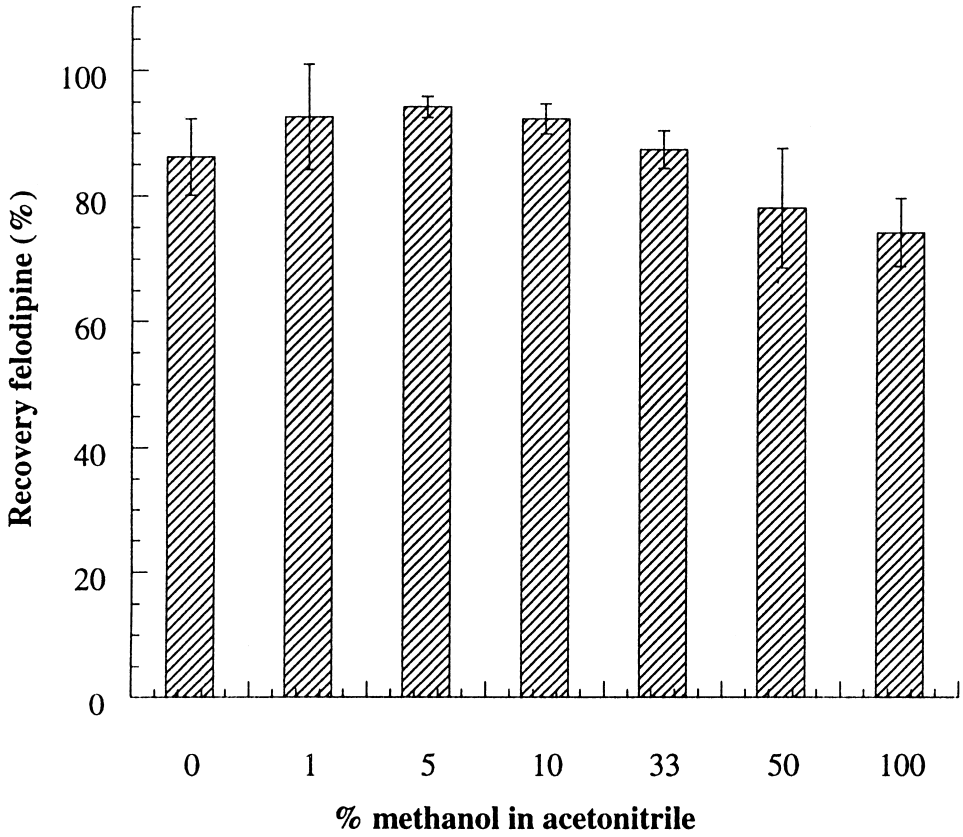

Fig. 3. The recovery of felodipine using different concentrations of methanol in acetonitrile. Extraction time, 60 min; extraction temperature, 60°C; $n=3$.

had occasionally high recoveries approaching 100%. The reason for the large R.S.D. values in this interval is that the outer layer is less efficiently dissolved for one or more of the different tablets. As discussed earlier this decreases the mass transfer rate of the analyte out into the bulk solution. The uncertainty of this solvating process at low methanol concentrations makes lower concentrations than ca 4% unacceptable for routine analysis.

Accordingly, the influence of temperature on recovery was further investigated for methanol concentrations above 4%. The results in Fig. 4b show that 5–10% of methanol at 40°C gives recoveries of ca 100% and low R.S.D. values (<2%). Fig. 4c shows that about 100% recovery and low R.S.D. values are obtained in the whole interval of 5–10% of methanol at 80°C. (Average value 98% and corresponding RSD value 0.7%.)

3.3. Extraction time optimization

In an attempt to decrease the extraction time, a mixture with 5% of methanol in acetonitrile was extracted at 40, 60 and 80°C. The results are shown in Table 2.

High recoveries were obtained in all cases except for a 3-min extraction at 40°C. This was due to one uncracked tablet, giving in this case an incomplete extraction. To test the reliability of using a temperature of 40°C, a full rack of 12 tablets was extracted for 10 min. The recovery obtained was 93.4% with an R.S.D. of 15% ($n=12$). This relatively low recovery was again caused by one tablet being uncracked. Thus 40°C is too low a temperature to be used on a routine basis. Looking at the 60 and 80°C values it was possible to get a quantitative extraction at extraction times down to 1.5 and 3 min, respec-

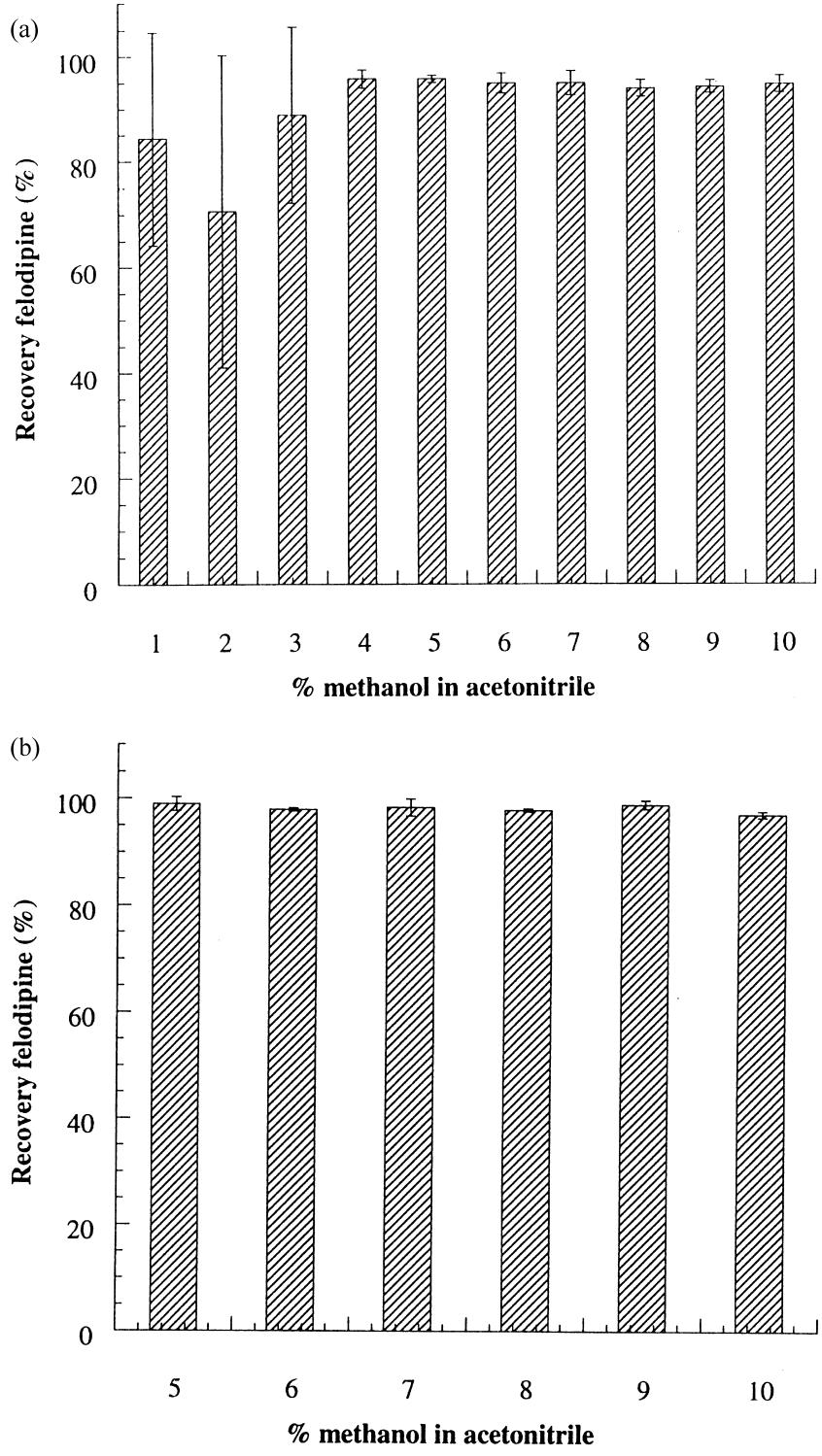

Fig. 4. The recovery of felodipine using different concentrations of methanol in acetonitrile. Extraction time, 20 min; extraction temperature; (a) 60°C, $n=5$; (b) 40°C, $n=3$; (c) 80°C, $n=3$.

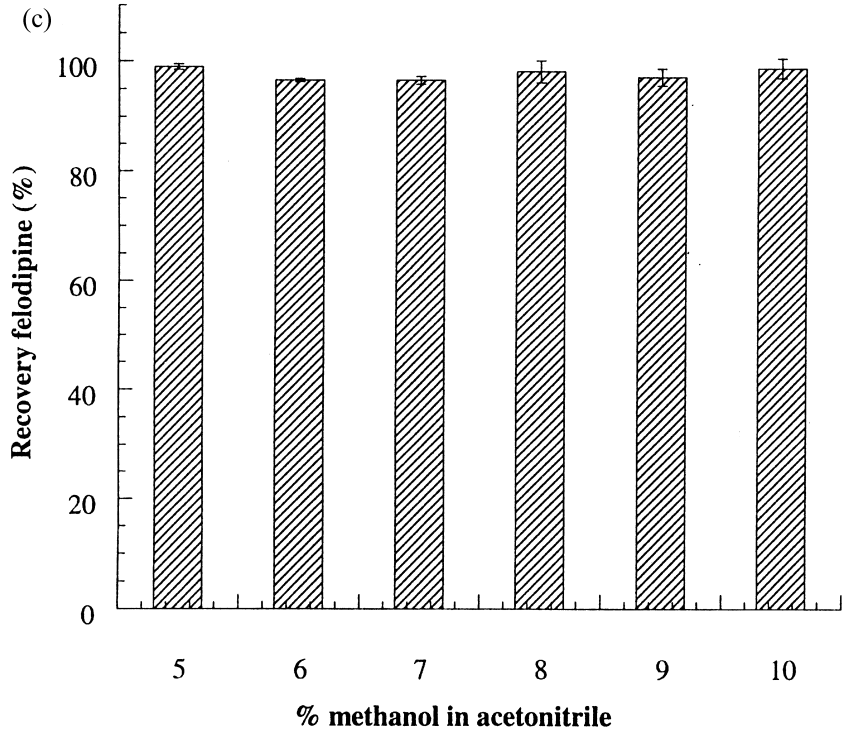

Fig. 4. (*continued*)

tively. These were the lowest times possible in order to reach the specified temperature. To test the reliability of the method at these higher temperatures once again 12 vessels were loaded with tablets. For 60°C two extractions were made at 3 and 10 min. The recoveries were 98.2% (R.S.D. 4.0%, $n=12$) and 98.8% (R.S.D. 1.4%, $n=12$), respectively. The 80°C extraction was performed for 5 min giving a recovery of 98.9% (R.S.D. 1.0%, $n=12$). This demonstrates that the reliability of the method is increased when temperature is increased from 40 to 60 or 80°C. It might also be preferable to use an extraction time of 10 min if 60°C is to be used compared to 5 min at 80°C.

One disadvantage using 80°C is that the cooling time is increased from 10 min (60°C) to 20 min. This

Table 2
The recovery and relative standard deviation (R.S.D.) of felodipine from tablets using microwave extraction with 5% methanol in acetonitrile and different temperatures ($n=5$)

Extraction time (min)	Temperature (°C)					
	40		60		80	
	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)
0.5	95	3				
1.5	96	5	98	1		
3	78	27	99	2	100	3
5	98	3	101	1	99	1
10	99	1	99	1	100	2
15					99	1

also means that the shorter extraction time needed at 80°C (5 min) compared to the 10 min using 60°C can partly be caused by the longer cooling time. To test this and also to shorten the sample handling time, two new experiments were performed when the extracts were cooled on ice for 2 min immediately after the extraction. This time was checked to be long enough to lower the temperature below 35°C in both cases. The recoveries for the 60°C, 10 min extraction and the 80°C, 5 min extraction were 98.1% (R.S.D. 1.5%, $n=12$) and 98.4% (R.S.D. 1.9%, $n=12$), respectively. No difference could be observed, indicating that the 80°C extraction is preferred since this gives a shorter total time of 7 min compared to the 60°C extraction, where a 12-min extraction is needed. It is also unlikely that a tablet will stay intact at a higher temperature, which is important considering the results above. This have clearly demonstrated that there are differences in the resistance toward breakage between different tablets.

3.4. Evaluation of final method

In order to test the optimized extraction method (80°C, 5% MeOH in ACN, 5-min extraction time and 2-min ice cooling) more extraction data were collected. In this case the developed LC mobile phase described above was used in order to determine not only felodipine, but also H152/37. Running two racks with a total number of 24 vessels gave a recovery of felodipine of 97.6% (R.S.D. 3.7%, $n=24$) and of H152/37 of 99.8% (R.S.D. 8.5%, $n=24$). The similar recoveries obtained for the active compound and its degradation product confirms that the initial ration (600:1) remains unchanged after microwave processing. The tendency to decreased extraction efficiency compared to the above 80°C (5 min) value of 98.4% is explained by some tablets not being totally cracked (visually observed), which is also expressed by the relatively high R.S.D. value. This demonstrates that 5 min is too short an extraction time, when determination of long series is to be made. Hence, two new racks were run with a total extraction time of 10 min which was the final method.

The recoveries of the final method were normalized against the values determined by the routine method, which for felodipine was 10.10 mg (R.S.D. 1.1%, $n=20$) and for H152/37 was 0.171% (R.S.D. 8.3%) expressed as peak area percent of felodipine peak area. The final MAE method gave a recovery of 99.0% (R.S.D. 1.5%, $n=24$) for felodipine and 99.2% of H152/37 (R.S.D. 5.3%, $n=24$).

The R.S.D. values for the degradation product H152/37 are higher than for felodipine due to the fact that it is determined near the limit of quantitation. The precision can be improved by avoiding dilution before analysis. However, because of the large differences in concentrations between felodipine and the degradation product this would require duplicate analysis of each sample.

It is possible to compare MAE values for felodipine with results obtained utilizing PLE [25] or SFE [24]. With PLE 98% (R.S.D. 4%, $n=10$) [25] of the felodipine could be extracted in 20 min at 50°C with acetonitrile as solvent, including a 5 min pre-extraction step. Using SFE a recovery of 98.6% (R.S.D. 1.2%, $n=5$) [24] was obtained with an extraction time of 80 min using 8% methanol as modifier. However in both cases only one sample can be run at a time compared to the 12 vessels simultaneously extracted using MAE.

This clearly demonstrates that MAE is a very promising alternative to other modern extraction methods, and to existing traditional liquid extraction methods for drug determination in tablets. It should be noted, however, that a comparison with the traditional liquid extraction method might be somewhat unfair since there is a possibility that these methods are not always completely optimized. Improvement of the ultrasonication method is not covered within the frame of this work, but ultrasonication might be interesting as a straightforward alternative to increased sample throughput.

3.5. Multi-tablet extractions

The possibility of extending the single tablet method, which gives a value of the within tablet variation of felodipine in a batch, towards determining the average felodipine value of a batch was investigated by adding ten tablets in the extraction vessel. Preliminary extractions demonstrated that the extraction solvent volume for ten tablets in one vessels should be somewhere between 10 and 30 ml. In volumes larger than 30 ml some of the tablets did

not crack giving very low recoveries, probably due to inadequate stirring of the solvent by the microwaves at larger volumes. At low solvent volumes the tablets do crack, however the extract is highly viscous which, just as described above, slows down the kinetics of the extraction process by trapping some of the analytes inside the matrix. The results from three different solvent volumes in this interval (15, 20 and 25 ml) and two extraction times are presented in Table 3.

Quantitative recovery was obtained with the smallest solvent volume (15 ml) and the longest extraction time (20 min). This final multi-tablet extraction method was evaluated by a total of 60 tablets divided into six vessels. The recovery of felodipine was 99.6% (R.S.D. 1.7%, $n=6$) and of H152/37 94.8% (R.S.D. 8.2%, $n=6$).

3.6. Extraction of stressed tablets

Tablets were stored at 50°C for 1 month and extracted using both the single tablet, and the multi-tablet method. For the single tablet method, the recovery of felodipine was 98.9% (R.S.D. 1.2%, $n=24$) and of H152/37 96.2% (R.S.D. 8.5%, $n=24$). Corresponding values for the multi-tablet extraction were 99.9% (R.S.D. 0.6%, $n=6$) and 99.4% (R.S.D. 3.5%, $n=6$).

This clearly demonstrates that the conditions chosen are capable of quantitatively extracting felodipine and its degradation product even from stressed tablets.

3.7. Sample throughput

With MAE 12 tablets can be extracted simultaneously in 20 min. However working time for the preparation of samples before extraction, further sample handling after the extraction and washing of the used vessels is estimated to some 40 min. This means that about 120 samples can be processed by MAE each day. Hence, the throughput will normally be determined by the subsequent LC analysis. Every LC run takes some 18 min and with duplicate determinations and autosampler 40 samples can be analyzed on one LC setup. Thus, to handle all the samples processed in MAE during a working day at least three pieces of LC equipment are needed. The manpower needed for these 120 samples is estimated to 8 h.

The MAE procedure can be compared to PLE with a throughput of 40 samples/day with a manpower requirement of about 6 h [25]. A similar estimation for SFE would be 16 samples/day [24] (extraction time, one sample/h and running a new eight-sample carousel overnight). The manpower requirement/sample will be similar or slightly higher than using PLE. This means that manpower requirement will be ca. 2.5 h for the SFE procedure.

The manpower requirement for one sample will be ca. 4 min for MAE and 9 min for PLE and SFE. Thus, the MAE procedure will in this case give both considerably higher sample throughput and lower manpower requirement/sample.

4. Conclusions

The developed MAE method is robust and can be used for determination of within tablet variation of felodipine as well as to give the average value of a batch. It seems possible to extend the methodological approach towards other types of tablet formulations provided the properties of the tablet matrix con-

Table 3
The recovery and relative standard deviation (R.S.D.) of felodipine from ten tablets per vessel, using microwave extraction at 80°C, with different solvent volumes (5% methanol in acetonitrile, $n=3$)

Extraction time (min)	Solvent volume (ml)					
	15		20		25	
	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)
10	97	2	93	1	82	4
20	99	2	95	3	95	1

stituents are carefully considered. Especially important is the solubility of the polymeric matrix constituents in the chosen solvent. With a proper optimization, the extraction time may be considerably reduced saving time and money. One major advantage with the present approach is the minimal sample treatment with a direct extraction of whole tablets without any grinding procedure.

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