Use of Supercritical Fluid Extraction for Sample Preparation of Sustained-Release Felodipine Tablets

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Abstract □ Supercritical fluid extraction (SFE) was shown to be an accurate and precise alternative to liquid extraction for sample preparation of sustained-release felodipine tablets (5 mg potency) while realizing an 80% reduction in solvent consumption. Extractions of felodipine spiked on an inert support were used to evaluate the solubility of felodipine in CO_2 as well as analyte trapping after SFE. Even though the pure drug was found to be soluble in pure CO_2, extractions of felodipine from the tablet matrix required moderate modifier concentrations [8.7% (v/v) methanol in CO_2] in order to overcome strong matrix–drug interactions. Sequential static/dynamic extraction steps were also required to quantitatively recover the drug from the tablet matrix, indicating that the drug extraction was diffusion-limited. Average recoveries (n = 5) for the optimized SFE method were determined to be 4.93 mg felodipine/tablet (98.6% claim) with an RSD of 1.2% versus those for the liquid extraction procedure (n = 5, 4.98 mg/tablet, 99.6% claim, 2.4% RSD). Similar levels of drug degradation (0.12% expressed as felodipine) were also obtained with both the traditional liquid extraction and with the SFE method.

Innovations in high-performance liquid chromatographic (HPLC) instrumentation and column technology have made HPLC the analytical method of choice in the pharmaceutical industry. These instrumental features yield accuracy and precision unsurpassed by most other analytical techniques. However, the analysis of multicomponent solid samples (i.e., formulated drug products) presents unique problems for the analyst since these samples may not be analyzed directly by HPLC. In other words, some means of sample pretreatment is required prior to assay. Furthermore, the accuracy and precision gained by HPLC is often compromised by the sample preparation procedure.

For routine application in the pharmaceutical industry, there have been no significant advances in sample preparation technology which match those seen in HPLC. Most solid dosage form extractions are still accomplished by liquid–solid extraction techniques. For example, in the case of tablets, the dosage form is mechanically distintegrated (i.e., shaking, stirring, or sonication) in a fixed amount (>50 mL/tablet) of extraction media (water, organic/water mixtures). Grinding the tablet prior to extraction is not preferred since segregation and/or drug loss could occur during grinding and/or transfer. Tablet grinding is also labor intensive. Isolation of the solvated drug and any soluble excipients from the insoluble excipient particles is then achieved by centrifugation, filtration, and/or preparative microcolumn chromatography. The drug solution from the sample preparation is then assayed by HPLC.

This liquid–solid extraction procedure has many disadvantages. First, determination of degradate products, of growing concern to regulatory agencies, is significantly hindered by the high volume, low-concentration sample solutions obtained by this procedure. Second, large amounts of disposable solvent waste are generated, the disposal of which is very costly. This is particularly true for organic/water mixtures since their value as fuel for combustion is low, therefore, making their disposal costs high. Third, the above procedure requires much sample handling which can be both error-prone as well as hazardous to the laboratory worker in terms of contact with the drug substance and organic solvents.

Supercritical fluid extraction (SFE) is one innovation in sample preparation that has not been widely explored in the pharmaceutical industry. SFE typically employs carbon dioxide based fluids which require no disposal. Small amounts (<20%) or organic solvents can be added in order to enhance the polarity and therefore the solvating strength of the supercritical fluid (SF). The extracts generated from this procedure are typically low-volume, high-concentration solutions, ideal for degradate analysis. The procedure is also automatable since both parallel (several samples extracted simultaneously) as well as serial (multiple samples extracted one after another) commercial SFE instrumentation are available. Liquid–solid extractions cannot be automated without robotics since sample preparation equipment are not centralized on one unit (i.e., shaker, centrifuge) as with SFE. In addition, hazards to the laboratory worker are reduced since SFE requires only one step for the laboratory worker (i.e., loading the sample in the vessel). Furthermore, the small amount of organic waste generated reduces hazards as well as minimizes solvent procurement and disposal costs.

Quantitative inverse SFE has been successfully applied to a semisolid dosage form, Zovirax (acyclovir) (5% w/w) ointment.[1] With this technique, the ointment matrix was removed by the SF, leaving the highly polar drug behind in an extraction vessel insert. The drug was then recovered from the insert by sonicated rinsing and assayed by reversed phase HPLC/UV. With this method, 99% (n = 3) of the drug was recovered from a 100 mg ointment sample with an RSD of 3.3%. Direct SFE of drugs[2–4] from animal feeds has also been demonstrated. In one study[4], the extraction method was successfully applied to animal feed samples with varying amounts of drug present (0.0335–1.1208% w/w), thus demonstrating the ruggedness of the SFE procedure. Recoveries of over 95% were obtained for all but the lowest level, which yielded an 89% recovery. Agreement with the traditional liquid–solid extraction method was excellent. Lastly, the SFE of an anti-histamine from a transdermal patch has been shown to be quantitative as well.[5] Analysis of solid oral dosage forms (i.e., tablets and capsules) using SFE has not been quantitatively evaluated in the literature to date. However, qualitative investigation of SFE has been performed on two tablet dosage forms,[6,7] Darvon (propoxyphene HCl)[6] and ibuprofen[7] tablets. In the former, on-line SFC analysis was employed for assay. In the latter, on-line HPLC was usedfor assay.

The goal of this work was to employ SFE to quantitatively

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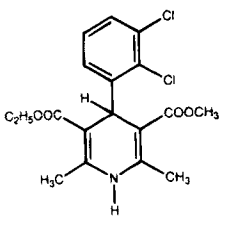
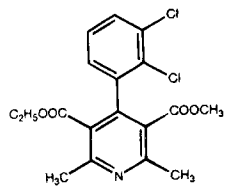
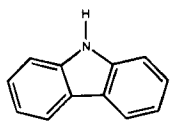


FELODIPINE



H152/37



CARBAZOLE
(Internal Standard)

Figure 1—Felodipine and H152/37 chemical structures.

(vs traditional liquid extraction recoveries) remove a drug from a tablet matrix. More specifically, felodipine, a calcium channel blocking agent, was removed from a sustained-release tablet with methanol-modified CO_2. Various parameters were examined in developing an optimized SFE method, such as modifier concentration, extraction mode, extraction pressure, and temperature. Special matrix considerations for the SFE of tablets were also demonstrated.

Experimental Section

Chemicals—All reagents (acetonitrile, water, methanol, potassium phosphate monobasic) (Fisher Scientific, Inc., Pittsburgh, PA) employed were of HPLC grade. Felodipine drug, H152/37 (oxidative degradation product) (Figure 1), and 5 mg sustained-release felodipine tablets were provided by Merck Research Laboratories, West Point, PA. Carbazole, used as a chromatographic internal standard, was purchased from Aldrich (Milwaukee, WI).

SFE Equipment—Two different commercial SFE systems were used. The majority of the extractions were performed on a Suprex PrepMaster SFE system equipped with an on-line modifier addition pump, an AccuTrap solid-phase trapping system and a DuraFlow manually operated variable restrictor (Figure 2). This extraction system employs a dual head reciprocating pump to deliver the pure SFC grade CO_2 (Scott Specialty Gases, Inc., Plumsteadville, PA) to the extraction system. When modifier was employed, the pure CO_2 was mixed with modifier in a mixing chamber prior to introduction into the thermally controlled extraction vessel chamber. The flow rate of the DuraFlow restrictor was manually adjusted with a wrench. A silanized glass bead trap was used to capture the extracted analytes after SF decompression. The decompressed CO_2 was vented through the trap and into the vessel used to collect the solid-phase trap rinse (Figure 2). After SFE was completed, the trap was rinsed with methanol (5 mL). The solutions were collected in a 100 mL volumetric flask. The use of a smaller volume flask would have been possible, but the larger volume was necessary in order to accurately compare to the liquid extraction method (described later). After trap rinsing, a nitrogen gas purge was used to clear any residual methanol from the trap. The methanolic trap rinse was then diluted with 50 mM potassium phosphate buffer (pH 3) before injection into the HPLC in order to avoid peak splitting. Method concentration for these extractions was 0.05 mg/mL. Unless otherwise noted, each single tablet was crushed in a folded piece of weighing paper with a mortar, quantitatively transferred to an extraction vessel and then extracted. Other SFE conditions (flow rate, pressure, temperature, trap rinse volume, extraction mode) are noted specifically in either the text or the Figure captions.

For early feasibility studies, an HP Model 7680T SFE system was employed. Its operation is very similar to that of the Suprex PrepMaster in that it has a reciprocating SF pumping system, a variable restrictor, and a solid-phase trapping system. Several instrumental options were different, however. The variable restrictor in the HP system was computer-controlled and the vessel size was limited to 7.5 mL. For the HP system, the decompressed CO_2 is not vented into the collection vessel but is instead vented through a separate line. Lastly, premixed tanks of methanol-modified (2 and 8% w/w) CO_2 were employed with this particular version of the HP system. Both on-line (Suprex) and premixed modifier addition was found to be equivalent. For the HP SFE experiments, pure CO_2 was obtained from Air Products and Chemicals, Inc., Allentown, PA. For spike studies, the inert support, cotton balls, was obtained from a local drug store. Although the cotton did not have a certified purity or grade, no interference was observed with UV detection. All SF methanolic extracts obtained from the HP SFE system were analyzed without further dilution via SFC/UV (described later) (1 mg/mL).

Traditional Sample Preparation—Single tablets were each ground to a fine powder with a mortar and pestle and placed in a 50 mL flask. Twenty milliliters of acetonitrile and 10 mL of methanol were added to the flask, which was then sonicated for 5 min. Fifteen milliliters of 0.01 M NaH_2PO_4 (pH 3) was added and the flask was sonicated for an additional 30 min. After cooling to room temperature, the flasks were diluted to volume with the pH 3 buffer. A 5 to 25 dilution of this solution (0.02 mg/mL) was then made with mobile phase (acetonitrile/methanol/pH 3 buffer, 40:20:40) prior to HPLC analysis. All extraction recoveries (SFE and traditional sample preparation) were expressed as percentage claim since the actual drug content of each tablet is an unknown due to manufacturing variability.

Extract Assay—Both packed column supercritical fluid chromatography (SFC) and reversed phase HPLC were used for SFE extract analysis. The equivalency between these two chromatographic separations was demonstrated previously for the analysis of felodipine tablets.[8] Ultraviolet absorbance (UV) was utilized for detection. An HP Model 1205A SFC system was used for all SFC analyses under the following conditions: 6% (v/v) methanol-modified CO_2 SF, 280 bar pressure, 45 °C, 2 mL/min (liquid) flow rate, 200 × 2 mm i.d. Hypersil Silica column (d_p = 5 μm), 5 μL injection volume. The method concentration for SFC analysis (100% level) was 1 mg/mL. Only pure methanol solutions were injected.

A Hewlett-Packard Model 1090 HPLC equipped with an autosampler and a Kratos Model 957 variable wavelength UV detector (254 nm) was employed for the reversed phase HPLC assay. An acetonitrile/methanol/50 mM Na_2HPO_4 buffer (pH 3) (40:20:40) at 1.5 mL/min and a 15 cm × 4.6 mm i.d. Hypersil C_{18} column (Keystone Scientific, Inc., Bellefonte, PA) at ambient temperature were used to achieve the separation between felodipine and its oxidative degradation product, H152/37. Method concentration was 0.05 mg/mL. Typical HPLC/UV separations of a felodipine and H152/37 standard solution (A) and an SFE extract (B) are given in Figure 3.

Results and Discussion

Spike Extraction Studies—In order to achieve quantitative SFE, the analyte(s) of interest must be (1) soluble in the SF, (2) accessible to the SF, and (3) "trapable" after SF decomposition. In order to assess criteria 1 and 3, SFE of a felodipine-spiked inert matrix (cotton balls) was performed using the HP system and SFC/UV analysis. (Again it should be noted that SFC and HPLC analyses were demonstrated to be equivalent through previous studies[8] for the analysis of felodipine tablets). Felodipine (2.5 mg) was spiked on the cotton balls via a 100 μL spike of a 25 mg/mL methylene

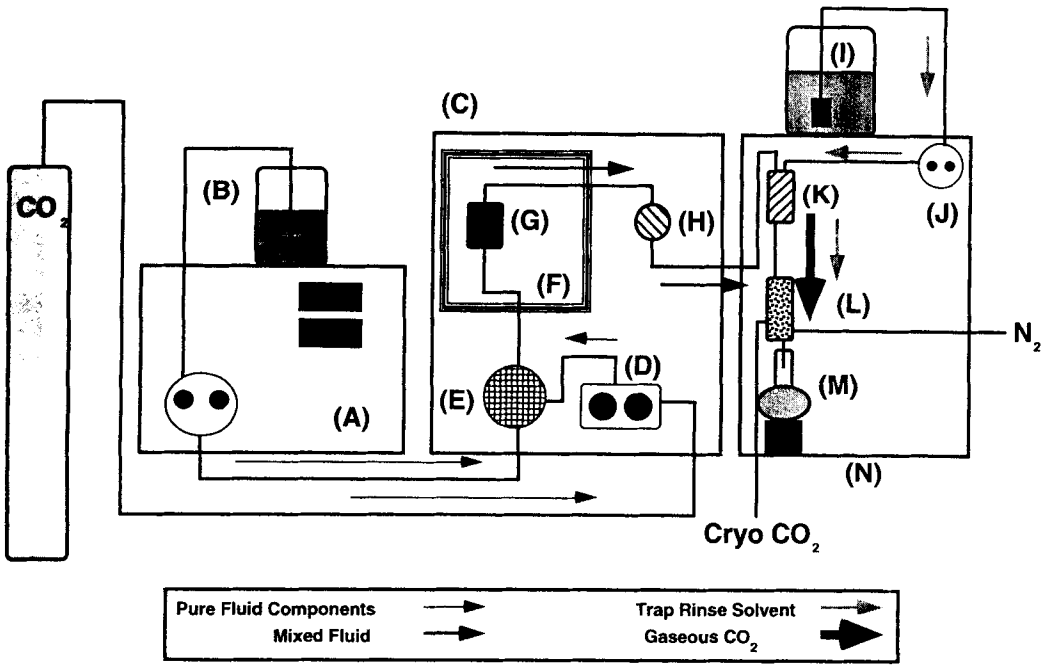


Figure 2—Schematic of the Suprex PrepMaster SFE system. Components are as follows: (A) modifier addition pump, (B) modifier solvent reservoir, (C) PrepMaster extractor unit, (D) reciprocating CO_2 pump, (E) mixing chamber, (F) thermally controlled extraction chamber, (G) extraction vessel, (H) static/dynamic switching valve, (I) trap rinse solvent reservoir, (J) rinse solvent pump, (K) DuraFlow variable restrictor, (L) solid-phase trap, (M) trap rinse collection vessel (volumetric flask), and (N) AccuTrap SF extract trapping unit.

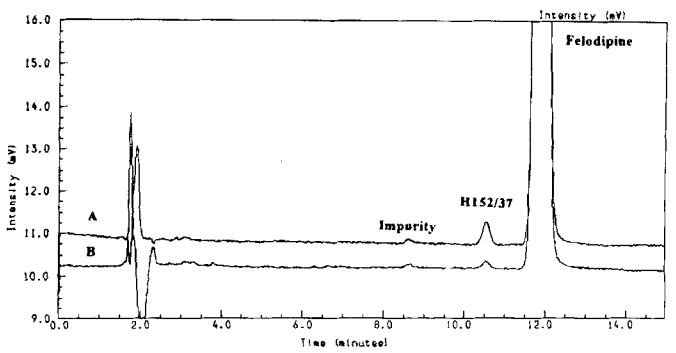


Figure 3—Typical HPLC/UV SF extract separation of (A) felodipine and H152/37 standard solution and (B) a SF felodipine tablet extract. Conditions are given in the Experimental Section.

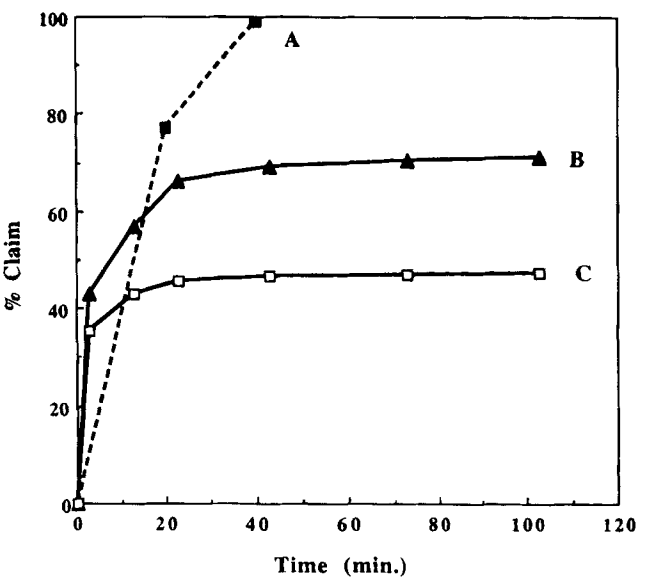


Figure 4—SFE of felodipine using dynamic mode SFE and pure CO_2. Profiles were generated from the SFE of (A) spiked felodipine drug on cotton at 316 atm and 45 °C, SFC/UV analysis, (B) a crushed felodipine tablet at 450 atm and 45 °C, HPLC/UV analysis, and (C) a crushed felodipine tablet at 450 atm and 80 °C, HPLC/UV analysis. Other extraction conditions were as follows: 50 °C restrictor temperature, 0 °C trap temperature during extraction, 45 °C trap temperature during trap rinsing. After each step the trap was rinsed with two (1.4 mL each) aliquots of methanol.

chloride solution. The methylene chloride was allowed to evaporate prior to extraction. The extraction was carried out with pure CO_2 (0.90 g/mL density) as the extraction fluid in two steps, each consisting of 2 min static and 20 min dynamic extraction periods (See Figure 4 for other extraction and assay conditions). Dynamic SFE entails passing fresh SF continuously through the vessel while static extraction utilizes a fixed amount of SF in contact with the sample for a fixed amount of time. High-density conditions, low temperature, and high pressure (vs critical parameters for CO_2) were chosen in order to achieve the greatest SF solvating power. Lower extraction temperature also avoided degradation of the drug. The two-step procedure (44 min total extraction time) produced overall drug recoveries of 99.0% with an RSD of 0.27% ($n = 3$) and the extraction profile shown in Figure 4A. (Figure 4B, C was obtained for dynamic mode SF extractions and will be discussed later.) In addition, the extraction profile obtained indicated favorable extraction kinetics for felodipine in that approximately 75% (1.875 mg felodipine) of the spiked drug was removed in the first extraction step (10 mL SF). Lastly, the spike experiments verified that felodipine could be quantitatively collected in and recovered from the trap under the given conditions. Lastly, felodipine oxidative degradation to H152/37 was not observed in any of the extract chromatograms.

Tablet Extractions: Dynamic Mode SFE—Dynamic SFE with pure CO_2 of whole felodipine tablets was first investigated as a result of the felodipine spike studies. Under the conditions used (316 atm, 45 °C, 100% CO_2) for the spike extraction study, only 1.5 mg of felodipine (30% claim) was removed from the sustained-release tablet (5 mg) in 75 min.

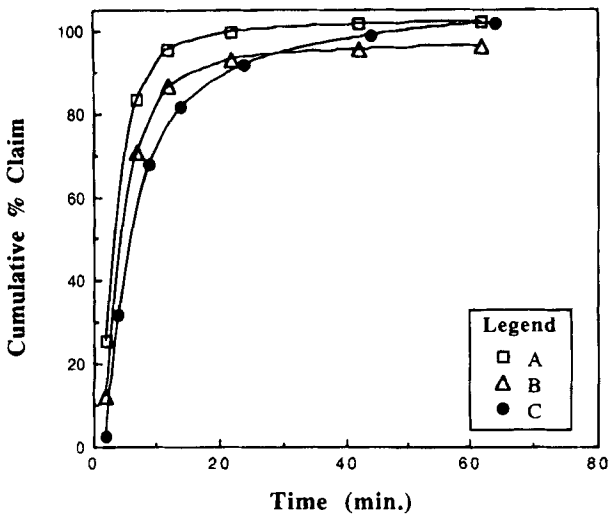


Figure 5—SFE profiles of felodipine tablets using dynamic mode extraction and methanol-modified CO_2. Profiles notation is as follows: (A) SFE with 2.4% (v/v) modifier at 80 °C, (B) SFE with 10% modifier at 80 °C, (C) SFE with 2.4% modifier at 45 °C. Other conditions are as in Figure 4. Extract analysis by HPLC/UV.

Even when a crushed tablet was extracted under these conditions, only 3.2 mg of felodipine (64% claim) was removed.

As a result, extraction conditions were altered in an attempt to increase felodipine extractability from the tablet matrix. The Suprex extraction unit was utilized since it afforded a smaller extraction vessel (0.5 mL) which more suitably matched the volume of a single crushed felodipine tablet. Higher pressure (450 atm) could also be employed with this unit, which yielded greater SF density (0.982 g/mL, 45 °C). A total of 5 mL of methanol was used to rinse the trap which was collected in a 100 mL volumetric flask. The rinse was then diluted with pH 3 buffer to volume and assayed by HPLC/UV. Under these SFE conditions, a total of 71.3% claim (Figure 4B) was extracted from a crushed felodipine tablet with only pure CO_2, indicating the possibility of drug–matrix interactions. An increase in extraction temperature (to 80 °C), in order to enhance SF diffusivity, only served to further decrease the felodipine recovery (47.4% claim) (Figure 4C). Therefore, with pure CO_2 as the extraction fluid, SF solvating power, appeared to be the main factor affecting felodipine extractability. No oxidative degradation to H152/37 was observed even when an extraction temperature of 80 °C was used.

Methanol-modified CO_2 was therefore introduced to extract the crushed felodipine tablet in an attempt to both (1) increase SF solvating power and/or (2) disrupt any drug–matrix interactions (Figure 5). The methanol in this case was added on-line via an auxiliary pump which allowed the composition to be easily changed. Higher extraction temperature (80 °C) and high CO_2 pressure (450 atm) were used to maximize SF density (0.851 g/mL) and diffusivity. Good cumulative recoveries (102.1 and 96.3% claim, respectively) were observed when both 2.4% (v/v) and 10% (v/v) methanol-modified CO_2 were employed as the SF (Figure 5A and 5B, respectively). The lower recovery obtained with the 10% methanol-modified fluid was thought to be a result of inadequate solid-phase trapping at high modifier concentrations.[9] As can be seen by the steepness of the 80 °C profiles, higher temperature did cause the extraction kinetics to improve due to higher SF matrix permeability vs those observed at 45 °C. The initial steepness and time needed for the curve to level off can be used to qualitatively gauge extraction kinetics. However, the amount of felodipine degradation seen at 80 °C (0.45% expressed as felodipine) was approximately double that observed at 45 °C (0.26%). Therefore, SFE method precision was examined under profile C (Figure 5) conditions (45 °C), except that a single 90 min extraction step was used. The average drug recovery of 4.63 mg/tablet (92.6% claim, RSD = 4.1%, n = 4) obtained was not considered quantitative considering the value obtained with the liquid extraction method (n = 5, 4.98 mg/tablet, RSD = 2.4%).

Tablet Extractions: Combined Static/Dynamic Mode SFE—Since quantitative recoveries were not obtained with purely dynamic SFE and modified CO_2, extraction from the sustained-release tablet matrix was suspected to be diffusion-limited. Further evidence for diffusion-limited extraction kinetics was found when the tablet manufacturing method was examined. Prior to compressing the drug/excipients into tablets, a granulation must be made. In the case of felodipine, a wet granulating procedure was employed where the dry tablet ingredients (drug and excipients) were mixed with a solvent (ethanol). After mixing is complete, the wet granulation mixture is heated to remove the residual solvent and the dried mixture is ground or milled to produce hard granules. Since felodipine is highly soluble in ethanol, it is possible that ethanol solvated some of the drug and carried it into the interior of the polymeric excipient particles thereby making it less accessible to the SF when dynamic SFE is employed.

Combination static/dynamic extractions were subsequently explored. Static SF extractions enhance penetration into the matrix, thereby allowing analytes to diffuse to the matrix surface. The dynamic step is necessary to flush the solubilized analytes from the vessel. In many diffusion-limited extractions (i.e., additives from polymers), the use of this combined extraction mode has been shown to be beneficial. The extraction of felodipine from the sustained-release tablet matrix is analogous to the polymer additive extraction in that the drug is a small organic molecule (like the additive) trapped within a polymer (tablet matrix). The combined mode SF extractions were initially performed stepwise with a trap rinse occurring after each step unless otherwise noted. This method of trap rinsing was necessary in order to prevent mechanical removal of analytes from what was expected to be a modifier saturated solid-phase trap. A large extraction vessel (7 mL) was employed in order that a greater amount of SF could be trapped within the vessel during the static periods. In Figure 6 the effect on felodipine recovery of modifier concentration as well as static/dynamic extraction time is demonstrated. The reason for this is that the higher modifier percentage probably prevented the SF from becoming saturated with felodipine. As opposed to the dynamic mode SFE experiments performed previously, the amount of modifier was found to be more critical in achieving good felodipine recovery. Recoveries (96%, Figure 6D) were further increased from that of purely dynamic SFE (92.6%) by the use of a higher modifier concentration (8% w/w) when a four step, 80 min total extraction time was employed. The use of a longer static period (10 min) followed by a short dynamic period (10 min) for each step was found to be optimal.

Comparable recoveries to the liquid extraction method (n = 5, 4.98 mg/tablet, RSD = 2.4%) were still not obtained regardless of the length/method of extraction used. As a result, analyte trapping was suspected as the source of felodipine loss since felodipine solubility in SF–CO_2 had been previously confirmed via spike extractions. In order to avoid this analyte loss, two measures were taken. First, the PrepMaster SFE unit was used since it, unlike the HP model, vents the gaseous CO_2 into the collection vessel. This plumbing scheme provided a second opportunity to trap any analytes that were being mechanically removed from the solid-phase trap. Second, a shorter dynamic period was used since it was believed that the dynamic flow of SF served only to move

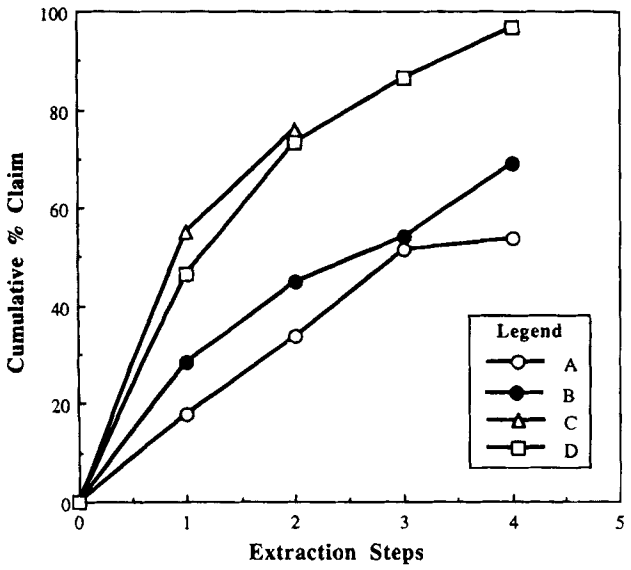


Figure 6—SFE profile of felodipine tablets using combined static/dynamic mode extraction and methanol-modifed CO_2. Profile notation is given as static extraction time/dynamic extraction time/percent (w/w) methanol modifier: (A) 5 min/10 min/2%, (B) 10 min/10 min/2%, (C) 10 min/60 min/2%, (D) 10 min/10 min/8%. Each point on the plot represents a single static/dynamic step.

Table 1—Method Precision[a] of Optimized SFE Method vs Traditional Liquid Extraction

Tablet	SFE Method Recoveries (mg/tablet)	Liquid Extraction Method Recoveries (mg/tablet)
1	4.93	5.14
2	5.00	4.86
3	4.85	4.93
4	4.93	5.06
5	4.82	4.89
average (mg/tablet)	4.93	4.98
RSD (%)	1.3	2.4

[a] All tablet sample solutions were analyzed via HPLC/UV. See Experimental Section for specific chromatographic conditions.

solvated analytes from the matrix surface to the trap. Lastly, the solid phase trap was rinsed only once after all four extraction steps were complete with 5 mL of methanol. As is evidenced by Table 1, these conditions were successful in achieving quantitative felodipine recovery (4.93 mg/tablet) in a four-step static/dynamic extraction. The level of the felodipine oxidative degradate, H152/37, was also similar for both traditional and SFE methods (0.12% expressed as felodipine). In addition, the method precision obtained for the SFE method (RSD = 1.2%) exceeded that obtained with the traditional method (2.4%). (It should be noted that both precision values also represent intertablet manufacturing variability as well as the precision of the respective methods).

An interesting result was observed when complete felodipine recovery was achieved. Since the extracts were analyzed by HPLC/UV, the pure methanolic extract solution was diluted with pH 3, 50 mM Na_2HPO_4 buffer prior to injection. Upon addition of the acidic aqueous buffer, a fine white precipitate was formed which was later identified by FTIR as a fumaric acid analog which could possibly be the half-ester of sodium stearyl fumarate, a tablet excipient. Addition of the acidic buffer produces the fumaric acid half-ester from the sodium stearyl fumarate. The extraction of this excipient was not expected due to its polar, ionic nature. Furthermore, this excipient precipitate was not found in the SFE trap rinse solutions where felodipine recoveries were less than quantitative (99% claim) and when SFC analysis[8] was used. In the latter case, the methanol SF extract was analyzed as is without buffer dilution so the precipitate would not have been observed. It appears that the final 7% of felodipine recovered is bound to the sodium stearyl fumarate since the fumaric acid precipitate appears only when felodipine recovery is greater than 93%. Sodium stearyl fumarate would not be extractable on its own due to its ionic nature. However, the extraction of ionic species has been shown by Hedrick and Taylor[10] to be possible if it is bound or attached to a large less polar moiety. Unlike the liquid extraction procedure, the SFE sample preparation was able to demonstrate strong excipient–drug interactions since the excipient bound to the drug was evidenced in the extract solution. All other excipients, due to either their high molecular weight and/or polarity, remained behind in the extraction vessel.

Table 2—Solvent Usage Comparison of SFE vs Traditional Liquid Extraction Method

	SFE Method (mL of solvent/sample)	Liquid Extraction Method (mL of solvent/sample)
Disposable solvent used for sample preparation	4 (extraction) 5 (trap rinse) Total = 9	**50**[a] Total = **50**
Disposable waste generated if HPLC/UV analysis is used	**22.5** (mobile phase) **25** (dilution, includes trap rinse) Total = 51.5	**22.5** (mobile phase) **25** (additional sample dilution) Total = 97.5
Disposable waste generated if SFC/UV[8] analysis is use	7.2 (mobile phase) total = 16.2	7.2 (mobile phase) total = **82.2**
Disposal cost/55 gal.[b]	\$48 = Pure organic	**\$175 = Aqueous/organic**

[a] Values given in boldface type are composed of organic/aqueous waste. [b] Disposal costs obtained from Waste Management Department, Merck Research Laboratories, West Point, PA.

Conclusions

Felodipine was quantitatively recovered from a 5 mg potency sustained-release tablet when static/dynamic mode SFE was used for sample preparation. These results compared favorably (accuracy, precision, and felodipine degradation level) with those obtained with the traditional liquid extraction procedure. SFE method precision was found to be comparable to that of the liquid extraction procedure. SFE sample preparation time was slightly longer (60 min/sample) than was the liquid extraction procedure (45 min/sample); however, organic solvent use for sample preparation was drastically reduced with the SFE procedure (Table 2), particularly when SFC/UV[8] was used for extract analysis. In fact, when SFC/UV analysis[8] was employed, no aqueous/organic waste mixtures were generated, the disposal of which is much more expensive than pure organic solvent waste (Table 2). Lastly, drug binding was shown to occur with the SFE procedure since a portion of the felodipine (~6% claim) present in the tablet was only extracted when an excipient, sodium stearyl fumarate, was coextracted.

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