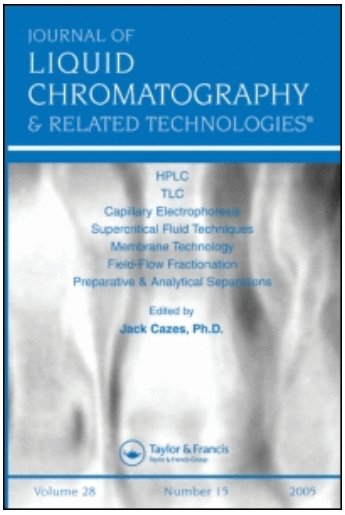

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Novel Method for the Determination of Piperazine in Pharmaceutical Drug Substances Using Hydrophilic Interaction Chromatography and Evaporative Light Scattering Detection

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ABSTRACT

A novel method for the determination of piperazine in pharmaceutical drug substances was developed using high performance liquid chromatography (HPLC) with evaporative light scattering detection (ELSD). This method uses the hydrophilic interaction chromatography (HILIC) mode on a cyanopropyl (CN) bonded stationary phase. Optimization of organic modifier and acid composition in the mobile phase resulted in robust

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chromatography conditions with excellent resolution, peak shape, and retention time for the piperazine peak. The method was further evaluated with respect to linearity, precision, selectivity, limit of detection (LOD), and reproducibility. Based on the data provided, this HPLC–ELSD method demonstrated acceptable levels of linearity, precision, LOD, and selectivity for determination of piperazine.

Key Words: Hydrophilic interaction chromatography; Evaporative light scattering detector; Piperazine; High performance liquid chromatography; Counterion; Salt form.

INTRODUCTION

Analysts typically evaluate pharmaceutical compounds for bulk drug substance purity, which includes quantitation of the inorganic counterion from salt forms. The most common pharmaceutical salt forms are sodium salts of acids and hydrochloride salts of amines.[1] The selection of the correct salt form early in the development process can prevent repeating toxicology, biological, and stability studies, thus avoiding delays in the development timeline. However, the most common salt forms do not always possess the best physicochemical or developable properties, such as hygroscopicity, solid-state stability, crystallinity, dissolution rate, and solubility. In these cases, a multidisciplinary salt selection process is necessary to find alternative acceptable salt forms. Automated salt selection systems can be used to screen numerous counterions in various solvent systems, which can result in atypical salt forms. Analytical methodologies are needed to quantitate these counterions to ensure proper stoichiometry to confirm salt formation. During the salt selection process, piperazine has been used as a counterion to form salts of acidic pharmaceutical drug substances. Piperazine has also been used to treat roundworm and threadworm infections in humans, as well as in animals, which indicates an acceptable toxicity profile. A variety of techniques have been utilized in detecting and quantitating piperazine, including derivatization,[2] spectrophotometry,[3] capillary gas chromatography,[4] gas chromatography/mass spectrometry and high performance liquid chromatography (HPLC)/fluorescence,[5] gravimetric,[6] infrared spectrophotometry,[7] volumetric,[8] polarography,[9] and HPLC/refractive index.[10] A method using HPLC with ultraviolet (UV) detection has not been employed because piperazine lacks a chromophore, but a simple, cost-effective, direct, and fast alternative method is still desired.

When the chemical entity lacks a sufficient UV chromophore, the development of chromatographic methods can be especially challenging.

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Although various derivatization schemes for these types of analytes are possible to enhance UV absorption, such manipulations tend to be very tedious and introduce their own source of errors into the analytical procedure. In HPLC, evaporative light scattering detection (ELSD) has been a valuable alternative for applications where UV detection is not feasible. Numerous publications demonstrate the applicability of the HPLC–ELSD system for the determination of phospholipids,[11] triglycerides, fats, and fatty acid esters,[12] carbohydrates,[13] synthetic polymers,[14] steroids,[15] and amino acids.[16,17] The HPLC–ELSD system has also been extremely useful in pharmaceutical applications for the determination of impurities, raw materials, inorganic counterions, cleaning verification, and small organic compounds.[18–26] Others have discussed the theory of operation of commercially available ELSDs as sensitive universal detectors.[27] The aim of this paper is to show the applicability of an evaporative light scattering detector to accurately determine piperazine in pharmaceutical drug substances.

EXPERIMENTAL

Chemicals

Piperazine, piperazine citrate, naproxen, and phenylbutazone were purchased from the Sigma-Aldrich Company (St. Louis, MO). Estropipate was obtained from the United States Pharmacopeia, (Rockville, MD). Acetonitrile and 2-butanone were obtained from Fisher Scientific (Fair Lawn, NJ), acetone was purchased from EM Science (Gibbstown, NJ), and ethanol was obtained from the Sigma-Aldrich Company (St. Louis, MO). Nitric acid was purchased from EM Science (Gibbstown, NJ), hydrochloric acid (1N and concentrated) and trifluoroacetic acid were purchased from Fisher Scientific (Fair Lawn, NJ), and formic acid was obtained from the Sigma-Aldrich Company (St. Louis, MO). The sodium chloride salt was obtained from Fisher Scientific (Fair Lawn, NJ) and the lithium chloride and potassium bromide salts were purchased from EM Science (Gibbstown, NJ). The water was deionized and filtered through a Milli-Q water purification system (Millipore, New Bedford, MA). National-formulary grade nitrogen (>97.0%) was used for the evaporative light scattering detector. Piperazine citrate and estropipate were dried at 105°C prior to use.

Apparatus

The HPLC system used for this study consisted of a Hewlett Packard 1050 pump and auto sampler (Wilmington, DE) integrated with an Alltech

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500 evaporative light scattering detector (Alltech Associates, Deerfield, IL). An Alltech Alltima Cyano (250 × 4.6 mm) column was used for the separation. The differential scanning calorimetry (DSC) data was acquired with a TA Instruments DSC 2910 (New Castle, DE).

Salt Preparation

Two lots of both naproxen piperazine (A, B) and phenylbutazone piperazine (C, D) were crystallized from the free acids at Eli Lilly and Company (Indianapolis, IN). For lot A, naproxen was dissolved in acetone and then piperazine was added in a 1 : 1 ratio. For lot B, naproxen was dissolved in 95% ethanol and then piperazine was added in a 2 : 1 ratio. The solvents were evaporated in the hood, while each salt crystallized. The percent recovery for lots A and B were 78.4% and 89.2%, respectively. For lot C, phenylbutazone was dissolved in 2-butanone, and then piperazine was added in a 2 : 1 ratio with heating and stirring. For lot D, phenylbutazone was dissolved in acetone and then piperazine was added in a 1 : 1 ratio with heating and stirring. The solvents were evaporated in the hood, while each salt crystallized. The percent recovery for lots C and D were 74.6% and 59.8%, respectively. Crystal formation was confirmed for each lot by microscopic evaluation. The melting points for lots A, B, C, and D were determined using DSC. Values of 212.3°C, 212.8°C, 184.9°C, and 188.9°C were obtained for lots A, B, C, and D, respectively. The melting points for naproxen and phenylbutazone were 156°C and 107°C, respectively. The melting point difference indicates the piperazine salts were formed. The HPLC–ELSD methodology described in this paper was used to confirm the counterion formation and the correct stoichiometry.

RESULTS AND DISCUSSION

Method Development

The effect of the organic modifier composition was first established for this new HPLC method. The acetonitrile (ACN) composition was increased from 80% to 98%, with deionized water and 0.1% trifluoroacetic acid (TFA) compensating to 100%. Piperazine citrate samples were injected twice for each mobile phase composition. As the ACN composition was increased from 80% to 90%, the piperazine peak and the citrate peak slowly merged together. As the ACN percentage was increased from 90% to 98%, the resolution between the two peaks increased and the capacity factor for piperazine

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increased. At a concentration of 95% ACN, the best peak shapes and resolutions with minimal noise were obtained. We believe that this chromatographic effect was attributed to hydrophilic interaction chromatography (HILIC).[28,29] The HILIC mode employs hydrophilic interactions in the presence of mixed aqueous/organic mobile phases for the establishment of a stagnant enriched water layer on the surface of the stationary phase, into which the analyte may partition based upon the polarity. This mechanism has been very effective for the retention and separation of highly polar compounds. The separation mechanism of HILIC is, therefore, opposite to that of reversed-phase chromatography, and is also different from the traditional normal phase chromatography and polar organic modes of chromatography. In contrast to normal phase, the HILIC mobile phases are relatively high in water content (5–50%), an environment that can provide significant advantages in regard to the solubility of many biologically active compounds.

Five different acids were then tested at a percentage of 0.1% for the mobile phase: TFA, acetic acid, formic acid, nitric acid, hydrochloric acid (concentrated), and hydrochloric acid (1N). The piperazine and citrate peaks merged when the acetic acid was used, while the formic and hydrochloric acids resulted in too much noise in the chromatographic analysis. However, TFA and nitric acid provided the best peak resolution between the piperazine and citrate peaks with minimal noise. Therefore, the composition of these two acids was tested to observe the best response for piperazine. The composition of both the acids was increased from 0.01% to 0.4% in the mobile phase. Nitric acid at a concentration of 0.15% resulted in the best peak shape and greatest response for piperazine.

The conditions for the ELSD were tested along with the mobile phase flow rate using the piperazine citrate standards once again. While keeping the nitrogen gas flow rate constant, the ELSD drift tube temperature was decreased from 85°C to room temperature with decreasing mobile phase flow rates from 1.0, 0.5, and 0.2 mL/min. The signal to noise ratio was evaluated at each interval. A mobile phase flow rate of 0.5 mL/min and drift tube temperature range of 70–75°C resulted in the highest signal with lowest noise. Therefore, the higher temperature of 75°C was chosen based upon the manufacturer's recommendation for optimization.

The nitrogen gas flow rate for the ELSD was optimized last. While keeping the drift tube temperature constant at 75°C, the nitrogen gas flow rate was decreased from 2.75 to 1.50 standard liters per minute (SLPM), with decreasing mobile phase flow rates from 1.0, 0.5, and 0.2 mL/min. The signal to noise ratio and peak shape was evaluated at each interval. A gas flow rate of 1.75 SLPM with mobile phase flow rate of 0.5 mL/min resulted in the best signal to noise ratio for the piperazine peak in the piperazine citrate standard.

Based upon method development experiments, the optimized conditions were established for piperazine determination. The mobile phase comprised

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95% ACN, 4.85% deionized water, and 0.15% nitric acid. The flow rate for the mobile phase was 0.5 mL/min, and the injection volume for each sample was 10 μL. The ELSD nitrogen gas flow rate was 1.75 SLPM, and the drift tube temperature was set at 75°C. The run time was 780 seconds.

Method Validation

Performing linearity determinations over a wide range of sample concentrations allows an analyst to fully assess the linear dynamic range of the detection system. The linearity of this method was determined by injecting 16 standards of piperazine citrate, representing a range of 10–751 mcg/mL piperazine. The linear range of piperazine was determined to be 50–500 mcg/mL. This range included ten standards and resulted in a correlation coefficient of 0.9993.

The precision of the method was evaluated in two ways, an instrumental precision and an assay precision. For the instrumental evaluation, ten replicate injections of the same sample of piperazine citrate were injected to determine the reproducibility of the method apart from analyst error. The concentrations of the samples used for the instrumental precision represented the beginning and end of the linear range for piperazine, 0.05 and 0.5 mg/mL piperazine made from piperazine citrate. The precision of the assay was evaluated by injecting ten separate preparations of piperazine citrate (0.3 mg/mL piperazine), and quantitating these samples versus a three point standard curve (0.2–0.4 mg/mL piperazine) made from piperazine citrate. The results indicated 2.7% RSD for the 0.05 mg/mL and 2.0% RSD for the 0.5 mg/mL replicate injections. The RSD for the ten separate sample preparations of piperazine citrate was 2.2%.

The limit of detection (LOD) is defined as the lowest concentration of sample that can clearly be detected above the baseline noise on a chromatogram. The LOD for the method was experimentally determined to be 100 ng on a column corresponding to a 10 μL injection of 10 mcg/mL piperazine sample.

A method must be proven to be selective for the analyte of interest as part of the USP guidelines for validation. Selectivity was assessed by separating piperazine from potential interfering peaks, including sodium, potassium, and lithium. By injecting piperazine, sodium chloride, potassium bromide, and lithium chloride, the retention times of sodium, potassium, lithium, and piperazine were 459, 464, 453, and 502 seconds, respectively.

Sample Analysis

Three piperazine salts, estropipate, naproxen, and phenylbutazone, were analyzed versus piperazine citrate standards using this optimized method.

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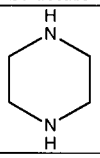
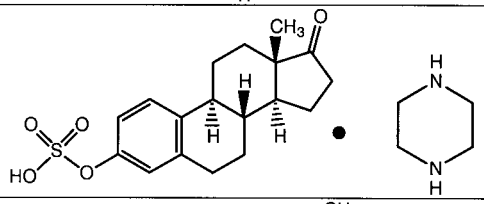
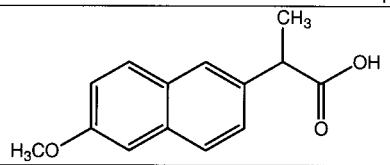
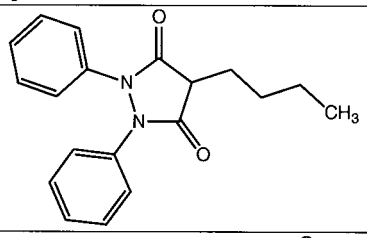
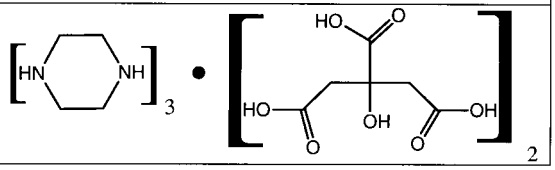
Table 1. Structures of the test analytes.

Compound Name	Structure
Piperazine	
Estropipate (piperazine salt of estrone sulfate)	
Naproxen	
Phenylbutazone	
Piperazine Citrate	

The structures of these compounds are shown in Table 1. Three analysts analyzed the USP standard, estropipate, on different days to confirm the accuracy of the method. The average of these analyses by the new HPLC method was 20.77% piperazine versus theory of 19.73% piperazine. Although, slightly higher levels of piperazine were observed compared to the theoretical calculated amount, additional experiments were not performed to determine the cause. However, the bias may be attributed to volatiles present in the reference sample material due to lack of complete characterization to establish this material as a characterized reference standard. The individual results for

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Table 2. Percentage of piperazine in estropipate determined by HPLC–ELSD.

Compound	Lot	Day/analyst	Average ($n = 3$) percentage of piperazine by HPLC–ELSD*	RSD (%)
Estropipate	I	1/1	21.23	1.30
Estropipate	I	2/1	20.42	1.47
Estropipate	I	1/2	20.58	1.54
Estropipate	I	2/2	20.65	2.40
Estropipate	I	3/2	20.84	1.31
Estropipate	I	4/2	21.09	1.34
Estropipate	I	1/3	20.35	1.24
Estropipate	I	2/3	21.01	0.76

*Theoretical piperazine = 19.73%.

piperazine in estropipate using the HPLC–ELSD method are shown in Table 2, and typical chromatograms of the standard and a sample are shown in Fig. 1.

Next, the four lots of naproxen and phenylbutazone piperazine salts synthesized in our laboratory were evaluated using this HPLC–ELSD system. The results are tabulated in Table 3. The percentage of piperazine for the synthesized salts were about the same as a 2 : 1 ratio of acid to base, leading to

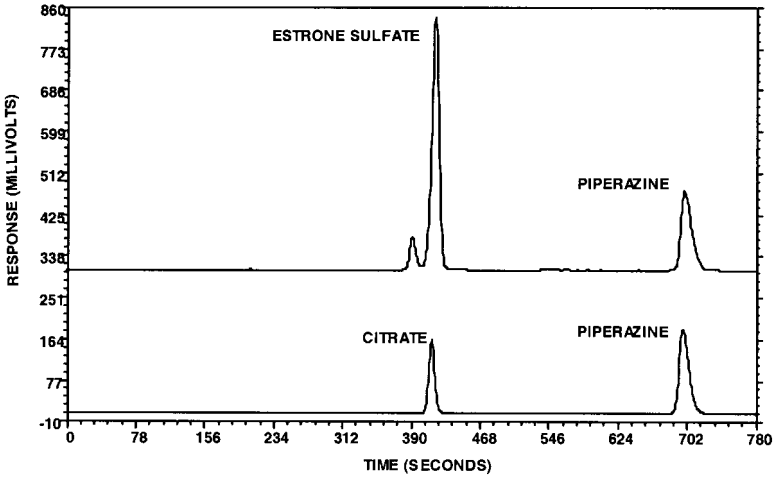

Figure 1. HPLC–ELSD chromatograms of piperazine citrate standard (bottom) and estropipate (piperazine salt of estrone sulfate) sample (top).

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Table 3. Percentage of piperazine determined by HPLC–ELSD to confirm the stoichiometry of the salt selection process.

Compound	Lot	Salt selection percentage of piperazine (theoretical ratio drug : piperazine)	Average ($n = 3$) percentage of piperazine by HPLC–ELSD	RSD (%)
Naproxen piperazine	A	27.22 (1 : 1)	17.40	2.13
Naproxen hemipiperazine	B	15.76 (2 : 1)	16.93	0.65
Phenylbutazone hemipiperazine	C	12.26 (2 : 1)	15.36	3.12
Phenylbutazone piperazine	D	21.83 (1 : 1)	13.70	3.99

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the conclusion that the hemi-piperazine salts were the only isolatable salts and confirming the stoichiometry for each process.

CONCLUSION

The applicability of ELSD for the determination of piperazine, which lacks an UV chromophore, in pharmaceutical drug substances has been demonstrated. Acceptable levels of linearity, precision, LOD, and selectivity were demonstrated using the optimized method conditions. Compared to other techniques and the USP gravimetric method, this HPLC–ELSD method provides a simple and precise alternative for the determination of piperazine.

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