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Rapid Communication

# Water Determination in Solid Pharmaceutical Products Utilizing Ionic Liquids and Headspace Gas Chromatography

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ABSTRACT

A rapid, accurate, and precise headspace gas chromatographic (HSGC) analytical method was developed for the detection and quantification of water in drug products. The analysis is able to be performed in 10 min and automated. The HSGC method used an ionic liquid (IL) based open tubular capillary gas chromatographic column to increase the ruggedness of this method and provide improved peak shapes for water. Due to the ionic liquids low vapor pressure, unique physiochemical properties, and high thermal stability, they also make idea solvents for HSGC. Unlike Karl Fischer titration methods, this HSGC method is not affected by side reactions. The developed method was shown to be broadly applicable. The water content in 12 different samples was found to range from 1%-7% water. The use of HSGC was highly sensitive and only required 10 mg of sample. In addition, it was found to have greater precision and accuracy than Karl Fischer titration and greater precision and speed than loss on drying.



## Introduction

Water content is determined at various stages through the drug manufacturing process and in the final product. When pharmaceutical compounds contain different concentrations of water, it affects the physiochemical properties of the finished drug formula.[1-6] If the water content is increased above a critical threshold, microorganisms are able to grow in drug formulations.[5] Microorganisms can be harmful, causing medications to have adverse effects. During manufacturing, the presence of water on the surface of drug formulation will modify the electrostatic charge and surface energy causing variations in solid flow properties.[2-6] However, when there is excessive water, an increase in cohesion and adhesion is observed which decreases the flow properties.[4,5] When there is a disruption in flow in the hoppers (i.e., arching and bridging), it can lead to halts in production or compound segregation.[4] Segregation in compounds causes composition variations or inconsistent dosages.[4] In addition, the reproducibility of tablet weight and hardness will be reduced with any decrease or inconsistencies in flow properties.[4]

Atmospheric moisture can interact with therapeutic drug particles in numerous ways, modifying the water content. Both the active pharmaceutical ingredients and inert materials and excipients can attract water and will modify the water content.[2,3,5,7] The drug formulation will only be able to absorb a certain amount of moisture from the atmosphere which is dependent on the temperature at which the finished pharmaceutical product is stored, the size distribution of the particles, and the surface area of the powdered drug formulation.[1-3,5,8] When amorphous material is formed via voids or fractures in the crystalline structure, a higher content of water is present in the finished drug product.[1,5] Atmospheric conditions, seasonal effects, along with geographical variations in moisture in which the active pharmaceutical ingredients are synthesized, prepared, and stored can also impact the amount of water present in the finished drug products.[5] The process by which the finished drug products are manufactured (e.g., wet granulation, spray drying, milling, lyophilization, recrystallization) can increase or decrease the moisture in drug tablets.[2,3,5] Milling can modify the moisture of the powder drug formulation because it decreases the size of the particles and increases surface area.[4] In addition, fractures to the crystal structure and increases in the formation of amorphous regions are produced when milling.[4] Air milling uses nozzles to form numerous air jets breaking down the particles, which will also dry the newly formed smaller particles.[4]

There are a few ways to measure water content in pharmaceutical products, Karl Fischer titration (KFT) is a method recognized by the US Food and Drug Administration for determination of water in therapeutic drug formulations.[9] This technique is favored because it is a water-selective method and has a wide dynamic range; however, samples and conditions must be rigorously controlled to

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obtain reliable results.[7,9,10] If the atmospheric moisture is not controlled and the titration cell is filled with air, then the relative humidity will affect the measurement of water. In one case, it has been shown that if air with a relative humidity of 50% is introduced to the titration vessel, it will increase the measurement of water by 1 mg.[10] To reduce the effects of atmospheric moisture, titration cells are heated before analysis, dry gas is purged into the titration cell, and only a single sample is analyzed per titration cell.[11] The presence of thiol, ketone, aldehyde, amide, and siloxane functional groups in the active pharmaceutical ingredient or excipient can lead to interactions with iodine causing the water content measured to be artificially high. A multiple solvent system or additives are utilized when the active pharmaceutical ingredients and excipients have limited solubility in the Karl Fischer solvent/medium.[12] The Karl Fischer medium has limited shelf stability, and being a hygroscopic solvent, it absorbs moisture from the atmosphere which leads to changes in the solvent blank over time.[12] KFT has low throughput and is labor intensive.[9] An automated system can be utilized, where samples are preweighed into small cells and then titrated, however, they are not sealed from environmental conditions.[9] If the drug (active pharmaceutical ingredient or excipient) is hygroscopic, it will continuously absorb moisture until it is analyzed, giving inaccurate results.[9] Near infrared is a recent method developed for determination of water in drug products that contains appreciable amounts of water. However, even in the "high water samples" the error is significant compared to the method developed herein.[13,14]

Ionic liquids (ILs) are used as gas chromatographic (GC) stationary phases and are also exceptional solvents in headspace gas chromatography (HSGC).[15] ILs are ideal due to their tunable nature allowing for selection of desired traits (e.g., solubilizing power, thermal stability, viscosity, and hydrophobicity).[16-26] The tunable nature of ILs allow for unique selectivity as gas chromatography stationary phases.[16,17] The columns have high selectivity between common residual solvents and water.[18] The ability to change anions allows for the use of trifluoromethanesulfonate ($TFO^-$) which results in a better peak shape for water.[18,19] ILs produce robust stationary phases which do not degrade in the presences of water or air.[18]

The high thermal stability of ILs also makes them useful HSGC solvents.[16] The lack of volatility and degradation products eliminates the solvent peak and reduces the number of contaminant peaks which could interfere with the peaks of interest.[16,17] In this publication, 1-ethyl-3-methylimidazolium tris(pentafluoroethyl) trifluorophosphate (EMIM FAP) is utilized as the headspace solvent because it was previously shown to be effective when analyzing water in active pharmaceutical ingredients.[15] The high hydrophobicity provides low residual water and low water uptake.[17,27,28] The hydroscopic and hydrophobic nature of EMIM FAP produces low background inference and therefore a lower limit of detection. The water in common solvents can be removed with time consuming and labor intensive methods or the solvent can be purchased as anhydrous solvents; however, residual water is still present and tends to increase significantly with age and use.[29,30] Finally, the EMIM FAP has a relatively low viscosity for ease of handling.[27,28] The properties stated above makes EMIM FAP an ideal solvent for water analysis with HSGC.

## Materials and Methods

### *Apparatus and Conditions*

All analyses were carried out with a Tracera GC-2010 Plus (Shimadzu Scientific Instruments, Kyoto, Japan) equipped with a barrier ion discharge detector. Two autosamplers were utilized for automated injections, AOC-5000 Plus Autosampler (Shimadzu Scientific Instruments) equipped with a heated 2.5-mL headspace HD-type syringe (Hamilton, Reno, NV) or a HS-20 headspace autosampler (Shimadzu Scientific Instruments) furnished with a 1.0-mL sample loop. The integration was performed with LabSolutions (version 5.71 SP1). All analyses were performed utilizing a split ratio of 100:1 and a constant flow of helium at 1.5 mL/min. The helium was dried with a high capacity gas purifier and an OMI® Purifier Tube (Supelco Bellefonte, PA) The oven, injection port, and detector were kept at 170°C, 280°C, and 250°C, respectively. The Watercol™ 1910—fused silica capillary column coated with IL, 1,11-di(3-hydroxyethylimidazolium)3,6,9-trioxaundecane trifluoromethanesulfonate, synthesized as previously reported or commercially acquired from Sigma-Aldrich had dimensions of 60 m × 0.25 mm ID × 0.2 μm film coat thickness was utilized for the analysis of water. All samples were measured on an AR1140 Adventurer balance (Ohaus Corp., Pine Brook, NJ).

### *Materials*

The Advil and Gelusil were both purchased from Pfizer (Kings Mountain, NC). The Citracal, Claritin D, and Equate Aspirin were obtained from Bayer Corporation (Whippany, NJ). The Arthritis Pain and Vitamin C were both bought from Costco Wholesale Corporation (Issaquah, WA). The Zicam was purchased from Zicam L.L.C. (Phoenix, AZ). The Excedrin Migraine came from Novartis Consumer Health Inc. (Parsippany, NJ). The 12 Hour Decongestant was obtained from Kroger's Co. (Cincinnati, OH). The Acetaminophen was purchased from Walgreens Company (Deerfield, IL) and Target Corporation (Minneapolis, MN). The EMIM FAP was purchased from Merck KGaA (Darmstadt, Germany). The 22 × 75 mm screw-thread vials and the magnetic screw-thread covers for the autosampler were purchased from Restek (Bellefonte, PA).

### *Sample Prep*

First, the pharmaceutical products are finely ground, then the HSGC samples are made by adding 500 mg of EMIM FAP and 9.8—10.3 mg with an average of 10 mg of the desired pharmaceutical product to an empty 10-mL vial. The vials are immediately capped with a blue polytetrafluoroethylene/silicone 1.5-mm thick septum metal cover. When the HS-20 autosampler is utilized to purge the vials, the samples are first pressurized to 200 kPa for 2 min at room temperature. After pressurizing, the diluted headspace is extracted for 1 min. The sample's pressurized headspace is slowly drawn into a 1 mL sample loop for 2 minutes and then a 0.5 minute injection is made into the GC. When a syringe type autosampler, AOC-5000, is used, the vials are first manually purged for 2 min using a 20 G, 1½″ long needle. The vials are immediately capped and purged a second time for 15 s with 2 smaller 25 G, 5/8″ long needles (one to insert argon and one to relieve pressure). The vials are then heated at 125°C for 20 min. After heating, 500 mL of headspace is analyzed with GC.

Samples were prepared for loss on drying by adding 100-mg finely ground pharmaceutical product into an empty preweighed vial. The sample is then heated at 60°C for 12 h. The sample is weighed and then heated again at 60°C for another 12 h. If after the second heating, the mass of the sample is not consistent, then the sample is heated at 105°C for another 12 h. The vials are then weighted and reheated in 12-h increments until the mass is stable.[11]

The analysis utilizing KFT was performed by Robertson Microlit Laboratories, first the atmospheric and residual moisture in the KFT cell was analyzed by adding 3 mg of sulfosalicylic acid dehydrate to the Hydranal Coulomat AG in the titration cell. The standard is then