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Original Article

A novel UV-photolysis approach with acetone and isopropyl alcohol for the rapid determination of fluoride in organofluorine-containing drugs by spectrophotometry

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ABSTRACT

A UV photolysis decomposition (UVPD) method for the determination of fluoride in fluorine containing pharmaceuticals by spectrophotometry is reported. It is based on the use of high intensity UV-irradiation in the presence of a digesting solution comprising a mixture of acetone and isopropanol. For the optimization of the UVPD procedure, three bulk drugs (levofloxacin, nebivolol and efavirenz) were chosen as representatives of three diverse compounds containing a single fluorine atom, two fluorine atoms, and trifluoromethyl groups respectively. Operational conditions of the UVPD method, such as concentration and volume of reagents (acetone and isopropyl alcohol), and UV irradiation time (1–6 minutes) were optimized. The efficiency of digestion was evaluated by the determination of fluoride in sample digests. Using the developed method, it was possible for complete conversion of the organofluoride to free fluoride ion for its subsequent determination by spectrophotometry based on bleaching of Zr–xylenol orange-color complex. Quantitative recovery (>98%) of the fluorine in the drug samples could be achieved using a mixture of 2% acetone + 2% isopropyl alcohol + 0.003% Na_2CO_3 in just 5 minutes of UV irradiation, which can be considered an important aspect considering the difficulties involved in the cleavage of the C–F bond. Accuracy was evaluated by comparison of results obtained by the UVPD method with the values estimated using formula weight of the compound and no statistical difference was observed between the results. Therefore, the proposed method is suitable for application in routine analysis of fluoride in organofluorine-containing drugs.

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1. Introduction

Fluorine has become an essential element in pharmaceutical industry. The inclusion of one or more fluorine atoms by replacing hydrogen atoms or hydroxyl groups in potential medicines can enhance their metabolic stability or modulate their physicochemical properties, binding interactions, and selective reactivities, making them more selective and increasing their efficacy [1–6]. One of the most important factors in drug design takes into account the fact that fluorine is much more lipophilic than hydrogen, thus incorporation of fluorine atom/atoms in a molecule makes it more fat soluble and hence more bioavailable. Many fluorinated compounds are currently widely used (in the treatment of various diseases) as antidepressants, anti-inflammatory, antimalarial, antipsychotics, antiviral agents, steroids, general anesthetics, antihyperintensive, antifertility, and central nervous system drugs [6].

However, one of the major limitations of introducing fluorine as substituent in to drug products is that it poses increased challenges in the manufacturing process. Hence, the accurate determination of fluoride in fluorine-containing pharmaceuticals allows to ensure the formation of target compound with proper fluoridation after synthesis. It is also for the consumer to know the truth in labeling as per the drug manufacturer, in relation to safety and efficacy of the drug. Hence, the number of samples submitted for fluoride analysis, is continuously growing.

Ionic fluoride can be easily determined by analytical techniques such as fluoride ion-selective electrode [7] and/or spectrophotometry [8–10]. However, the fluorine in organic compounds (in this case drug materials) is mainly bound to carbon. Hence, it is necessary to destroy the organic matrix (i.e., conversion of organofluorine to free fluoride ion) prior to the determination of fluoride content. Quantitative decomposition of organic fluorine compounds is often extremely difficult. Due to this, very few studies have reported the determination of fluoride in pharmaceutical samples [1,11–19]. However, these methods are generally not robust enough to be applied to routine analysis. This fact probably is due to the complexity of the drug matrix, especially for the samples containing one or more trifluoromethyl groups as one of the moiety, making the application of conventional techniques for fluoride determination much more difficult where fluorine is bound more firmly making stringent treatment conditions necessary for its liberation. We have previously reported a simple, effective and reliable UV photolysis digestion (UVPD) method for the determination of fluoride in pharmaceuticals containing fluorine as one of the constituents [20]. Although this was a simple and convenient method for the determination of fluoride, it suffers from limitations including two-step digestion process using 10% HNO_3 and relatively long digestion time (~25 min). Hence, we sought improvements in the procedure within the context of *green chemistry* principles [21,22], which aimed to reduce the amount of toxic chemical reagents at the same time simplifying and accelerating experimental procedures.

The decomposition of organic matter under the influence of UV radiation was initially described by Armstrong et al [23] as an efficient sample preparation method. UV photolysis decomposition/digestion is based on radical mechanism, involving many intermediate reactive species such as the excited states of hydrogen peroxide, hydroxyl radicals, singlet oxygen, super oxide ions, and other radicals generated during photolysis and reacting with organic molecules, degrading them [24]. Because of these excellent properties, UV irradiation process has already been well exploited for a number of analytical applications such as speeding up solid–liquid extraction of elements/species of interest for the determination of total-element contents and speciation analysis and a number of other analytical and industrial applications [25–32]. Various studies on the analytical applications of UV-irradiation for the determination of various elements including fluoride in a wide variety of matrices have earlier been reported from our laboratory [33–37].

The main objective of this study is to develop a simple, rapid, and environment-friendly sample preparation method with the aid of UV photolysis for the conversion of bound fluorine to free fluoride ion in a wide variety of drug samples containing single to multiple fluorine constituents and its subsequent determination by spectrophotometry based on the destruction of the colored complex of zirconium–xylenol orange by the generated fluorides. In this work, the efficacy of the UV photolysis digestion method using a mixture of acetone and isopropyl alcohol (IPA) for the quantitative determination of fluoride was evaluated. A previously reported two-step method based on the use of 10%HNO_3 (v/v) [20] was also utilized for comparison purposes.

2. Experimental

2.1. Instrumentation

All the photolysis experiments were carried out using a UV digester (Model No. 705, Metrohm, Herisau, Switzerland) assembly, incorporating a high-intensity mercury lamp (500 W, 10 MPa). The 705 UV digester is equipped with a sample holder with a provision for holding 12 quartz tubes of 15-mL capacity. In each set of samples, one quartz tube was reserved for monitoring the digestion temperature using a thermometer. The temperature of the UV photolysis unit was maintained at 85 ± 5°C with the help of a water-recirculating system integral to the digester.

2.2. Reagents and materials

Deionized water further purified to get ultrapure water of > 18 MΩ resistivity by passage through a Milli-Q system (Millipore Corp., Billerica, MA, USA) located in a class 200 area, was used for dilution of the standards, reagents, preparing the samples and the final rinsing of the acid-cleaned vessels.

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