Study on detection methods for salbutamol in food and biological samples

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Abstract
Salbutamol is one of the β2-agonists used in human and veterinary medicine for the treatment of pulmonary disorders. It is also extensively misused in farm animals, where high doses give rise to a preferential muscle to fat ratio, resulting in financial gain for the farmer. This abundant misuse raised serious concerns about a toxicological risk for the consumer. Therefore, a rapid, simple, convenient, and effective method to monitor therapeutic use as well as to control the illegal use of salbutamol is essential. In this article the studies of detection methods for salbutamol in recent years are reviewed.

Keywords: salbutamol; β2-agonists; determination; detection; sensor.

1. Introduction
Salbutamol [2-(tert-butylamino)-1-(4-hydroxy-3-hydroxymethyl) phenylethanol], also known as albuterol, is β2-agonists, which works by relaxing the muscles and air passages in the lungs so that airflow becomes easier and improves breathing, which was originally developed for the clinical treatment of patients with asthma, bronchitis, emphysema and, in general, breathing diseases with bronchoconstriction [1-3]. The β2-agonist has a significant economic benefit in commercial meat production because it can enhance muscle growth and decrease fat deposition. Therefore, the β2-agonist has been illegally used as growth promoters in livestock animals [4-6]. However, the β2-agonist is easily deposited into the edible animal tissue, and the depositions in animal tissue can cause cardiovascular and other side effects to humans when the β2-agonist is administered at a dose higher than those required for therapeutic use. To guarantee the rights and interests of consumers, the fast and effective analysis of the β2-agonist in the meat industry is of utmost importance [7-9]. In this paper, the attributes of different analytical technique for the determination of salbutamol in recent years are reviewed.

2. Analytical Methods

2.1. HPLC method. High-performance liquid chromatography (HPLC) is a powerful tool that enables the separation of complex mixtures into individual components, and is a highly sensitive and reproducible analytical technique. In recent years, HPLC has been combined with many sensitive detection techniques and has experienced continuous improvement of stationary phases, which have improved its sensitivity and specificity. HPLC is currently widely used for the analysis of drugs and dosage forms with respect to quality control, quantitative determination of active ingredients and impurities, monitoring drug blood concentration in patients, and bioequivalence assessment [10-12].

Zhang et al. [13] developed and validated a sensitive and selective liquid chromatography coupled to tandem mass spectrometry for the determination of salbutamol in human plasma and urine. Salbutamol and the internal standard acetaminophen in plasma and urine were extracted with ethyl acetate, separated on a C18 reversed-phase column, eluted with mobile phase of acetonitrile–ammonium acetate, ionized by positive ion pneumatically assisted electrospray and detected in the
multi-reaction monitoring mode. The lower limits of quantitation of salbutamol in human plasma and urine by this method were 0.02 and 1 ng/mL, respectively. In conclusion, the validation results showed that this method is robust, specific and sensitive, and could successfully fulfill the requirement of clinical pharmacokinetic study of salbutamol in healthy Chinese volunteers.

Guo et al. [14] developed a rapid, selective and sensitive liquid chromatography–tandem mass spectrometry assay method for simultaneous determination of ambroxol and salbutamol in human plasma using citalopram hydrobromide as internal standard. The sample was alkalized with ammonia water and extracted by single liquid–liquid extraction with ethyl acetate. Separation was achieved on Waters Acquity UPLC BEH C18 column using a gradient program at a flow rate of 0.2mL/min. Detection was performed using electrospray ionization in positive ion multiple reaction monitoring mode by monitoring the ion transitions. Calibration curves were linear in the concentration range of 0.2–20.0ng/mL for salbutamol. The method was successfully applied in a clinical pharmacokinetic study of the compound ambroxol and salbutamol tablets.

2.2. Electrochemical method. Since the early 70s electrochemistry has been used as a powerful analytical technique for monitoring electroactive species in living organisms. Electrochemical methods are the preferred methods for the detection of β-agonists, because most of the β-agonists can be oxidized at bare or modified electrodes [15-17].

Zou et al. [18] deposited a composite Langmuir_Blodgett film prepared from DNA and polyaniline on the surface of a glassy carbon electrode to give a new voltammetric sensor for the β2-agonist salbutamol. They employed cyclic voltammetry and electrochemical impedance spectroscopy to study the characteristic of the modified electrode. They investigated the electrochemistry of salbutamol at the modified electrode at pH 6.8 by cyclic voltammetry and differential pulse anodic voltammetry. The oxidation of salbutamol at this electrode was an adsorption-controlled irreversible process. They worked out a sensitive electroanalytical method that displayed high precision and good reproducibility for the determination of salbutamol. The method was applied to quantify salbutamol in tablets with satisfactory results.

Attaran et al. [19] introduced a fast and direct electrochemical method for the determination of salbutamol using an iron titanate nanopowder-modified carbon paste electrode. The electrochemical behavior of salbutamol was studied by differential pulse adsorptive stripping voltammetry. Factors affecting the performance of the adsorptive stripping such as the modifier percent, the electrolyte pH and accumulation time and potential were optimized. The resulting electrode exhibited a linear response in the range of 0.2–25 nM of salbutamol with a detection limit of 90 pM. The proposed method was successfully applied to determine salbutamol in pharmaceutical formulations and human blood plasma.

2.3. Capillary electrophoresis method. In recent decades, capillary electrophoresis (CE) has been developed for trace analysis because of its small sample size of only nanoliters to femtoliters, short analysis time, and biocompatible environments. In addition, rapid separations are feasible with CE because high voltages can be applied to short capillaries and separation efficiency is not dependent on column length. To identify biological and pharmaceutical analysis, CE is coupled to a variety of detectors, including fluorescence, mass spectrometry, and electrochemical detection [20,21].

Bao et al. [22] developed a capillary electrophoresis coupled with tris(2,2′-bipyridyl) ruthenium(II) electrochemiluminescence detection system to determine salbutamol and clenbuterol in urine. They investigated some factors that affected the performances of separation and detection. Under the optimized conditions, one single quantitative analysis of salbutamol and clenbuterol was achieved at a separation voltage of 15 kV within 9 min, and the LODs (S/N=3) and LOQs (S/N=10) of salbutamol and clenbuterol were 8.43 × 10\(^{-7}\) mol/L, 2.61 × 10\(^{-7}\) mol/L and 2.73 × 10\(^{-7}\) mol/L, 8.21 × 10\(^{-7}\) mol/L, respectively. The recovery obtained from the analysis of spiked urine samples was between 88.6% and 104.7% with RSDs lower than 6.70%. The method was successfully applied to determine salbutamol and clenbuterol in urine samples.

Fan et al. [23] developed the sensitive determination of clenbuterol and salbutamol in swine urine by using CE with a moving reaction boundary-based stacking method. Under the optimum conditions, the moving reaction boundary-based stacking procedure produced an improved concentration sensitivity of 70.5-fold for clenbuterol and 24.7-fold for salbutamol. The improvement resulted in a limit of detection of about 0.26 ng mL\(^{-1}\) and 0.96 ng mL\(^{-1}\) for clenbuterol and salbutamol, respectively. The method has been successfully used for the analysis of clenbuterol and salbutamol in swine urine, and the RSD was less than 5.0%, the recoveries were in the range of 96.8–103.6% and the linear ranges of clenbuterol and salbutamol were 0.003–10.0 mg mL\(^{-1}\) and 0.01–20.0 mg mL\(^{-1}\), respectively.

2.4. Other methods. In addition to these main approaches mentioned above for salbutamol detection, still a few special techniques with high sensitivity have been applied. Yan et al. [24] developed a label-free immunosensor for the determination of salbutamol based on localized surface plasmon resonance biosensing. Tang et al. [25] reported the determination of salbutamol using R-phycocerythrin immobilized on eggshell membrane surface as a fluorescence probe. Samir et al. [26] reported the development and validation of simultaneous spectrophotometric and TLC-spectrodensitometric methods for the determination of...
beclomethasone dipropionate and salbutamol in combined dosage form. Chai et al. [27] designed the development of a portable sensor based on a molecularly imprinted membrane for the rapid determination of salbutamol in pig urine.

3. Conclusions

Salbutamol is extensively used as a bronchodilator in asthmatic patients. However, the illegal use of salbutamol as growth-promoting agents in animals is still a public concern due to its potential risk to the health of individuals consuming animal products contaminated with the residue of β2-agonists [28-30]. Thus, it is necessary to establish quick and accurate methods to detect salbutamol residues. This review has highlighted the significant developments in rapid and alternative techniques for the detection of salbutamol in recent years. We believe the development of salbutamol sensors with better sensitivity and specificity, lower cost, simplicity, along with in vivo analytical technique is still the future effort.

Acknowledgments

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