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Review Paper

Significance and challenges of stereoselectivity assessing methods in drug metabolism ☆

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ABSTRACT

Stereoselectivity in drug metabolism can not only influence the pharmacological activities, tolerability, safety, and bioavailability of drugs directly, but also cause different kinds of drug–drug interactions. Thus, assessing stereoselectivity in drug metabolism is of great significance for pharmaceutical research and development (R&D) and rational use in clinic. Although there are various methods available for assessing stereoselectivity in drug metabolism, many of them have shortcomings. The indirect method of chromatographic methods can only be applicable to specific samples with functional groups to be derivatized or form complex with a chiral selector, while the direct method achieved by chiral stationary phases (CSPs) is expensive. As a detector of chromatographic methods, mass spectrometry (MS) is highly sensitive and specific, whereas the matrix interference is still a challenge to overcome. In addition, the use of nuclear magnetic resonance (NMR) and immunoassay in chiral analysis are worth noting. This review presents several typical examples of drug stereoselective metabolism and provides a literature-based evaluation on current chiral analytical techniques to show the significance and challenges of stereoselectivity assessing methods in drug metabolism.

Contents

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1. Introduction

In clinic, chiral drugs that contain at least one chiral center are widely used and play an important role in treating human diseases. Over half of therapeutic drugs are chiral, and the majority of them are administered as racemates, mixtures containing equal proportions of (R)- and (S)-enantiomers [1,2]. Owing to the different three-dimensional configurations of enantiomers, although the individual drug enantiomers present identical physicochemical properties in an achiral environment, they generally show different pharmacological activities in a chiral environment, such as in the body [3]. The phenomenon that only one enantiomer is effective against a particular disease while the other enantiomer has different pharmacological activity or even toxicity exists commonly in many chiral drugs [4,5]. For example, (R)-flurbiprofen can modulate γ-secretase and has the potential to treat the symptoms of Alzheimer's disease, while (S)-flurbiprofen is more toxic because it can inhibit cyclooxygenase directly [6,7].

Thus, there has been an increased awareness of the effects of stereoselectivity in drug metabolism. Developing single enantiomer drugs has been a tendency in recent years due to their advantages, i.e., lower administered dose, simpler dose–response relationship and lower toxicity [3,8]. Among the 127 new molecular entities (NMEs) approved by U.S. Food and Drug Administration (FDA) between January 2010 and December 2014, chiral NMEs were the major component (81 (64%) of the 127 NMEs), and among the 81 chiral NMEs, single enantiomers were the great majority (Fig. 1) [9].

In this case, many people doubt that the importance of stereoselectivity assessing in drug metabolism is limited and will steadily decline. However, it is essential to assess stereoselectivity in drug metabolism before we decide to develop a single-enantiomer or racemic drug. Nowadays, most countries' governments have stipulated that research on enantiomers should be carried out in pharmacology, toxicology and metabolism separately during the development of new drugs. Chiral drugs can be produced as racemates only if there is no obvious effect on the efficacy or toxicity when the two enantiomers coexist, because racemic drugs require lower costs of production but have more risks of application than single-enantiomer drugs. In addition, since many old drugs are still given as racemates, it is essential to monitor the blood concentration of each enantiomer respectively in therapeutic drug monitoring. Here, we review several typical examples of drug stereoselective metabolism from the aspects of fundamentals, types, and effects in order to further show that stereoselectivity assessing in drug metabolism is of great significance for pharmaceutical research and development (R&D) and the rational use in clinic. Additionally, current chiral analytical techniques, including high-performance liquid chromatography (HPLC), gas chromatography (GC), supercritical fluid chromatography (SFC), capillary electrophoresis (CE), nuclear magnetic resonance (NMR), and immunoassay, are evaluated. Although these techniques have made great contributions to stereoselectivity assessing, many challenges have not been overcome.

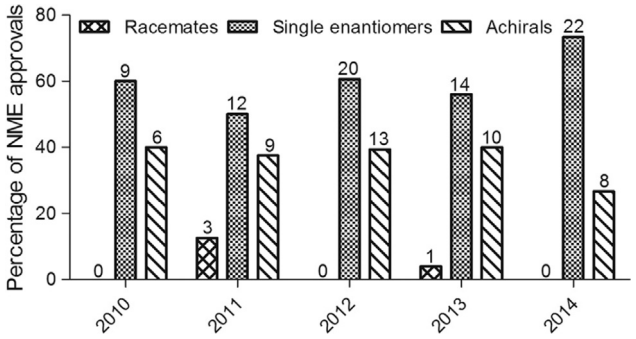

Fig. 1. The chirality of NMEs. The percentage (shown on the *y*-axis) and number (shown above the bars) of FDA-approved NMEs according to the chirality of the NME are shown for the 2010–2014 period.

2. Stereoselectivity in drug metabolism

Among all pharmacokinetic processes, metabolism is the most stereoselective process due to the involvement of the enzymatic system, such as cytochrome P450 enzymes (CYPs) and uridine 5′-diphospho (UDP)-glucuronosyltransferases (UGTs). CYPs and UGTs are the major determinants during the metabolism of most drugs on the market [10,11]. CYPs catalyze the oxidative reactions in Phase I metabolic reactions, while UGTs catalyze the glucuronidation reactions in Phase II metabolic reactions. They have a wide range of substrates and present great stereochemical sensitivity, i.e., different affinities and/or reactivities for two enantiomers of a chiral drug.

According to where the chiral discrimination in drug metabolism occurs, metabolic stereoselectivity can be classified into substrate stereoselectivity (the differential metabolism of two or more stereoisomeric substrates), product stereoselectivity (the differential formation of two or more stereoisomeric metabolites from a single substrate) and their combination, and substrate–product stereoselectivity, which contains a unique phenomenon, chiral inversion [12]. Some examples [13–23] showing stereoselectivity in drug metabolism are presented in Table 1.

2.1. Substrate stereoselectivity

Substrate stereoselectivity refers to the phenomenon that two enantiomers are metabolized at different rates in a reaction that neither creates nor adds a stereogenic element when forming the metabolites [12]. Enantiomers usually have different affinities with enzymes, which induces different metabolites and different metabolic rates. Therefore, they often show different pharmacological activities and elimination rates in the human body. In order to minimize toxicity and reduce the total dose of an administered drug, the majority of newly approved chiral drugs are not developed as racemates but as single enantiomers, which means that it is essential to study the substrate stereoselectivity of a chiral NME to decide which enantiomer should be produced.

The substrate stereoselectivity in drug metabolism is exemplified by the metabolism of a proton pump inhibitor, omeprazole (Fig. 2). The asymmetric sulfur of omeprazole generates two enantiomeric forms, (S)- and (R)-omeprazole. Their main routes of metabolism, i.e., sulfoxidation and hydroxylation, have been shown to be mediated via CYP3A4 and CYP2C19, respectively [15,16]. The predominant metabolism for the (S)-enantiomer is catalyzed by CYP3A4, which generates omeprazole sulfone. The (R)-enantiomer is metabolized primarily by CYP2C19, which generates hydroxyomeprazole and a minor metabolite, 5-O-desmethylomeprazole (Fig. 2) [24,25]. As a consequence of the