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Manufacture, Structure Confirmation and Quality Control of the Chiral Drugs

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1. Introduction

The general thinking of quality control of the chiral drugs is that we need to conduct the research following the characteristic of the chiral drug besides principles already existing[1]. During the research, according to the way by which the chiral center being introduced, we should adopt the effective measurement to control the optical purity of chiral material and each step resultant; choose the appropriate way (direct or indirect) to prove the absolute configuration according to compound's unique feature as well as research foundation already existing such as its preparation craft, the comparison of structure confirmation, the literature data and so on.

2. Synthesizing technology for chiral drugs

Chiral drug is a kind of special chemical drug. Its particularity must be considered in the research except the guideline for chemical drug[2]. We need to pay more attention to the change of chiral center and the optical purity in the process momentarily.
During the research, both the optical purity of the starting material and the control of the process are important, which may have effect to the final product. So the internal control standard should be established especially the control of the optical purity. According to the way by which the chiral center being introduced, we should adopt different method to control the optical purity of each intermediate material. Moreover, we should monitor the change of the configuration in the reaction by establishing the appropriate process control target.

2.1 Route analysis for synthesizing technology of chiral drug

As it was said in the guideline[3], both asymmetrical synthesis and the resolution have superiority to obtain chiral drug - although the selectivity is better and the optical purity of final product is higher, asymmetrical synthesis has more steps; on the contrary, the route of resolution method is shorter, but the chiral purity is not meet the requirement sometimes, especially when there are more than one chiral center exist in the drug. We can choose the rational method according to the feature in the actual application.
For the process of asymmetric synthesis, we consult the relevant literature as much as possible before establishing the process, and adequately understand the mechanism, reaction conditions and stereoselectivity about the different reactions, then find out the corresponding

reaction. Because the steric hindrance of materials, some reactions have larger stereoselectivity, and the needed configuration may be the one that is obtained from the reaction. If the needed is not the predominance configuration or that is not ideal proportion, some measurement should be adopted to improve the reaction selectivity, introducing a large group into the starting material such as salt or ester, then improve greatly the stereoselectivity. For example, some chiral drug evaluating needs to form two chiral carbons, the researchers induce a tert-butyl group to the starting material, after forming the chiral center, the inducing group is eliminated, the result confirm the inducing group that will improve the stereoselectivity from 60% to 98%, then get high yield, and the sequent purification process had been simplified synchronously. The strategy to the synthesis such as figure 1.

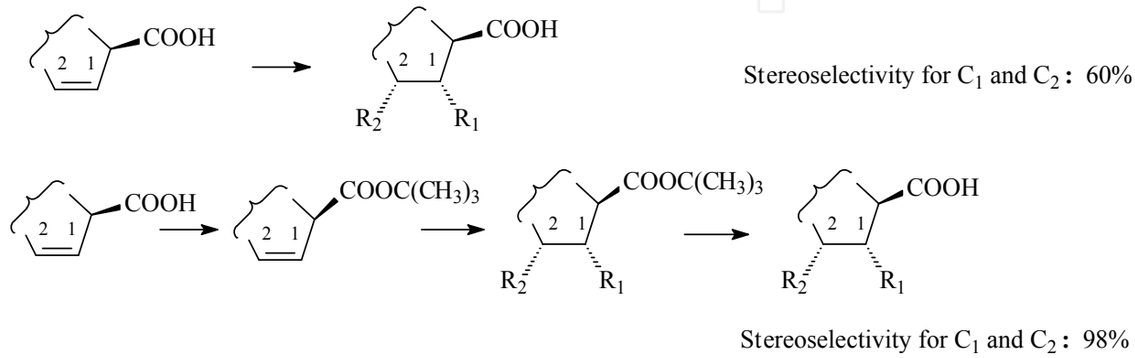

Fig. 1. The strategy to the synthesis: improving the stereoselectivity

In addition, the different reaction conditions such as temperature, pressure and the addition of special chiral catalysts may likely affect the stereoselectivity of the reaction, there are a lot of books and literature can be consulted, the test can be designed according to the actual situation and the literatures. It should be noted that the current use of some common chiral catalysts such as ruthenium, rhodium, etc have high toxicity, and so the strictly measurement should be adopted to control the residues of the mental catalysts. Identify of the limits can consult Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents issued by the EU EMEA[4].

2.2 Control of the starting materials

The chiral starting materials, besides some common chiral materials like L-amino acids, D-tartaric acid, other chiral starting materials purchased from other companies should be established the corresponding chiral purity control item, and should be provided the production techniques and detailed quality control about it, evaluated the rationality of the process. In the actual evaluation, a lot of applicants did not provide the production techniques and detailed quality control about the chiral starting materials purchased, and did not carry out the optical control on the chiral starting materials, directly impact on the quality control of starting materials and the evaluation on its quality. For example: a purchased key side-chain has two chiral centers that is used in the synthesis of antilipemic drug Atorvastatin calcium by some applicants (the structure described in Fig. 2), but the applicants don't accomplish the corresponding chiral purity control item, that will affect on the evaluation of the drug application, and the drug standard doesn't include the chiral quality index about the product, so that the application isn't approved.

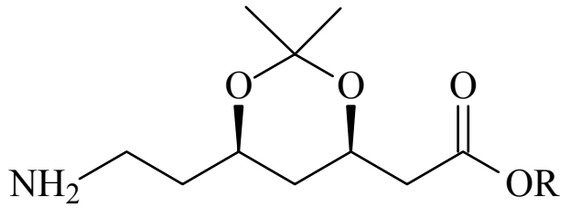

Fig. 2. The key side chains in the synthesis of Atorvastatin calcium

And some applicants have already accomplished a rough chiral purity control item, such as controlling the optical rotation of the starting materials. but the control of optical rotation is not enough to ensure the high content of the optical isomerism, especially when the starting material contains two or more chiral centers, and the different chiral center will contribute to the addition of optical rotation, it's not enough that only to utilize the optical rotation of the starting materials to afford a high content of steric isomerism. in addition, the range of the optical rotation is usually too rough, even if there is considerable quantity of of isomerism impurities, the optical rotation can still meet the requirement of the limit. For example, the optical rotation is usually controlled in the range ± 5° in the current specification, if a chiral drug contains one chiral center, even if there is only 5% enantiomers in the final product, the determination of the optical rotation traps in the range of the standard, and these should be limited more exacting than the limits. So if the optical rotation is used as a chiral purity control item, sufficient validation about its accuracy and precision should be made to ensure its confidence, and must be shown an accurate definition. There is a chiral drug with multiple chiral carbon atoms, because each chiral carbon atom contributes to the apparent optical rotation of the final product, then it will is more complex to calculate the optical rotation, here to control the optical purity through the optical rotation of the product will be more difficult. If a following chemistry reaction is achieved by the use of a low purity of the starting material, it will be more difficult to develop the sequent purification and quality control, and it will greatly increase the cost of the synthesis of final product.

Based on those reasons, we suggested that appropriate optical purity guideposts about the chiral starting material should be established, and the chiral HPLC method should be used if necessary. In addition, it should provide detailed production process of chiral starting material and detailed quality control process to evaluate the rationality of the craft.

2.3 Intermediates control

In addition to the introduction of chiral centers from chiral starting materials, it may also be introduced during the reaction. We should focus on steps that generate chiral centers. The intermediate, which will generate the new chiral center, should be controlled and internal quality control standard should be established. After introducing this chiral center, possible stereomeride should be focused on and monitored. In order to fully control the optical purity of products, we should understand the reaction mechanism of introducing chiral center, analysis isomer structure and different isomer proportion; establish effective isomers separation control method. It could not only depend on refining to improve the optical purity of final products. It needs to note that if this starting material used containing more than one chiral center, and this step reaction did not affected other chiral center, then this step reaction formed the diastereoisomer which could be separated by the ordinary HPLC methods. This requires adequate method validation. By those, we could control such key intermediates effectively intermediates.

2.4 Process control and process control index

Comparing with non-chiral drugs, in-process control is very important in synthesizing of chiral drugs, especially when the chiral drugs containing more than one chiral center. Each step stereoisomer impurities should be detected, analyzed and possibility of conformational changes be monitored, rather than using an ordinary HPLC monitoring method or TLC method.

Optimizing reaction parameters, monitoring the optical purity of reaction products could help us to determine this step reaction process condition and reaction products optical purity control item. After the introduction of chiral centers, follow-up reaction can make configuration changes. According to the difficulty of the final product quality control, different control methods were used to control the optical purity of the final product.

During the process research, the stereoisomers of impurities were detected after the introduction of chiral centers in each step, the possibility of conformational changes were analyzed and monitored. If there were no configuration changes, it should strictly control the process parametersits in the preparation process according to the results of process optimization and verification. If such changes may occur, indicators should also be targeted using the optical purity of the intermediate control, in addition to strictly control the process parameters.

With the reaction mechanism in each step and possible side effects, we should comprehensive analysis the stereoisomers structure of impurities, determine the scope of the possible structure of impurities, and to verify the method of structural confirmation. So to reduce the work load of the impurities structure confirmation. For example, an innovative chiral drug, the reaction generated 4 diastereoisomer in step; these isomers were isolated and determined by NMR spectra. Combined with the reaction principle and the theoretical values determined different isomers structure were confirmed, and the formation of these isomers ratio of process parameters were optimized, and also provides a strong proof to the confirmation of the final product structure.

3. Characterisation research of chiral drugs

3.1 The general principles to the structure identification of chiral drugs

During the study of structural confirmation of chiral drugs, it should not only be consistent with the general principles of structural confirmation, but also pay particular attention to the research and conclusive evidence of configuration according with the requirements of the guiding principles. For innovative chiral drugs, chiral centers on the absolute configuration should be confirmed clearly; for generic drugs absolute configuration should be confirmed with orignal drugs. Since enantiomers have the same general physical and chemical properties, chromatographic retention behavior (non-chiral packing column) and spectral characteristics (IR, Ultraviolet spectrum, nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry), so the conventional method can not corroborate the configuration of chiral drugs, even if the conventional structure comparison with the configuration of standard product, still can't confirm their stereo configuration. In the actual evaluation about chiral drugs, we can often see that some drugs have multiple chiral carbons, but the applicants work over only by the four conventional spectrum analysis methods in the structure corroboration, not for chiral center,which causes the supplement rate of these drugs higher than the normal drugs in the structure corroboration.

It should be known that, the methods of structure corroboration about chiral drugs are classified, and the main method of configurational corroborating respectively is introduced, which are comprehensive. The methods concreted and their principles may refer to the guiding principle and relevant professional books, which are not mentioned in this no longer. In the following, only the questions found in the structure corroboration and the specific application of various methods will be stated.

3.2 The direct methods

Single-crystal X-ray diffraction method belongs to the direct methods, and is the preferred method of configuration corroboration about chiral drugs. The indirect methods need a lot of jobs to do, especially in corroborating innovative drug configuration or in the drugs of multiple chiral centers. but the single-crystal X-ray diffraction method can provide directly configuration information. So we should get the drug samples of single crystal determination of single crystal X-ray diffraction as far as possible through various measures. Of course, if the indirect method is simple, and can be relatively easy to identify the absolute configuration, there is no need to perform the single crystal determination. The point need stressed is that the object of single-crystal X-ray diffraction structure analysis only to be one crystal among the samples to be measured, which will not be representative. So it is necessary that the drug samples will be measured with powder X-ray diffraction, and gets the theoretical powder X-ray diffraction spectrum of chiral drugs through the calculation of single crystal structure data., and then is compared with that of sample drugs powder. The single-crystal sample will be proved to be representative when two crystal diffraction spectrums are consistent, and then corroborate configuration of the chiral drugs. Although the point is stressed in this guiding principle, but the declaring enterprises all do not have a research about this, which can cause evaluation personnel some questions, ever if some samples have a detection of the single-crystal X-ray diffraction. So attention must be brought to the applicants.

3.3 The indirect methods

When it is difficult to raise single crystal, more indirect combined application methods should be made. Usually, an indirect method to identify the absolute stereo configuration is limited, should as far as possible use more than one indirect methods to mutual self-evident. In the following, the application of indirect methods will be introduced though some examples in the evaluation.

3.3.1 The specific rotation

For the chiral drug only containing a chiral center, such as Levocarnitine, (S)-Amlodipine, its stereo configuration can be determined by rotation detection and enantiomer control. If the result of rotation detection is consistent with literature value, and the enantiomer can be generally effective controlled in the quality standards, the chiral drugs' stereo configuration may be identify in according to the conventional method. But if the chiral drugs are innovative drugs, their absolute configuration should still be corroborated.

3.3.2 Chiral HPLC positioning method and specific rotation

For the chiral drug containing two chiral centers, such as Sertraline Hydrochloride, it has a enantiomer and two diastereomers. These isomers can be separated and positioned through

chiral HPLC conditions in the reference when their configuration are corroborated. According to the result of specific rotation detection, we affirm that its configuration would be consistent with the marketed drug if they have the same chromatograms. If marketed standard substance to be available, we affirm that its configuration would be consistent with the marketed drug through the way combining chiral HPLC method with NMR spectroscopy.

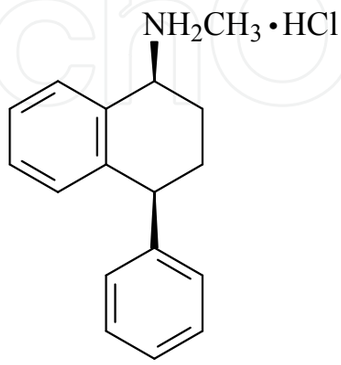

Fig. 3. Sertraline Hydrochloride

3.3.3 Literature comparative method

For the chiral drug containing multiple chiral centers, the determination of other items must be detected in order to corroborate three-dimensional structure of every chiral center besides specific rotation detection. For these compounds, the literature data obtained outside is also very important, except for the methods mentioned in this guiding principle of direct or indirect method. Because of multiple chiral centers, the presence of the final product including enantiomers are less, rather than non-enantiomers in the NMR spectrum are obvious differences, through the literature data by comparison with the measured data confirm the stereochemistry. Such as the muscle relaxant Vecuronium Bromide (Figure 4),

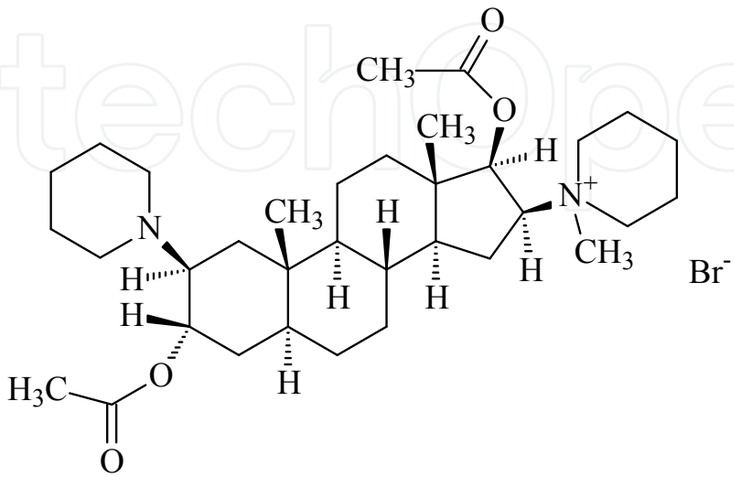

Fig. 4. Vecuronium Bromide

the structure contains ten chiral carbon, but one of the six chiral carbon in a rigid steroid ring, in the subsequent reaction of steroid body chiral carbon on the ring flip is unlikely occurrence, follow-up of non-response is only possible non-enantiomers. The literature clearly shows the various possible non-enantiomers of the NMR data and maps, which compare the sample through the NMR measured values with the literature, combined with other evidence of testing to confirm the relatively easy three-dimensional product configuration.

3.3.4 The inverse method of intermediate configuration

The determination of the intermediate single crystal X-diffraction is significant to the determination of the structure of the final product. Sometimes, the end product of the single crystal can not be obtained. At the same time, they can study and explore the availability of the last step reaction of the intermediate 1,2-crystal. When the intermediates of single crystal can be obtained, and chiral center does not changes or changes in control centers in the subsequent reaction, these intermediate configuration of the confirmation of the final product configuration is the very useful evidence for confirmation. such as the Chiral drug A, its single crystal is not available. But the intermediate steps before a chiral drug L-Menthylacetat single crystal is available, through its configuration can be anti-speculation chiral drug A by the conclusive evidence, shown in Figure 5.

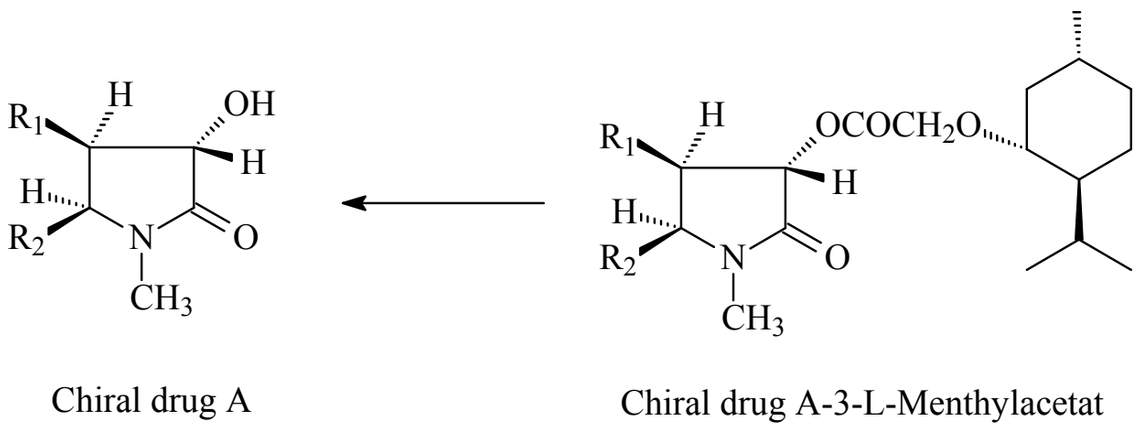

Fig. 5. Anti-speculation process

3.3.5 NMR

NMR is useful to the confirmed of general structure of the drug. But he confirmed of the structure of chiral drugs has serious limitations, because the isotropic probe in the NMR determination is connatural. It makes the map of measured isomer NMR spectrum is identical. If distinguished by NMR mapping isomers, enantiomers shoud be changed into diastereoisomers, and then receive the appropriate tests. The methods of Common detection include: adding chiral shift reagent, add chiral solvent and chiral derivatization method and so on. After adding chiral derivatization reagent, it can make the formation of chiral drugs covalent bond. Then though the determination of NMR spectra, it can effectively distinguish different enantiomers with the configuration of the end product. This method is in common, and the different structure of chiral drugs can have a variety of derivatization reagent for selection. Referring to the specific relevant professional books, the guidelines are an increase Mosher Law adding chiral derivatization method.

3.3.6 Theoretical analysis & NMR

Reasonable theoretical analysis for the validation of the configuration of the final product is important. When a chiral drug in the chiral center from the starting material or reagent introduced, and the chiral centers in the subsequent reaction is not affected, or the configuration of chiral center of the quantitative impact is clearly occurring At this point, if the starting materials or reagents of three-dimensional structure is known, by classical chemical correlation method can be confirmed in the API configuration of chiral centers. Such as cisatracurium besylate (structure shown in Figure 6) confirmed the structure of the drug exists in four chiral centers, configuration is 1R, 1'R, 2R, 2'R type, and its structure confirmed by theoretical analysis and nuclear magnetic resonance methods: the synthesis of this product to R-Tetrahydropapaverine synthesized R-Tetrahydropapaverine does not involve the chiral carbon papaverine chiral reversal, the basic validation of 1,1 '-bit conformation; 2,2 '-bit configuration determined using NOESY spectra, NOESY spectra of C1-bit display connected to the methylene on the benzyl hydrogen and N2 connected propionate methylene hydrogen are related, but and N2-methyl hydrogen does not exist on the relationship, indicating that the connection C1 and N2 connected benzyl propionate in the cis part of the basic goods can confirm the stereochemistry.

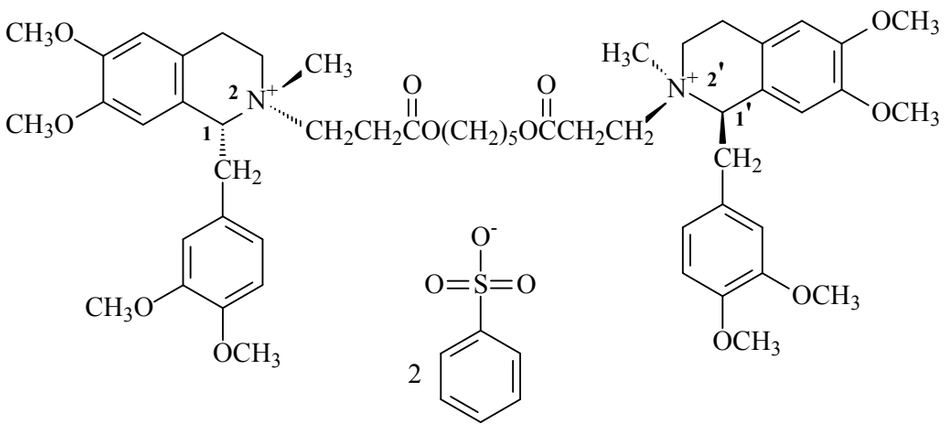

Fig. 6. Cisatracurium besylate

In addition, impurities can be combined with process research and study results to determine the configuration of end products, such as some examples in the Technology Application Unit of which the results of theoretical synthesis of the four possible isomers were separated and identified, but also for configuration of the main components of the quality of the establishment and follow-up study provides strong evidence.

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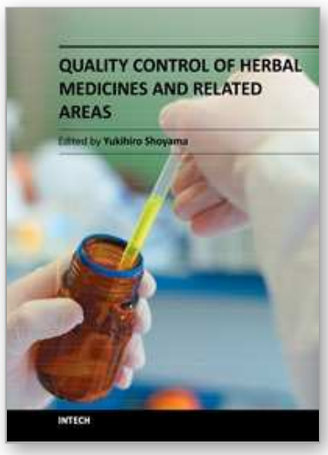

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The authors of this thematic issue provide a comprehensive summary of most recent knowledge and references on quality control in wide fields. Quality control is essential for natural products like natural medicine and related food products. In this issue fifteen chapters have been included, discussing in detail various aspects of quality control. It will certainly prove useful not only for phytochemical researchers, but also many scientists working in numerous fields. Much effort has been invested by the contributors to share current information. Without their efforts and input 'Quality Control of Herbal Medicine and Related Areas' could not exist.

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