Review

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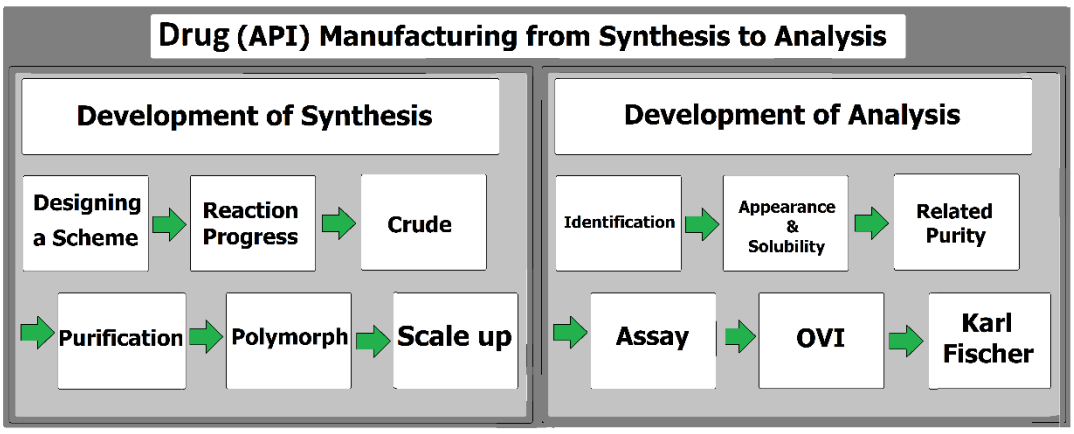
How to Manufacture a Drug API? A Simple Scheme from synthesis to analysis

Seyyed Amir Siadati,[(1)]✉ Mohammad Ali Ebrahimzadeh,[(2)]✉ Rezvan Yazdian Robati,[(1)] and Esmaeil Babanezhad[(3)]

[(1)] Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran
[(2)] Department of Medicinal Chemistry, School of Pharmacy and Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, 4815733971, Iran
[(3)] Department of Environmental Health, Faculty of Health, Mazandaran University of Medical Sciences, Sari, Iran

✉ Correspondence to: Chemistry_2021@yahoo.com (Siadati), MA.Ebrahimzadeh@mazums.ac.ir (Ebrahimzadeh)



Abstract: Simply, production of a drug needs two main steps; the first step is the chemical synthesis, and the second one is the pharmaceutical analysis. At the first step, the desired drug must be synthesized via the lowest possible production cost. The synthesis scheme must be designed to proceed the reaction with the highest yield, cheapest solvents, and mildest possible conditions. It should also be user friendly (for operators of the production unit), as fast as possible, with lower steps leading to a highly pure active pharmaceutical ingredient (API). The pharmaceutical analysis step contains a series of the main analytical tests such as instrumental (HPLC, GC,

XRD, and …), as well as physicochemical ones (like solubility, ash, heavy metals, …). These tests determine the quality of an API for being applied in the finish line formulation of a drug.
In the present paper, we have simply described the two main steps for manufacturing a drug API which contains the synthesis step as well as the pharmaceutical analytical part. Also, some key notes for drug synthesis step will be presented.

Keywords: drug synthesis; pharmaceutical analysis; Drug manufacturing; pharmaceutical industry; API

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Introduction

Designing schemes to yield the pharmaceutically active components which are rarely available in the nature, will decrease their expensive prices. Especially, when the introduced scheme uses cheap materials, and it is easily operatable, green, or fine [1-3]. Such designation decreases the price of the expensive drugs in one hand, and increase the availability of these medicine to all, on the other hand [4]. Due to this, finding new methods for synthesizing of drug [5-8] and other organic compounds [9-15] have always been important for organic chemistry researchers. During years of attempts, chemical and pharmaceutical scientists all around the world have made attempts to develop methods for step-by-step synthesis of desired molecules or intermediates via cycloadditions, pericyclic reactions, coupling agents and many other approaches, and even performing theoretical works for understanding the mechanism of those reactions [16-26]. Also, some researchers reported the total synthesis of some precious drug APIs via retro synthesis schemes [27-30]. All of these attempts provoked the progress of science of construction of organic molecules, especially the pharmaceutically active ones [31-33]. Such scientific development results in abundance of rarely available pharmaceutically precious natural compounds as well as the manmade expensive drugs (which subsequently decrease their prices).

Due to the above-mentioned facts and also due to the emergency needs of some drugs in the especial times (like need for antivirals during the outbreaks), in this paper, we have made attempt to systematically list the major steps of synthesis and analysis of the drug APIs. Also, there are some precious reports that focused on API production [34-38].

Part 1: Notes for Synthesis of a drug

In this section, we have tried to list the most important points for designing a good method for synthesis a drug API; what we have practically experienced during our works.

Dropwise addition, controlling the pH, temperature, solvent volume to reactants weight, and reaction time, good workup, recrystallization purification and validation of scaleup, are of those.

Dropwise addition of a reactant or agent

In practice, it is personally observed that in some cases, synthesis a key intermediate or API should be proceeded via a careful dropwise addition of a reactant to the reaction vessel to prevent emerging unwanted impurities or oily crude; while by changing the solvent, pH, temperature, or even addition of a catalyst or something like an antioxidant, the dropwise addition might not be required anymore [39,40].

Careful control of the pH

Sometimes, it is experimentally observed that a reaction must be progressed by a very careful control of the pH of the reaction mixture. One of the reasons for such situation is that in the lower pH range, the reaction is blocked; while, in the upper range, impurities appear. Especially, where, elimination of those impurities is very hard, and time consuming [41,42]. In one case, it is observed that the optimized pH rang is between 0.8.

Control of the temperature

One of the important parameters that is experimentally observed to be important in the successful synthesis of APIs with high purity (enough to be used in drug formulation), is controlling the temperature. Of course, in many cases, changing the reaction temperature from 15 ºC to 40 ºC (about 30 ºC) does not change the fate of the process (does not lead to emergence of impurities). However, in some reactions, a little change of the temperature (for example from 5 ºC to 8 ºC) lead to significant changes. Somehow, below 5 ºC the reaction is blocked; while, upper than 8 ºC, high amounts of impurities are observed. What I have personally observed in some hydrolysis or deprotection reactions. On the other hand, in some of the other processes, like stereoselective ones, very low temperatures are crucial. Also, sometimes, using higher temperatures could lead to increase the color of the crude and ones need to use inert atmosphere or decrease the temperature of the reactor. Thus, in some drug synthesis processes, careful control of the reaction temperature is required but not for all cases [43,44].

Solvent volume to reactants weight (SV/RW) ratio

One of the other points about the drug synthesis is that in some cases, the reaction is progresses in a special solvent volume to reactants weight (SV/RW), while, at more SV/RW ratios the reaction is very slow, or even is blocked after a certain yield. Especially, at scaleup from laboratory batches to pilot or production unit batches, this effect is more observable. Sometime, it could not be made up by increasing the reaction temperature, or addition of excess amount of a reactant (mainly at the ends of a reaction) [45,46].

Control of the reaction time

Usually, when a reaction is progressed with a moderate level of speed, increase of the reaction time does not lead to significant increase in the impurity profile or color of the crude. But, in the case of fast reactions, careful control of the reaction time and its monitoring by thin layer chromatography (TLC) or even by HPLC is required. Somehow, after passing the normal reaction time, some impurities emerge or the color of the crude increases. On the other hand, if the reaction rate is slow, some other impurities like the decomposition products of intermediates might begin to form. Also, there is a possibility that during the scaleup, the rate of the reaction become slower and slower than the laboratory small scale. Thus, it would logical that the rate of drug synthesis reactions be in the moderate level [47,48].

Workup and reaching to the crude

After finishing the reaction leading to synthesis of a drug API, ones need to workup to reach to the crude. The workup process is a very important stage of the process which could change the fate of the reaction. A good workup could lead to a fine crude with high purity and significant yield; while, a weak and careless workup might result in impure, colored, and oily crude with low yield. Even if, the reaction progresses completely and purer, a bad workup could destroy the outcome of such nice reaction. At the end of the reaction, sometimes, crude begin to precipitate in a spontaneous manner. But sometimes, hours of patience are needed to see the reaction mixture becomes cloudy and subsequently it begins to precipitate. In some cases, the reaction mixture requires to be cooled to precipitate; while, in some other cases, cooling the reaction mixture leads it to be oily, two-phased, curd and doughy (especially where you have used anti-solvent). In such cases, increasing the temperature could make a single-phased reaction mixture (containing solvent and anti-solvent) which results in appearance of precipitation. Also, in such cases, increasing the rate of stirring and seeding could be helpful. Here, we have designed a systematic scheme to

show how one could purify most types of crudes via recrystallization (Figure 1). Moreover, sometime altering the pH of the reaction mixture could help to precipitation of the crude without emergence of impurities [49,50]. It should be noted the ”solubility” in Figure 1 is defined in each case (it is not equal with the definition of solubility of pharmacopia or other related texts.

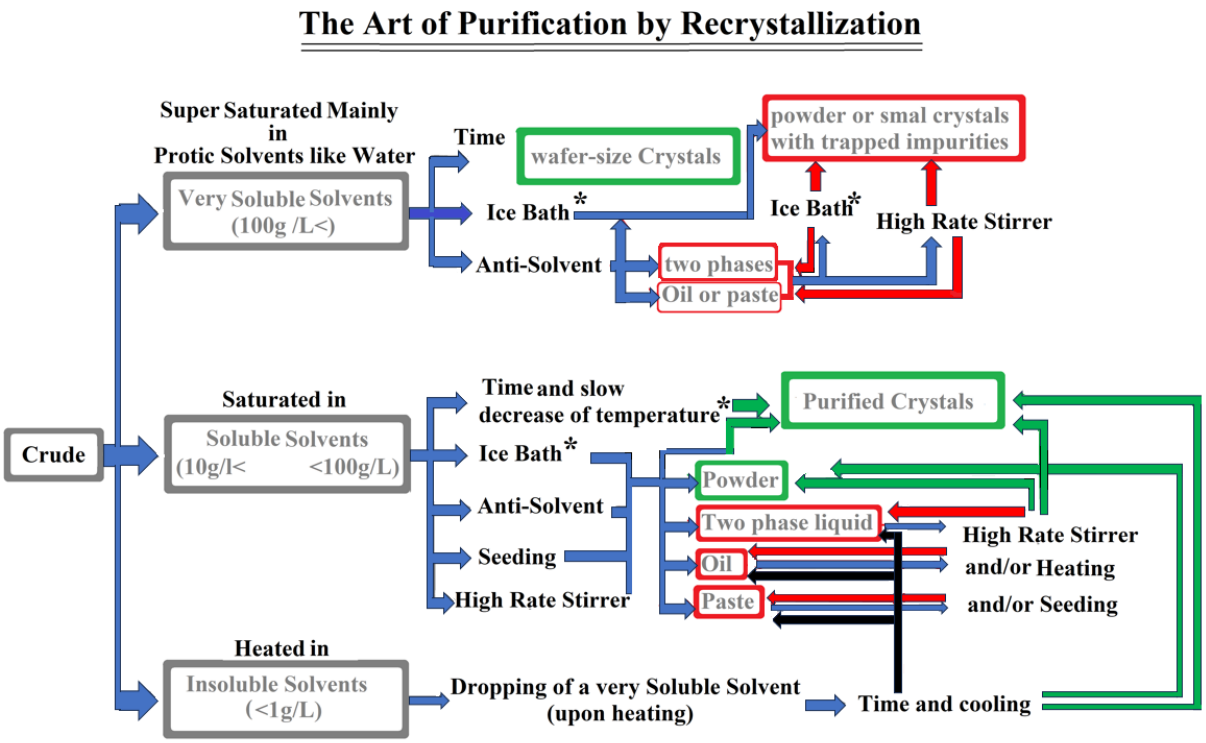

Figure 1. A schematic scheme for purification of the crude via recrystallization. * For most of solvents, solubility decreases by reducing the temperature. In such cases, ice bath might lead to precipitation or two separated oil-in-solution phases.

Purification via the change of pH has not been embedded in Figure 1. But, this map could also be used for purification of the crude in parallel with the pH change purification.

Purification via crystallization or chromatography

The purification step, is one of the most important stages of the drug synthesis, where the researcher has to purify the crude along with forming the desired probable crystalline form (if a special polymorph is requested). Also, it would be better that the purification proceeds along with formation of the reaction crude. It means, it is better that forming the desired crystalline form, and also the purification step be performed in the crude making step of the reaction. Totally, it would be beneficiary if the purification of the crude takes place via recrystallization instead of using the column chromatography. Because

applying the column chromatography could be time consuming, costly, and hard to do with the need of large amounts of organic solvents and silica gel to give a relatively small amounts of the drug API. Thus, if a crude could be purified by recrystallization process with a high yield, it would be better than chromatography [57,58].

Formation of a pharmaceutically suitable crystalline form (desired polymorph)

In many cases, a certain organic molecule (mainly an API) could be precipitated as several different crystalline forms (polymorphs). Usually, among several polymorphs, only one or two forms are pharmaceutically acceptable. Two main parameters which lead a crystalline form to be applied in drug formulations, is its thermodynamic stability, and its solubility. Usually, polymorphs with higher melting points which could be passed through long-term stability analyses, are considered as more stable ones. Also, the polymorphs that could be soluble in water, buffers, or other certain solvent or medias, are recognized as soluble ones. Such properties are analyzed via physicochemical solubility tests (presented in pharmacopeia texts) or dissolution tests (mainly by dissolution and HPLC instrument). Regarding the fact that among all polymorphs of a compound, only one or a few forms could be applied as API product, both formation and recognition of those are important [59,60].

There are several parameters that are effective in formation of a certain polymorph of a drug. Type of solvent (and probable anti-solvent) [61], the time of dropping of anti-solvent [62], the temperature of precipitation [63], the type sediment used for seeding [64], the time and speed of stirring [65], freeze-drying, or even spray-drying could be effective in formation of a special crystalline form of a drug API. Moreover, formation of two or more polymorphs with different ratios (in one reaction vessel) have been practically observed in some cases. Finally, in some practices, after reaching to the targeted polymorph, grinding and micronization before formulation is needed for a better solubility or release [66].

<u>The effect of scaleup</u>

It sometimes observed that in cases, the synthesis of a drug API is acceptable in the laboratory scale (usually about 50 g to 100 g); while, during the scaleup in the pilot or industrial scale, the process would be more complicated. Somewhere, the rate of the reaction will be slower, or even it does not finish and large amounts of impurities remain in the reaction vessel. It leads the crude to be oily and impure, and the yield decreases significantly. In such situation the operator might increase the temperature to provoke the reaction progress, but sometime, such decision would result in emergence of impurities or

increase the color of the crude, or even make it oilier. Thus, the workup would be more complicated and difficult.

On the other hand, in the large-scale reactors, some operations like fast changing the temperature could be difficult. Thus, reactions that need fast operation could show different behavior when scaleup. Therefore, all reactions leading to production of drug APIs should be validated by step-by-step scaleup [67].

Part 2: Pharmaceutical analytical analyses

As drugs are used for treatments of living things like the human race, their quality, purity and safeness are very important. In on hand, for many cases, impurities of the drugs are very hazard and dangerous for us. That is, analyzing the total and related purities and assay of drug APIs are crucial. On the other hand, other parameters such as organic solvent residues, water content, solubility, and the crystalline structure are important and effective in the quality of a drug. In this regard, in this section, we have tried to shortly describe the main parts of drug analyses (Figure 2).

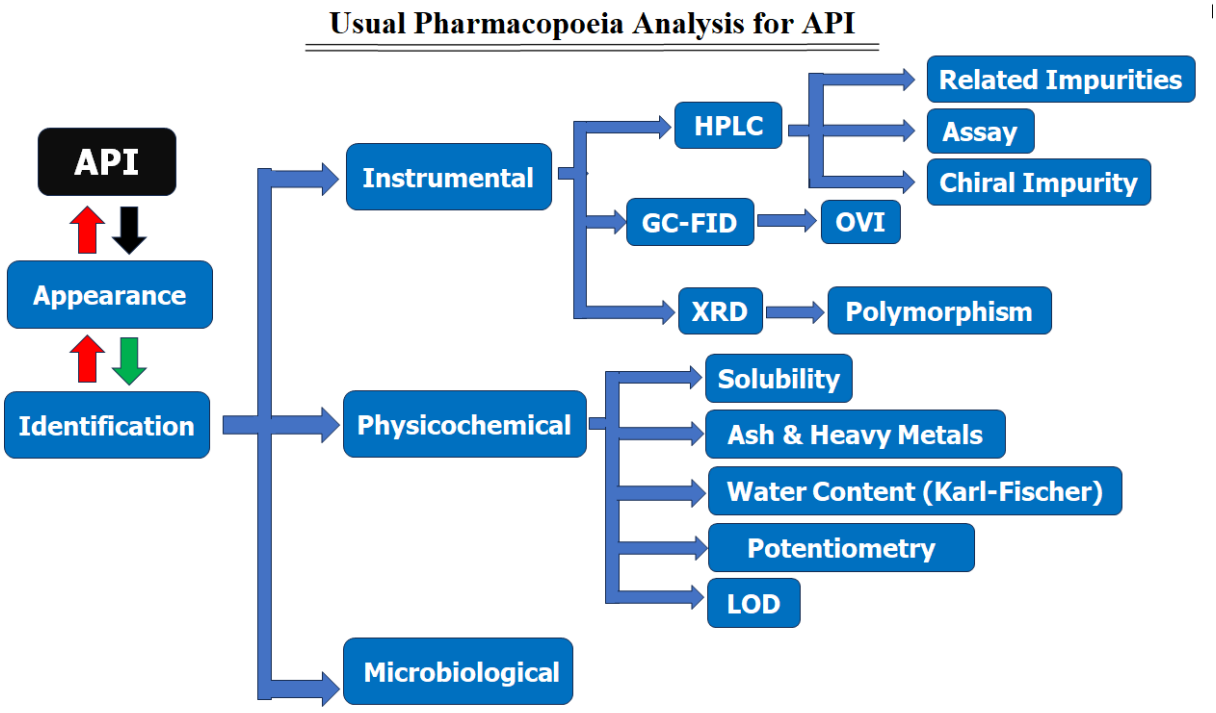

Figure 2. the most common pharmaceutical analyses for APIs.

Identification

Identification of a synthesized drug API usually is confirmed by comparison of the standard and the sample via Fourier-transform infrared (FT-IR) spectroscopy or HPLC

retention time (RT). In some cases, where there are special groups like phosphate in the API, excess identification tests like phosphate identification might be required [68]. Also, in opposition of the usual organic synthesis papers, NMR tests is not required for identification of each current production batch.

Appearance and solubility

The first line of analysis of an API is the appearance test [69]. Where, the phase (state), shape (crystalline form or powder shape), color, probable pollutions and heterogenous particle are detected. After passing the appearance test, the solubility test will be run. It is notable that in all pharmacopeia texts, most of the organic drug API must be assessed by the solubility tests. In this experiment, a special weight of a drug API is dissolved in a certain volume of each of the group of solvents (for example 1 g in 1 ml of a solvent for the *Very Soluble* grade). If a powder could not be dissolved in the determined volumes of the selected solvents, or be dissolved in the solvents which are reported to be insoluble in those, then, the polymorph or even the type of that API would be under question. The very soluble, freely soluble, soluble, sparingly soluble, slightly soluble, very slightly soluble and insoluble, are of the main solubility grades of pharmacopeia [70]. Also, it is notable that during this test, no heating or sonicating process is allowed.

Related purity, chiral purity and assay analysis

As mentioned above, in many cases, impurities of the drugs are very hazard and dangerous for us. This issue is more highlighted in the case of genotoxic impurities. That is, analyzing the total and related purities as well as assay analysis of the synthesized drug APIs are very important.

The related purity analysis is one of the most important analyses for assessing the quality of a synthesized API. This test is mainly carried out by using the high-performance liquid chromatography (HPLC) instrument. In this analysis, usually a 1000 ppm concentration of a produced drug is prepared as the concentrated sample and is injected to HPLC. Then, the sample is diluted to 10 ppm or 1 ppm (1/100 or 1/1000) and is injected to the HPLC as diluted sample (based on the instructions the dilute might be prepared via the standard stock solution). Subsequently, the amount of each impurity is calculated by comparing the area of each impurity peak with the area of the diluted sample peak. This is due to the deviation of area/concentration response at different concentrations (linearity validation) [71-73].

To investigate the chiral purity, usually the normal phase HPLC system with chiral pack columns is applied. Based on the instructions of the pharmacopeia, it could be calculated via simple purity integration or related purity method. In some cases, the specific optical rotation (SOR) analysis is used which is easier and cheaper than the HPLC methods.

The chemical assay analysis is mostly carried out by using HPLC-UV; while, sometimes it is calculated by using the potentiometric titration analysis. Based on the pharmacopeia instructions, when using HPLC instrument for assaying a synthesized drug API, usually, a 100 ppm of each sample and standard are prepared and injected. Then, after considering the related parameters such as water content, and salts percentages (like acetate or maleate) the area of sample is compared with the area of standard peak to give the assay of the sample. Usually, the accepted range of many drug APIs are between 98% to 102% (it could change by the instructions of pharmacopeia) [68].

Finally, assessing the assay content of drugs by potentiometric titrations is carried out by using the pH meter titrator for compounds which have one acid molecule like HCl (or a basic agent) in their structure. Also, this method might have some deviations due to the non-acidic molecules between the mostly acidic ones [37,74].

Determination of the pharmaceutically suitable crystalline form

The first and fastest line for recognition of a polymorph is appearance of a powder or the shape of a crystal. However, such observation is not trustable and must be supported by other approaches (even by using a microscope). The second test for confirming a polymorph of an API is the solubility test. In this experiment, a certain amount of a drug API is dissolved in a certain volume of each of the determined solvents or medias. Such test might give information about the polymorph of an API but it is not still enough. Sometimes, the FT-IR spectrum of the polymorphs of a drug compound might have different patterns. It is more observable when the polymorphs of the drugs have different hydrogen-bonding with different orientations [75].

The most important approach for recognition of a certain polymorph of a drug API is the X-ray diffraction (XRD) analysis [76,77]. With the aid of this technology and by considering the patterns of its spectra, the pharmaceutically suitable crystalline form of a drug (via comparing to the XRD of the standard polymorph) could be detected.

Organic volatile impurity (OVI) and losing on drying (LOD)

The residues of organic solvents which sometimes remain or even trapped in the crystals or powders of the synthesized drug, is one of the most important problems of drug

synthesis. The solvent residues are usually assessed by the Flame Ionization Detector Gas Chromatography (GC-FID). In this test, a certain amount of a drug compound is dissolved in a solvent (usually 50 mg in 1ml of DMF or DMSO and then 5 ml of water). After sample preparation, the vessel is heated and finally a headspace syringe sucks the steams of the upper atmosphere of the vial. The peak areas of the sample are compared by a standard calibration curve.

The LOD method (which is mostly contained of measuring the weight loss during the drying process of a certain amount of a drug in the vacuum oven over heating), is proceeded at different temperatures. It means that in some cases, the drug is placed in a vacuum oven at 60 ºC (for instance); while another drug is dried at 100 ºC or even 120 ºC (just as an instance). Thus, the pressure, temperature, and time of drying is different for one type of a drug to another. Therefore, the LOD of a drug maybe contained of its water content (especially for those drugs in which their LOD temperatures are more than 100 ºC, at vacuum) plus the amount of the volatile solvents. But it does not contain the LOD methods of all drugs. Finally, development of LOD method for a special drug will be more difficult, when solvent is trapped in its crystal structure; where, destruction of its crystal is needed [78-81].

Water content

Due to the fact that the LOD test would contain the water content plus many other solvent residues, it could not be used for assessing of exact weight of water. Thus, the Karl-fisher (KF) titration method is usually applied for measuring the amount for water in a drug API (reported as percent). The Karl-fisher titration method has been introduced 1935 by the German chemist Karl Fisher for determination of water content [82]. It contains a reaction in which I_2 molecule is consumed by water and alcohol molecules. Thus, assessing the water content of a drug which has alcohol or amine in its structure would lead to false results. To avoid such wrong data, the water contents of alcoholic or aminic drugs should be carried out by using alcohol-free or other special Karl-fisher reagents [77,78].

Conclusion

In summary, we have simply described the process of manufacturing a drug by dividing it into two main sections containing the synthesis and the analysis parts. In the synthesis step, the most important requirements for development of synthesis a drug API have been listed. Then, our experiences about the general key points of drug synthesis and production were presented. Also, the more important parameters of pharmaceutical analyses

for assessing the quality of a drug API were described to give a total view for the synthesis researchers (for a better scheme designing).

Finaly, it is notable that before designing a scheme for synthesis an API, one should consider the costs (for example the costs of solvents, catalysts, and energy of lower or upper temperatures), and the simplicity of the process (to be more user friendly for operators of the production unit), the total and related purities, the yield, the residual solvent, water content, and the crystalline form of the API.

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