

Review Article

Analytical Methods Need Optimization to Get Innovative and Continuous Processes for Future Pharmaceuticals

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Abstract: The quality of a pharmaceutical product is directly related to the health of patients. This consideration is evidenced by the results of studies of various researchers, which show that a practical and precise method of analysis can be the first step in the rational use of medicines. Most of the time, drugs and medicines even with all its importance and all its uses lack analytical methods in the literature and in most official compendia for their Quality Control. During the development of a new analytical method, as liquid chromatography, must be considered various factors, such as reliability, detection and separation of all compounds of interest, speed analysis to optimize equipment and analysts, reduced need for pretreatment of the sample, low final cost analysis when the reagents, procedures and machinery are accounted, and use of non-toxic reagents neither for the operator or for the environment, that is, environmentally friendly methods. Using techniques, green methods considered, as infrared spectrophotometric and turbidimetric methods make remediation of environmental impacts frequently observed nowadays unnecessary. The use of simple and easy methods of execution, fast, precise, accurate and environmentally friendly becomes more and more interesting for the pharmaceutical industry in Quality Control of drugs and medicines. The lack of environmental friendly methods for the analysis of pharmaceuticals with minimum generation of toxic waste and the consciousness of the analytical decisions is a gap that currently drives the research groups.

Keywords: green analysis, infrared spectrophotometry, liquid chromatography, turbidimetric, quality control.

INTRODUCTION

In the 21st century a great challenge for pharmaceutical industry is the development of innovative and ecological techniques to routine quality control. Recently the quality control of pharmaceutical laboratories have received renewed attention as an environmental risk factor for human being and environment.

This work focuses on the optimization of analytical techniques used in pharmaceutical companies to qualify their products. To define the optimization steps, some aspects were listed such as reliability, detection and separation of all compounds of interest, speed analysis to optimize equipment and analysts, reduced need for pretreatment of the sample, low final cost analysis related to reagents, procedures and machinery and use of non-toxic reagents neither for the operator or for the environment, that are, environmentally friendly methods. The association of these parameters could design a new plan and defined the optimization steps which allow the development of our propose to establish a new pharmaceutical strategy.

In our laboratory we have established a routine platform by using infrared (IR) spectrophotometric and turbidimetric analysis to quantify drugs and pharmaceuticals. More than 50 new analytical methods have been developed aiming less residues and no toxic solvents. These methods can be applied to quantify many active pharmaceutical ingredients and their pharmaceutical products such as azumolene, cafeic acid, cefalotin, cefazolin, cefoxitin, ceftazidime, ceftriaxone, ciprofloxacin, darunavir, doxycycline, enrofloxacin, fluconazole, fusidic acid, glimepiride, norfloxacin, orbifloxacin, teicoplanin, tigecycline. This research reports our newest results in analytical methods for promoting the healthcare and ecological concern for the 21st century pharmaceutical laboratories.

In this concept, the 'green analytical methods' were introduced as a key component of analytical method development in our laboratory.

Green chemistry is "the use of chemistry techniques and methodologies that reduce or eliminate the use or generation of feedstocks, products, by-

products, solvents, reagents, etc. that are hazardous to human health or the environment” [1] or simply “hurt not the earth, neither the sea, nor the trees” [2]. The thinking of the whole green chemistry benefits; benefit the community, the population, since the thinking is multidimensional focusing on the whole, the parties and, above all, the interaction between the parts of a system [3]. Green is the path to sustainability [4].

First of all, we tried to improve the high performance liquid chromatography (HPLC) technique by using less volume of solvent, less toxic solvents, and consequently less rinsing. Therefore, the washing steps were minimized and minor waste was generated. Therefore, the washing steps were minimized to generate a lower amount of waste. The efficacy of this analytical method was checked by systematic parameters defined by International Conference on Harmonization - ICH [5-7], Association of Official Analytical Chemists - AOAC [8] and other official compendia [9-11]. Then, method validation could be performed directly after time optimization by new plan and strategy, allowing speeding up the analytical life cycle.

In order to evaluate the interest of microbiological assay using turbidimetry as a quantitative technique, antibiotics and antifungal substances were selected as model compounds because of their singular characteristic in the medicinal uses. The turbidimetric method is supported in an official compendium [11]. It became indispensable in routine of

quality control in laboratories and pharmaceutical industries, because of its main strategic characteristic, release of results in short time, only 4 hours, against 21 hours using the microbiological method by agar diffusion.

In this paper, we will also describe and discuss some IR applications related to the quantitative area and to the pharmaceutical research. Therefore, beside the characterization and qualitative determination classically used for drug analysis, IR technique can represent an innovative and interesting procedure for quantify active pharmaceutical ingredient as well as pharmaceutical products.

INFRARED SPECTROPHOTOMETRIC

The spectrophotometry in the infrared region offers the possibility of obtaining spectra relatively quickly and provides interesting information, qualitative or quantitative. This technique has been used more and more for quantitative purposes, increasing its use that, formerly, was restricted only to qualitative analysis. An important factor is the relatively low cost of an infrared spectrophotometer, in addition to being a non-destructive technique with no generation of waste and solvents.

Drugs such as ceftazidime [12], ampicillin [13], cefuroxime [14] and darunavir [15] shown in Figure 1, were successfully quantified by spectrophotometry in the infrared region.

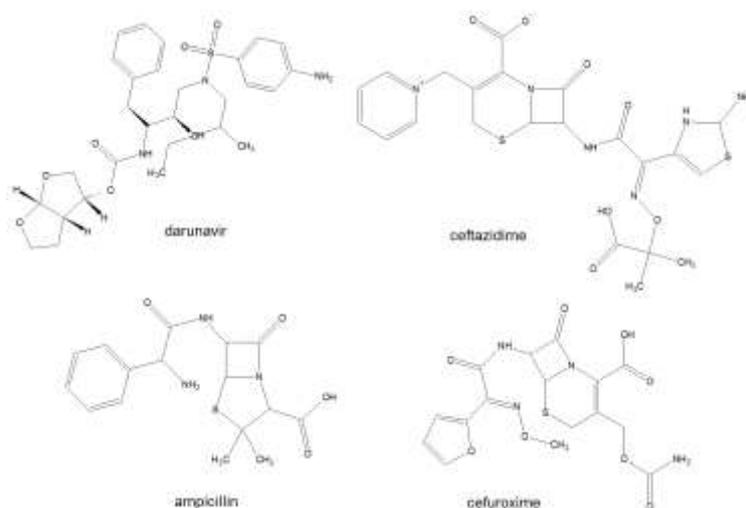


Fig-1: Chemical structures of darunavir, ceftazidime, ampicillin and cefuroxime.

All these advantages add strong commitment in support of this qualitative and quantitative alternative, in the monitoring of the production process of pharmaceutical companies that manufacture or handle drugs on a large scale, being this method easy to be implemented in an industrial environment aiming quality systems [16-18].

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Liquid chromatography occupies a special place because of its ease in effecting the separation, identification and quantification of chemical species, by itself or together with other instrumental analytical techniques. However, it is a more expensive technique,

by the cost of equipment, accessories, reagents and personnel training.

Thus, the optimization of composition of the mobile phase, the decrease in column wear, analysis time and the expense of reagents is fundamental in the evaluation of this technique as environmental friendly.

In addition to the specificity and resolution of all degradation products, concerns over the use of high concentration of ion pair reagent in the mobile phase, which reduces the useful life of the column and results in expensive routine analysis; simplicity or ease of application method; efficiency; sensitivity and cost were requirements, until then no concern to the scientific community, valued [19].

There are some exceptions using environmental friendly methods to analyse drugs by high performance liquid chromatography. For example for ampicillin [20], caffeic acid [21], Figure 2, and cefepime [22] where they utilize ethanol and purified water as mobile phase.



Fig-2. Chemical structure of caffeic acid.

TURBIDIMETRIC METHOD

The turbidimetric method is based on the inhibition of microbial growth measured by turbidity (absorbance) of the suspension of microorganisms susceptible to the antimicrobial agent, contained in a culture medium. The response of the micro-organism is a direct function of the concentration of the active substance.

Our research group is specialized in developing and validating analytical method by turbidimetry to evaluate the potency of antibiotics. Some examples of drugs (Figure 3) with turbidimetric method described in the literature are doxycycline [23], ampicillin [24], ciprofloxacin [25], cefuroxime [26], ceftazolin [27], tigecycline [28] and daptomycin [29].

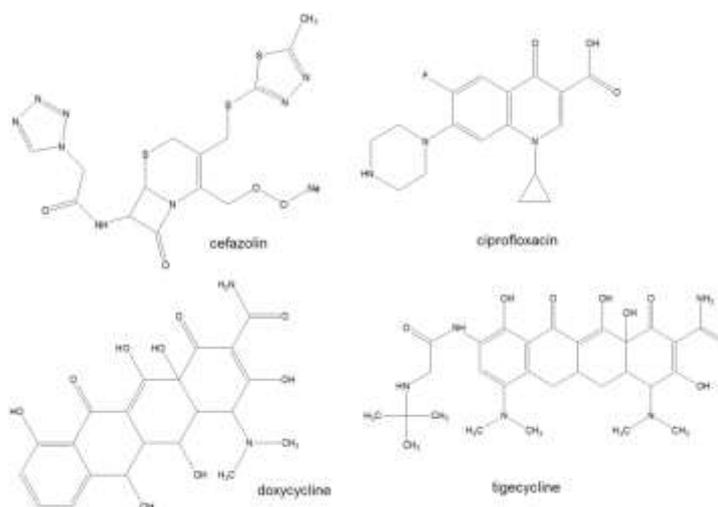


Fig-3. Chemical structures of doxycycline, ciprofloxacin, cefazolin and tigecycline.

The short analysis time provides optimization of the analyses, analysts and equipment. Thus, the logistics of pharmaceutical quality control is dynamited providing faster results and increased production. The final product reaches the consumer market in advance and as there are conditions of increased production, there is also increasing product supply in the market that may result in a decrease of prices for consumers. This is also called the Supply Chain, an action that begins in the choice of the analytical method to be used.

DISCUSSION

The use of simple and easy methods of execution, fast, precise, accurate and environmental friendly becomes more and more interesting for the

pharmaceutical industry in Quality Control of drugs and medicines.

The lack of environmental friendly methods for the analysis of pharmaceuticals with minimum generation of toxic waste and the consciousness of the analytical decisions is a gap that drives our research group.

The investigation of alternative methods such as these should be valued as well as reflections on their multidisciplinary, since this is social concern, environmental, economic and human. This shows the link between education, research and extension activities by the academy [30].

Universities have performed an important role serving as research centers for the development and validation of analytical methods environmental friendly for analysis of pharmaceutical products, contributing to the sanitary control activities and scientific enrichment in the area.

This process leads to the involvement of integrated research and the involvement of needs of society and the business sector, aimed at innovation and development of new techniques and products. Thus, professionals can develop their activities with more cooperation and organization, aiming at collective and strategic actions to optimize existing analytical methodologies.

CONCLUSION

The successful validation of HPLC, IR and turbidimetric methods were used for the analyses of pharmaceutical products. Our results show the importance of quantitative applicability of IR outside the academia research context. Applicability of the green techniques was confirmed by applying these methods for the quantification of several pharmaceutical ingredients. It is concluded that the developed methods can be used for routine analyses and this approach will yield innovative and ecological concepts in the chemical and pharmaceutical companies.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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