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DESIGN AND IMPLEMENTATION OF GREEN CHEMISTRY APPROACHES INTO PHARMACEUTICAL ANALYSYS OF BENZYDAMINE DOSAGE FORMES

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Мета. *Розвиток фармацевтичної галузі України та світу призводить до збільшення необхідності використання небезпечних та токсичних хімічних речовин та розчинників, що впливає на безпеку навколишнього середовища та безпосередньо працівників фармацевтичних компаній.*
Тому, одним з рішень даної проблеми є імплементація підходів «зеленої хімії» у лабораторіях контролю якості фармацевтичних підприємств.
Матеріали та методи. *Методи хроматографічного розділення використовуються для якісного та кількісного аналізу сировини та готових лікарських форм, визначення речовин що утворюються в процесі деградації активних речовин та дозволяють проводити експрес аналіз складних сумішей.*
Результати*. Для впровадження принципів «зеленої хімії» в лабораторії фармацевтичних підприємств потрібно оцінити можливість використання експрес методів контролю якості, таких як газова хроматографія, ультра високоефективна рідинна хроматографія, та абсорбційної спектрофотометрії в ультрафіолетовій та видимій області.*
Висновки*. Вивчено підходи до «озеленення» аналітичних процедур, які використовуються в контролі якості фармацевтичних препаратів. Запропоновано шляхи імплементації сучасних підходів методів «зеленої хімії» до хроматографічних методик. На основі розробленого дерева рішень запропоновано дизайн розробки та «озеленення» методик контролю якості бензидаміну в лікарських формах*
Ключові слова*: зелена хімія , бензидамін, рідинна хроматографія, газова хроматографія, абсорбційна спектрофотометрія*

1. Introduction

Global Pharmaceutical industry takes one of the leading places of constant evolvement and expansion. Such a huge growth of industry inevitably implies the growing concern of environment problems, which are pollution, wastes treatment, energy consumption and consequently adverse effect on the healthy future of nations [1].

Ukrainian market is not an exclusion. Nowadays there are more than one hundred pharmaceutical companies in Ukraine, and their amount increases from year to year [2]. The core strategy of domestic market development is expansion of volumes of drugs that are being released to the market and constant increase of new drug products, which emerge on the market as a result of research and development strategy.

At the same time, regulatory requirements for quality and manufacturing process enhance dramatically, tending to harmonization with European Union and Food and Drug Administration, resulting majorly the necessity of performing more tests for quality control, process validation, verification and quality by design experiments at the development stage of new formulations and during their lifecycle [3].

In contemporary pharmaceutical analysis major part play various chromatographic methods [4, 5]. They significantly differ one from another not only by their ability for separation, but also by the influence on the laboratory staff, waste production and resource consumption. In addition, if the API manufacturer obliged to use Pharmacopeia methods then the requirements for the finished dosage form are less strict and any validated in-house method can be used for quality control.

The outcome of pharmaceutical area evolvement implicates the growth of wastes, which need to be recycled, after utilization of huge volumes of toxic solvents and chemicals, the need of processes speed up in order to save energy and human resources, and finally the need of purchasing of new equipment and accessories for it [6, 7]. This issues become vital for environment and pollution regulation [8].

There is only one way to manage the outlined above issue. The solution is related with a green chemistry approach, the main goal of which is reduction of resources, minimization of wastes, energy consumption and where possible, substitution of toxic chemicals on less harmful and human friendly ones [9, 10].

Assessment of possibility of traditional analytical procedures conversion into green analytical methods with implementation of approach of minimization or reduction of toxic chemicals utilization, reduction of energy consumption and development of universal methods for simultaneous analysis.

Our aim is to concretize approaches for green analytical chemistry implementation in R&D laboratories for development of new chromatographic methods

of medicinal products quality control for both generic and original compositions, propose algorithm (decision tree) on green method elaboration and discuss possibility of its implementation during development of quality control methods for benzydamine hydrochloride oral spray.

2. Planning (methodology) research

Despite the need of conversion of traditional analytical procedures into green ones, the main goal of analytical chemistry should be taken into account. Thus, the purpose of any analytical procedure is revelation of parameters, which reflect the quality of a sample and give the possibility to make overall conclusion about the product, whether it is in or out of specification. Hence, the requirements for any method should be strict and include unambiguous selectivity, precision and accuracy. However, it might become a challenge not to lose crucial performance characteristics during the process of method «greening».

The main steps for reaching the aim of study were:

1. Analysis of the modern principles of green analytical chemistry
2. Discussion of the ways for HPLC method greening
3. Formation of decision tree for HPLC method greening
4. Planning of green analysis for benzydamine oral spray

3. Materials and methods

Information about the various methods of chromatographic separation and UV spectrophotometry were used in the current research that enabled to perform complex separation and researches of the quantitative and qualitative composition of mixtures.

The method of analysis and content survey were used for researching of main «green chemistry» concepts and sort out the essence of the approach for modern pharmaceutical analytical laboratories.

4. Results and discussion

The first declaration about green chemistry emerged in 1991 by Paul Anastas, who entered the term in the framework of green chemistry program [11]. The first approach to green analytical chemistry was proposed by M.de la Guardia and J. Ruzicka in 1994. Later on, J. Namiesnik proposed twelve principles of green analytical chemistry [12, 13] that were:

1. Direct analysis avoiding sample preparation.
2. Reduced sample size.
3. In situ analysis.
4. Use of integrated processes in order to save energy and prevent spending high amounts of reagents.
5. Automation and miniaturization.
6. Less or no derivatization.
7. Reduced waste.
8. Developments of methods for the simultaneous analysis of multiple analyses.
9. Reduction of energy consumption.
10. Use of renewable sources.
11. Replacement of toxic reagents or reduction of their use.
12. Great concern for the safety of analytical operator.

These principles begot four strategies for green analytical chemistry, which based on reduction of solvent consumption and consequently reduction of wastes, elimination of toxic chemicals utilization and minimization of energy consumption during the analytical process [14]. Given approaches of «green analytical chemistry» are too obscure and require more concrete decisions for a solution of a particular problem [15]. For chromatographic research laboratories, which specialize on development of new analytical procedures, it is important to emphasize processes and approaches that facilitate with «greening» existing methods or take into account these principles in a development process.

Contemporary pharmaceutical requirements evolve together with complexity of formulations. New finished dosage forms appear on the market and tend to be complex, with two or more active compounds and include variability in matrix of excipients. It means that the development of analytical procedure itself becomes a challenge for the scientist and attempts to match the green chemistry approach can affect a poor performance of the method itself and consequently cannot be assessed as appropriate for the quality control tool. However, modern approaches and techniques can facilitate with method “greening” even if it will doesn’t allow obtaining one hundred percent human friendly procedure.

The main role in contemporary pharmaceutical analysis plays high performance liquid chromatography [16]. Every year, modern single HPLC equipment produces up to five hundred liters of wastes, pumping through the column 1–1,5 ml per minute of mobile phase that comprise organic solvents, mobile phase modificators, buffer agents [17, 18]. Most common solvents in HPLC are toxic Acetonitril and harmful for people Methanol [19, 20]. Due to toxic properties pharmaceutical manufacturers make decision about their usage (Table 1). Their decision are very different and some solvents are preferred or recommended by one manufacturer and at the same time are used only in few issues by another ones. Also due to toxicity some solvents are recommended to be substituted.

Table 1

Solvent toxicity for solvent selection [20]

Class	Solvent	Conclusion (Pfizer)	Conclusion (GSK)	Conclusion (Sanofi)
Alcohols	Methanol Ethanol 1-Propanol 2-Propanol 1-Butanol 2-Butanol t-Butanol Ethylene glycol 2-Methoxyethanol	Preferred Preferred Preferred Preferred Preferred --- Preferred Usable ---	Some issues Some issues Some issues Some issues Few issues Few issues Some issues --- Major issues	Recommended Recommended Recommended Recommended Recommended Recommended Substitution Advisable Substitution Advisable Substitution requested
Hydrocarbons	n-Pentane Hexane(s) Cyclohexane Methylcyclohexane Heptane Isooctane Benzene Toluene Xylene(s)	Undesirable Undesirable Usable Usable Usable Usable Undesirable Usable Usable	--- Major issues Some issues --- Some issues Some issues Major issues Some issues Some issues	Banned Substitution requested Substitution Advisable Substitution Advisable Substitution Advisable --- Banned Substitution Advisable Substitution Advisable
Dipolar aprotic	DMSO Acetonitrile DMF DMAc* NMP	Usable Usable Undesirable Undesirable Undesirable	Some issues Major issues Major issues Major issues Major issues	Substitution Advisable Recommended Substitution requested Substitution requested Substitution requested

*Note: * – Listed as Dymethyl acetate in the original Pfizer publication*

Obviously, such a huge volumes of wastes become a real problem for environment and recycling. Therefore, possibility of replacement HPLC by another methods or its modification is nowadays the main way for analytical procedures greening.

The first step of waste reduction for HPLC method can be a consideration of alternative method selection. Among physico-chemical method, we can use some for decreasing of non-green properties of HPLC. Thus, UHPLC method is much friendlier for environment then traditional HPLC because it requires much less mobile phase that needs to be pumped through the chromatographic system. Yet, the sample preparation might still be an issue for the green method approach, as the sample needs to be diluted to the working concentrations that usually stay in range of micrograms. This method can be used if any other (UV, GC) methods are not fit for the implementation, resulting poor selectivity or accuracy of the method, ultra high performance liquid chromatography method can be opted as green chemistry friendly. It allows consuming much less volumes of mobile phase, smaller columns and the total time of a single run is usually about 5 minutes. Inconvenience of this method is difficulty in separation of some substances.

Another chromatographic method, which is widely used in analytical laboratories is gas chromatography. Therefore, another option for greening the HPLC assay method is selection of gas chromatography technic, which utilizes inert gases as a mobile phase, which is environment friendly, and the sample volume, is usually equals to 1 µl. The restriction of GC is the limited number of compounds that can be subjected to analysis, as the samples should be volatile. Derivatisation of a sample can be a solution to improve volatility; however, it goes against green chemistry principles. It is a much more "green" then HPLC, however sample preparation, such as sample dilution, extraction and derivatization are still a challenge for green chemistry.

For instance, the assay method by HPLC can be substituted by UV spectrophotometry method saving huge amounts of solvents. The UV- spectrophotometry method does not require mobile phase for the experiment and usually, dilution of a sample occurs in a water or inorganic buffer medium. So this method can be considered as one of the greenest analytical techniques. The issues that can affect the selectivity for UV spectrophotometry are complex sample matrix, containing compounds, with absorption at the same wavelength as the compound to be analyzed.

However, not all analytical procedures can be substituted with alternative green chemistry friendly, especially when dealing with hard separations of impurities or during the simultaneous determination of several compounds at one time. Inherently, HPLC is by far the strongest technic for such tasks, and in this case, method improvement can be done towards reduction of sample preparation, number of dilutions or sample volume (Fig. 1).

In the cases when determination can be carried out only by HPLC it is necessary to try decreasing toxicity by substitution of toxic mobile phases on less toxic,

for example, replacement of acetonitrile by ethanol. Main disadvantage of ethanol is its high viscosity, but the problem can be solved by increasing the temperature of elution. Ethanol is widely used nowadays in UHPLC and allows obtaining sufficient separation of different compounds.

Another option for substitution of toxic mobile phases is utilization of heated water. As water`s polarity decreases with temperature increase, it can be used instead organic solvents in some cases, especially when the compounds to be analyzed are thermally stable and do not tend to degrade with temperature growth.

The green chemistry approach (fig. 1) was implemented during pharmaceutical development of Benzydamine hydrochloride oral spray formulation. The dosage form contain benzydamine hydrochloride as API, methyl parahydroxybenzoate, glycerol, ethanol, polylobate and sodium saccharine, as excipients.

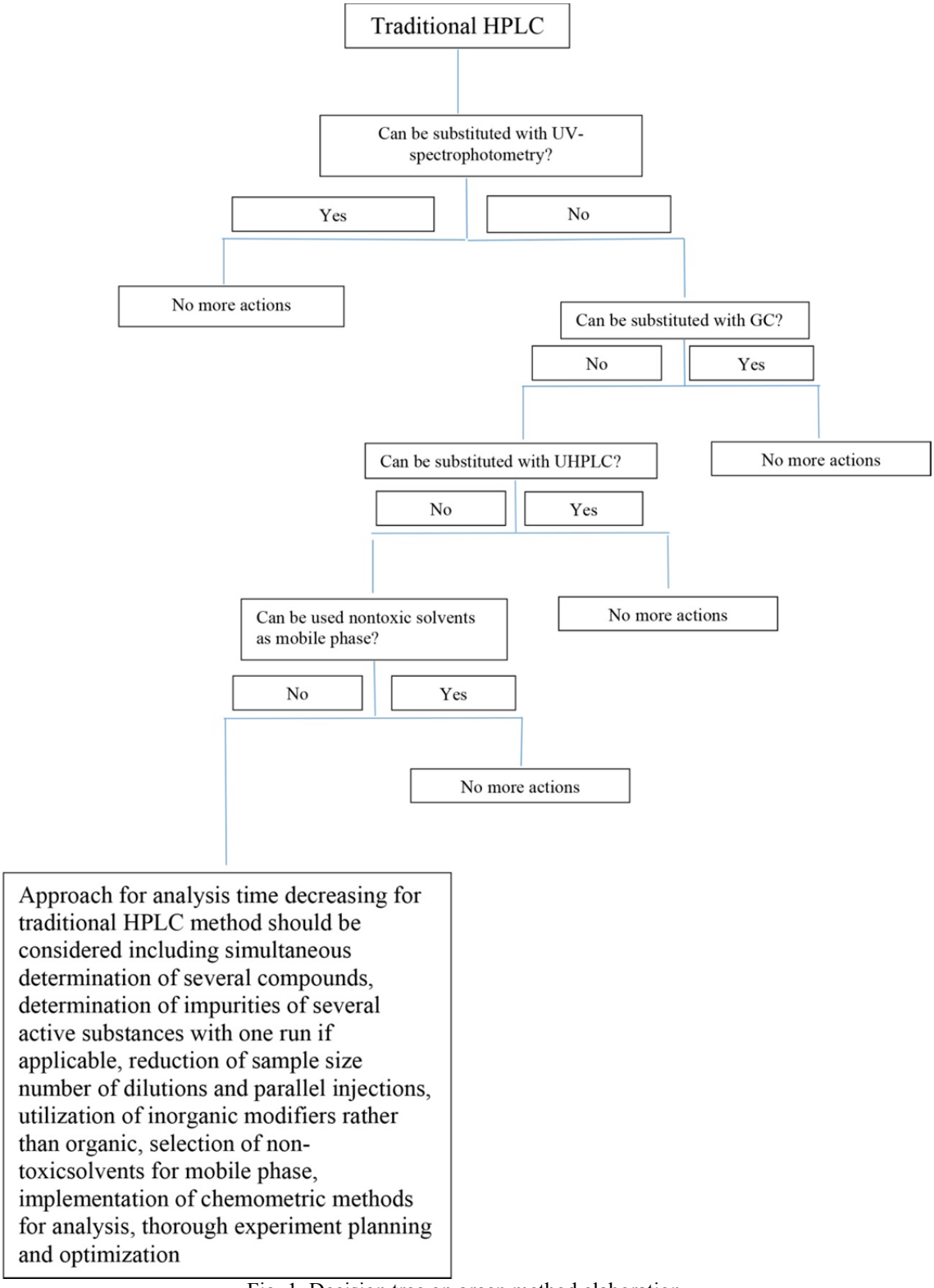

Fig. 1. Decision tree on green method elaboration

In the current dosage form, identification and quantification is mandatory for the API – benzydamine hydrochloride. HPLC and GC methods are common for this determination [21, 22]. Preservative – methylparabene, should also be quantified in the current formulation. For solution of this task, HPLC method is the most convenient [23], however GC method is also described for paraben determination [24]. Determination of Benzydamine impurities is also performed by RP-HPLC method [25].

From the viewpoint of «green chemistry» principles (8 - Developments of methods for the simultaneous analysis of multiple analyses) the best solution in our case is the simultaneous determination of the API, excipients and also related substances in one sample. Such approach allows reducing the energy consumption on equipment exploitation (principle 9 Reduction of energy consumption), decreasing of wastes, generated from the mobile phase (principle 7 Reduced waste), and toxic substances (principle 11 Replacement of toxic reagents or reduction of their use), minimization of time of negative exposure on the operator of analytical equipment (principle 12 Great concern for the safety of analytical operator).

After making of such a decision, we resorted to the analysis of a proposed decision tree (pic. 1) for the evaluation of a possibility of a further «method greening» and a substitution of HPLC method with another, more «green» one.

According to the decision tree, the first attempt was made to use the UV spectrophotometry method. However, it does not allow quantifying either active compounds or preservative, due to the matrix complexity.

The next step was made by evaluation of gas chromatography capabilities. The method enables quantification of several analytes with a single injection. In our case, benzydamine could be converted to the form of base after hydrolysis and extracted with a small amount of chloroform with subsequent gas chromatography. However, GC method is not selective for all impurities of benzydamine, and cannot be used in this case.

Thus, the decision tree lead us to the liquid chromatography method. In our case, the «green chemistry» approach implied simultaneous procedure for quantitative determination of active compound, preservative and related impurities with a single chromatographic run, with an attempt for selection of «friendly chemicals». Therefore, we chose the RP HPLC methodology substituting sodium octane sulphonate and phosphate buffer, which were used in British Pharmacopeia, on sodium perchlorate and perchloric acid that obviously are safer for environment and less expensive in comparison with organic modifier. The method was performed on C18 sorbent using acetonitrile-buffer solution as a mobile phase, reducing the time of total equipment exploitation, analyst working time and exposure with the chemicals.

Therefore, the «greening approach» was implemented for benzydamine dosage form and resulted the simultaneous determination of three parameters, such as two assays and impurities determination with a single liquid chromatography procedure, instead of at least two different HPLC procedures.

6. Conclusions

It is crucial to think in a green way while developing new analytical methods or changing existing ones. However, the new approach should not put on test the initial goal of analytical procedure, as the method should be fit for its purpose, be robust and give reliable results.

There have been described a lot of principles of analytical methods greening based on minimization of solvents utilization, use of fast methods like UV spectrophotometry, simultaneous analysis of several quality parameters with one analytical test that is supposed to be a crucial strategy for «green analytical chemistry», as the outcome may match key principles together with performance sustainability. Such strategy gives us a chance to get reliable results saving energy, time and exposure on the laboratory staff.

Techniques for «analytical methods greening», which are used in quality control of pharmaceutical products, were studied. The ways for implementation of contemporary methodologies of «green chemistry» were proposed. The design of «greening» for the quality control methods of benzydamine in dosage forms according to the devised decision tree was proposed. On the base of this algorithm an optimal method for quality control of oral spray was planned as simultaneous tests: assay of benzydamine, related impurities and assay of methylparaben.

Conflict of interest

No conflict of interest

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