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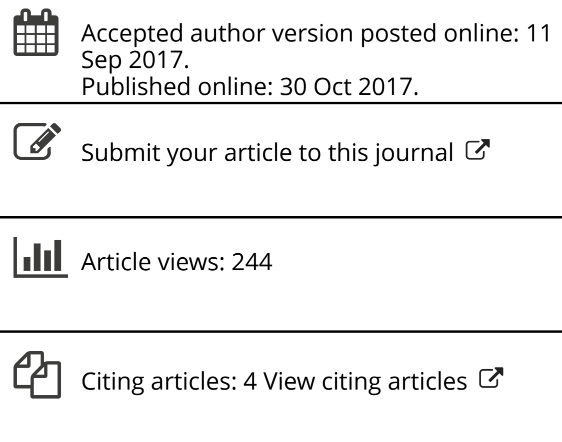

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Metformin: A Review of Characteristics, Properties, Analytical Methods and Impact in the Green Chemistry

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ABSTRACT
Diabetes mellitus (DM) is considered a public health problem. The initial treatment consists of improving the lifestyle and making changes in the diet. When these changes are not enough, the use of medication becomes necessary. The metformin aims to reduce the hepatic production of glucose and is the preferred treatment for type 2. The objective is to survey the characteristics and properties of metformin, as well as hold a discussion on the existing analytical methods to green chemistry and their impacts for both the operator and the environment. For the survey, data searches were conducted by scientific papers in the literature as well as in official compendium. The characteristics and properties are shown, also, methods using liquid chromatography techniques, titration, absorption spectrophotometry in the ultraviolet and the infrared region. Most of the methods presented are not green chemistry oriented. It is necessary the awareness of everyone involved in the optimization of the methods applied through the implementation of green chemistry to determine the metformin.

KEYWORDS
Analytical methods; diabetes mellitus; green chemistry; metformin

Introduction

Diabetes mellitus (DM) has a high incidence in the world and a high mortality rate, great impact on people's quality of life and its considered a public health problem.[11]

DM type 2 (DM2) is the predominant type that accounts for about 90–95% of cases of diabetes[42] and is also known as non-insulin dependent diabetes.[10] Insulin is a hormone produced by the beta cells of the islets of Langerhans of the pancreas, being released under conditions when there is an elevation of glucose in the blood, since insulin is responsible for transport and metabolism of glucose to generate energy.[11] DM2 is a metabolic disease characterized by a high level of glucose in the blood (hyperglycemia),[42] resulting from defects of secretion by destruction of beta cells of the pancreas (insulin producing) or defects of the action of insulin caused by the resistance to the action of insulin among others.[8]

The clinical symptoms of diabetes are: polyuria, polydipsia, polyphagia and unintentional weight loss (the "4 Ps"). However, in most cases, diabetes is asymptomatic, permanently undiagnosed until symptoms of complications are manifest.[8]

The main relevant complications of DM include ulcers, amputations, retinopathy, renal failure and heart diseases.[42]

Initial treatment is based on lifestyle changes with more exercise and dietary changes, in an attempt to maintain or reduce the level of glucose within normal parameters. If these measures do not regulate the level of blood glucose for these parameters, drug intervention is required.

Oral antidiabetic agents are classified according to their mechanism of action being these oral hypoglycemic agents or secretagogues (sulphonylureas and methyglinides); insulin action sensitizers (thiazolidinediones); neoglycogenesis reducers (biguanidines) and reducers in the rate of absorption of glycines (α-glycosidase inhibitors). New drugs have become available, for example, the incretinomimetics; inhibitors of dipeptidyl peptidase 4 (DPP-IV) and amylin analogues, with the aim of improving efficacy and reducing undesirable effects.[34]

Metformin is a drug that represents the class of biguanides, which aims to reduce the hepatic production of glucose. Glibenclamide, glimepiride and glycazide represent the class of sulfonylureas, which stimulate an insulin production. As thiazolidinediones increase and sensitize an action of insulin in the liver, adipose and muscle tissue. Arcabose represents the class of alpha-glucosidase inhibitors, which decreases the absorption of glucose by the intestine.[11]

Metformin is presented in the form of single-ingredient preparations in the USA as Fortamet®, Glucophage®, Glumetza®, Riomet®; in United Kingdom as Bolamyn®, Glucophage®, Metabet®, Metsol®; in Brazil as Diaformin®, Dimefor®, Formyn®, Glicefor®, Glifage®, Gliformil®, Glucoformin®, Meguanin®, Metform®, Metformed®, Metformix®, Metta®, Teutoformin®; in Canada as Glucophage®, Glumetza®, Glycon®; in Germany as Biocos®, Diabesin®, Diabetase®, Glucobon®,Glucophage®, Juformin®, Mediabet®, Meglucon®, Mescorit®, Met®, Metfogamma®, Metformdoc®, Siofor® and in Japan as Glycoran®, Melbin®.[6]

It is necessary to be concerned with the importance of developing effective and reliable analytical methods for quality control, otherwise such practices could lead to disastrous decisions and irrecoverable financial losses.[31]

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Metformin is the drug of choice for DM2 due to its wide use it is essential to develop new methods of analysis for its evaluation and quantification.

Appropriate methods of analysis may be the first step in the rational use of medicines.[29]

Currently, the methods of analysis follow the green chemistry line, being fast, without use or with reduction in the use of toxic solvents, with miniaturized samples, reduction in the number of steps and pre-treatments.[5,20,28,29]

The first proposal of analysis involving the green chemistry appeared in the decade of 90, through the concern with the results obtained during analysis, as well as with the operators and environment.[5]

Ecologically correct methods are those that minimize the impact on the environment, the operator who have direct contact with the solvents and as well as to the population in general, due to the concern with the final cost of the product. These methods must have high sensitivity, low cost of analysis, lower energy consumption and simplicity and efficiency compared to the time of analysis. Such concerns should be considered from the sampling process until disposal the final residue.[5,20,28,29]

The miniaturization of the samples and the substitution of toxic reagents are alternatives for the obtaining of ecologically green methods, for this to occur it is necessary that there are changes in all analytical process.[5,20,29]

Therefore, the objective of this review is to (i) carry out a survey of the characteristics and (ii) properties of metformin, as well as (iii) conduct a discussion on existing analytical methods for the quantification of the drug in pharmaceutical product aiming at green chemistry and (iv) its impacts on both the operator and the environment.

Metformin

Metformin (Figure 1) belongs to the class of biguanides is the treatment of choice for DM2 in most patients because it treats more effectively.[44] Metformin reduces glucose levels and improved insulin sensitivity.[49] According to the,[61] treatment intensified by metformin reduces 29% of microvascular complications and 32% of combined diabetes outcomes, whereas insulin and sulphonylureas accounted for only 25% and 12%, respectively. Regarding the reduction of cardiovascular events and mortality, only intensive treatment with metformin and intensive control of hypertension were shown effective.[61] In addition, metformin does not lead to hypoglycemia and does not promote weight gain. Salpeter and collaborators[54] suggest that it is a long-term safe drug even when used in clinical situations traditionally seen as contraindicated for its high risk of lactic acidosis.

Figure 1. Chemical structure of metformin (CAS 1115-70-4).

Action mechanism

Metformin is used in the treatment of non-insulin dependent diabetes that does not respond to dietary modifications. Metformin acts as a metabolic inhibitor and alters the metabolism of cellular energy throughout the body.

Its main mechanism of action in the disease is an inhibition of hepatic gluconeogenesis. Metformin interacts with the complex I the mitochondrial electron transport chain, thereby decreasing cellular ATP levels and causing an accumulation of AMP. The binding of AMP to the adenylate cyclase site inhibits its action in response to glucagon, thereby disrupting AMPc-PKA signaling. As a result, the activity of gluconeogenic pathway enzymes is inhibited in favor of glycolysis. This mechanism is probably the main mode by which metformin reduces the hepatic production of glucose.[49]

Pharmacokinetics

Metformin is employed in pharmaceutical formulations in the form of the hydrochloride salt of metformin. Metformin has an absolute oral bioavailability of 40–60%, and gastrointestinal absorption is apparently complete within 6 hours after ingestion.[39] There is an inverse relationship between the dose ingested and the relative absorption of therapeutic doses, which suggests the involvement of the saturable absorption process. Metformin is rapidly distributed and does not bind to plasma proteins. It does not undergo liver metabolism, and no metabolites or metformin conjugates have been identified. Metformin is excreted unchanged in the kidneys and has a mean plasma elimination half-life after oral administration between 2 and 6 hours. This elimination is prolonged in patients with renal impairment and is correlated with creatinine clearance.[24] Metformin is distributed in breast milk in small amounts.[39]

Physicochemical properties

Metformin hydrochloride is a white or almost white crystal, chemically identified as N, N-dimethylimidodicarbonicarbonidediamide hydrochloride. Its molecular formula is $C_4H_{11}N_5$.HCl[7,62] and its CAS number is 1115-70-4. Metformin has a molecular mass of 129.16 g/mol, whereas metformin hydrochloride has a mass of 165.6 g/mol.[9] It is freely soluble in water when hydrochloride (1.38 mg/mL), slightly soluble in alcohol, and practically insoluble in acetone and methylene chloride.[7] The melting point ranges from 223 to 226°C, its LogP is −0,5 and pKa 12.4 (basic).[9,51]

Analytical methods

The analytical methods for metformin evaluation were researched in the literature through scientific articles, as well as in official compendium.[7,9,18,25,39,47,62]

Table 1 shows the analytical methods described in the literature for the determination of metformin.

Table 1. Analytical methods described in the literature for the determination of metformin.

Method	Conditions	Analysis time (min)	Detection system	Matrices	Reference
HPLC–UV	Analytical column (250 mm × 4.6 mm; 10 µm), with pre-column Whatman SCX (7.5 mm × 4.6mm); MP: Solvent A: ammonium phosphate 0.05 mol/L, Solvent B ammonium phosphate 0.4 mol/L; flow 1mL/min and 2 mL/min	5.0	232 nm	Human plasma	[63]
HPLC–UV	Column of silica (250 mm × 4.6 mm; 5 µm), with pre Hichrom Silica H5 column (10 mm × 3.2 mm); At 40 °C; MP: acetonitrile (25%) and 75% pH 7 of 0.03 M hydrogen phosphate buffer; flow rate 1mL/min	7.8	240 nm	Human plasma	[13]
HPLC–UV	Column of cation exchange (250 mm × 4 mm; 5 µm), with pre-column of cation exchange Nucleosil (30 mm × 4 mm; 5 µm), maintained at room temperature; MP: tetramethylammonium phosphate buffer pH 3.7 (adjusting the pH of tetramethylammonium hydroxide 100 mM/L to 3.7 with 1mol/L phosphoric acid) and acetonitrile (80:20, v/v); flow rate 1mL/min	Uninformed	236 nm	Human plasma and breast milk	[67]
HPLC–EM/EM	Column C8 (150 mm × 4.6 mm; 5 µm) with pre-column Phenomenex C18 (4 mm × 3 mm; 5 µm); at 25°C; MP: acetonitrile: water: formic acid (70:30:1, v/v/v), flow rate 0.5 mL/min	3.4	Positive mode using selected reaction monitoring (SRM)	Human plasma	[12]
HPLC–EM/EM	Column C18 (250 mm × 4.6 mm; 5 µm) at 40 °C; MP: ammonium acetate buffer 10 mmol/L; flow 500 µL/min	Uninformed	Ion trap and electrospray ionization (ESI)	Oxidation end-product in aqueous solutions	[14]
HPLC–EM/EM	Column C18 (50 mm × 4.6 mm; 5 µm) maintained at room temperature; MP: ammonium acetate 10 mmol/L (adjusted pH 7 with triethylamine): acetonitrile: methanol 60:20:20 (v/v/v); flow rate 0.65 mL/min	Uninformed	Positive mode using multiple reaction monitoring (MRM)	Human plasma	[65]
HPLC–UV	Silica column (250 mm × 4.6 mm; 5 µm), with pre-column water spherisorb S5 W (30 mm × 4.6 mm); At 50 °C; MP: 40 mM acetonitrile, aqueous hydrogenated sodium phosphate (25:75, v/v), pH 6; flow rate 1.3mL/min	9.0	234 nm	Human plasma	[2]
HPLC–EM/EM	Ion exchange column (2 mm × 20 mm, 5 µm) at 60°C; MP: Solution A: sol. ammonium acetate 15 mM/L, Solution B: acetonitrile, Solution C: acetonitrile: 15 mM/L ammonium acetate (90:10, v/v), Solution D: methanol: water (50:50, v/v)	7.0	Electrospray operated in positive mode	Human plasma	[30]
HPLC–EM/EM	Column C18 (30 mm × 4 mm; 3 µm); MP: solvent A acetic acid 0.1% and solvent B acetonitrile (gradient elution); flow rate 0.8 mL/min	Uninformed	Positive mode using multiple reaction monitoring (MRM)	Human urine	[58]
HPLC–EM/EM	Column C18 (50 mm ×2.1 mm; 3 µm) maintained at room temperature; MP: methanol: water (containing 1% formic acid): acetonitrile (30:31:39; v/v/v); flow rate 0.2 mL/min	2.0	Operated in positive mode using triple quadrupole	Human plasma	[69]
HPLC–UV	Column C18 (250 mm × 4 mm) maintained at room temperature; MP: water/ methanol (70:30 v/v) (gradient elution); flow rate 0.5mL/min	Uninformed	233 nm	Tablets	[4]
HPLC–EM/EM	Column C18 (50 mm × 2.1 mm; 5 µm) with pre-column Phenomenex C18 (4 mm × 3 mm); At 30°C; MP: acetonitrile: 20 mM ammonium acetate: 96% formic acid (70:30:1, v/v/v); flow rate 0.2 mL/min	2.0	Positive mode using multiple reaction monitoring (MRM)	Human plasma	[17]
HPLC– EM/EM	CN column (150 mm × 4.6 mm; 5 µm) with pre-column Phenomenex C18 (2 mm × 4 mm) at 25°C; MP: 50% aqueous solution 0.01 mol/L ammonium acetate adjusted to pH 3.5 with acetic acid and 50% acetonitrile (50:50 v/v); flow rate 1 mL/min	Uninformed	Ion trap operated in positive mode	Human plasma	[21]
HPLC–EM/EM	Column C18 (100 mm × 2 mm; 3 µm) with pre-column varian (0.20 mm x 0.20 mm; 5 µm) at 30°C; MP: water: acetonitrile: formic acid (55:45:0.048, v/v/%); flow 0.3 mL/min	Uninformed	Operated in positive mode and electrospray ionization (ESI)	Human plasma	[38]
HPLC–EM/EM	Column C18 (50 mm × 4.6 mm; 5 µm) at 25°C; MP: 700 mL acetonitrile with 300 mL of 5 mM/L ammonium acetate at pH 3, adjusted with glacial acetic acid; flow rate 0.4 mL/min	3.5	Positive mode using multiple reaction monitoring (MRM)	Human plasma	[41]
HPLC–EM/EM	CN column (150 mm × 2 mm; 5 µm) at 40°C; MP: methanol: 30 mM/L ammonium acetate adjusted to pH 5 (80:20 v/v); flow rate 0.2 mL/min	11.0	Operated in positive mode using selected reaction monitoring (SRM)	Human plasma	[66]
HPLC–UV	Column C18 (250 mm × 4.6 mm; 5 µm) at 40°C; MP: ammonium dihydrogen phosphate 5.75 g in 900 mL of purified water, pH adjusted to 5.25 with sodium hydroxide, the volume was diluted to obtain 0.05 M solution; flow rate 1.5 mL/min	5.4	235 nm	Tablets	[1]
HPLC–EM/EM	Column C18 (150 mm × 2.1 mm; 5 µm), with pre-column C18 (4 mm × 3 mm) at 25°C; MP: acetonitrile and 0.05% aqueous solution of formic acid (60:40, v/v); flow rate 0.2 mL/min	Uninformed	Quadrupole and electrospray ionization (ESI)	Adulterated herbal products (capsules)	[45]
HPLC–EM/EM	Column C18 (33 mm ×4.6 mm; 5 µm) maintained at room temperature; MP: methanol: water (containing 0.5% formic acid) 80:20 (v/v); flow rate 0.6 mL/min	Uninformed	Operated in positive mode using triple quadrupole	Human plasma	[55]

(*continued on next page*)

Table 1. (*Continued*).

Method	Conditions	Analysis time (min)	Detection system	Matrices	Reference
HILIC–EM/EM	HILIC column (150 mm × 2.1 mm; 5 μm) at 42°C; MP: water: acetonitrile (30:70, v/v) with 0.1% formic acid; flow rate 0.65 mL/min	4.0	Electrospray operated in positive mode	Human plasma	[33]
Infrared diffuse spectroscopy	The samples were mixed and/or comminuted in a Speg Certiprep model 6750 freezer mill cryogenic mill with 148 ± 0.3 mg pellets	Uninformed	4000–650 cm^{-1}	Tablets	[46]
HPLC–UV	Column C18 (250 mm × 4.6 mm; 5 μm), maintained at room temperature; MP: acetonitrile, potassium dihydrogen phosphate buffer pH 6.5 (34:66, v/v) and sodium 3 mM dodecyl sulfate; flow rate 0.7mL/min	Uninformed	236 nm	Human plasma and urine	[19]
HPLC–UV	Column (150 mm × 4.6 mm) at 25°C; MP: acetonitrile: sol. 0.01 M aqueous sodium octanesulfonic acid (adjusted pH 2.5 with phosphoric acid) (21:79); flow rate 1 mL/min	Uninformed	232 ± 2 nm	Human plasma	[22]
HPLC–EM/EM	CN column (150 mm × 4.6 mm; 5 μm) at 25°C; MP: acetonitrile: sol. aqueous 10 mM ammonium acetate (adjusted to pH 3.5 with acetic acid) (50:50); flow rate 1 mL/min	Uninformed	Ion trap	Human plasma	[22]
UPLC–EM/EM	Column C18 (50 mm × 2.1 mm; 1.7 μm) at 40°C; MP: solvent A: acetonitrile containing 0.1% formic acid and solvent B: water containing 0.1% formic acid (gradient elution); flow rate 0.2 mL/min	6.0	Electrospray operated in positive mode	Drugs adulterated and dietary supplements Chinese	[32]
Absorption spectroscopy UV	Water as solvent (successive dilutions up to 0.001% w/v)	Uninformed	232 nm	Tablets	[9]
HPLC–UV	Column C18 (15 cm × 4.6 mm; 5 μm) at 40°C; MP: Dissolve 0.8 g of sodium lauryl sulfate in 620 mL of dilute phosphoric acid and add 380 mL of acetonitrile	Uninformed	235 nm	Tablets	[25]
HILIC–EM/EM	HILIC column (50 mm × 2 mm; 3 μm); MP: acetonitrile: water (80:20, v/v), with 2 mM ammonium formate and 0.1% formic acid; flow rate 0.4 mL/min	3.0	Operated in positive mode using multiple reaction monitoring (MRM)	Rat plasma	[68]
HPLC–EM/EM	Polar RP column (150 mm × 2 mm; 4 μm) with pre-Phenomenex column (4 mm ×2 mm) at 40°C; MP (elution gradient): solvent A: 0.1% formic acid (v/v) with ammonium formate 1 mmol/L; Solvent B: acetonitrile: 0.1% formic acid (v/v) with 1 mmol/L of ammonium formate, flow 0.2 mL/min and 0.4 mL/min	12.5	Positive mode using multiple reaction monitoring (MRM)	Human plasma	[23]
UPLC–EM/EM	HSS column (50 mm x 2.1 mm, 1.8 μm) at 40°C; MP (elution gradient): solvent A: 10 mM ammonium formate and 1% acetonitrile in water (adjusted to pH 3.0 with formic acid), solvent B: 0.2% formic acid in acetonitrile; The gradient starts with 1% of solvent A and changes linearly to 40% of solvent A within 3 min and returns to 1% within 0.1 min	3.5	Multiple reaction monitoring mode using positive electrospray ionization	Human plasma	[52]
HILIC–EM/EM	HILIC column (150 mm × 2.1 mm; 5 μm), with pre-Merck SeQuant column (20 mm × 2.1 mm; 5 μm) at 30°C; MP: water with 0.1% formic acid and acetonitrile with 0.1% formic acid (in linear gradient); flow rate 0.2 mL/min	Uninformed	Triple quadrupole	Whole blood	[56]
HPLC–EM/EM	Column C18 (50 mm × 4.6 mm, 3 μm); MP: acetonitrile: 10 mM ammonium acetate (pH 3.0 ± 0.05) (60:40, v/v); flow 1.1 mL/min	2.5	Operated in positive mode using quadrupole	Human plasma	[50]
Potentiometric titration	4 mL of anhydrous formic acid, and add 50 mL of acetic anhydride. Titrate with 0.1 M perchloric acid.	Uninformed	End-point of titration	Raw material	[62]
Absorption spectroscopy UV	Dilution in water to a concentration of 10 μg/mL	Uninformed	232 nm	Tablets	[62]
HPLC–UV	Column packing L1 (30 cm × 3.9 mm, 10 μm); MP: Acetonitrile and buffer solution (0.5 g/L of sodium heptanesulfonate and 0.5 g/L of sodium chloride in water, adjusted with 0.06 M phosphoric acid to a pH 3.85), 1:9; flow 1.0 mL/min	Uninformed	218 nm	Extended-release tablets	[62]
Absorption spectroscopy UV	Mix and stir 0.1 g of the sample with 70 mL of water for 15 min, dilute to 100 mL with water and filter, discarding the first 20 mL. Dilute 10 mL of the filtrate to 100 mL of water and dilute 10 mL of the resulting solution to 100 mL of water	Uninformed	232 nm	Tablets	[7]
Potentiometric titration	Dissolve 0.100 g in 4 mL of anhydrous formic acid. Add 80 mL of acetonitrile. Titrate with 0.1 M perchloric acid.	Uninformed	End-point of titration	Raw material	[7,18]
HPLC–UV	Column with benzenesulfonic acid groups (12.5 cm × 4.6 mm, 5 μm); MP: 1.7% w/v ammonium dihydrogen orthophosphate adjusted to pH 3.0 with ortophosphoric acid; flow 1.0 mL/min	Uninformed	218 nm	Oral solution	[7]

Notes: MP: Mobile phase; HPLC–EM/EM: High performance liquid chromatography coupled to sequential mass spectrometry; HILIC–EM/EM: Hydrophilic interaction liquid chromatography coupled to sequential mass spectrometry; HPLC–UV: High performance liquid chromatography with ultraviolet detection; UPLC–EM/EM: Ultra performance liquid chromatography coupled to sequential mass spectrometry.

The quantification of metformin in biological samples is very important for conducting pharmacokinetic studies, bioavailability, bioequivalence and consequently for the therapeutic monitoring of this substance. In the analyzed literature, there is a predominance of determination by high-performance liquid chromatography (HPLC), but also determinations using liquid chromatography of ultra-efficiency, titration, ultraviolet absorption spectroscopy and diffuse infrared spectroscopy.

It is necessary to emphasize the absence of analytical methods in the literature and pharmacopoeias for tablet form or other pharmaceutical product, most of them are only for the raw material. This absence is dangerous and can trigger many public health problems. The most commercially available product of metformin is the tablets. Thus, the pharmaceutical industry must have analytical methods for evaluating the quality of the final product before release to the consumer market. If quality control does not exist or it is ineffective, products with a doubtful content will be found in the market. The consequence of this is patients without treatment improvement who will return to the health services, which will be overloaded.

Another question is the type of analytical method. The big pharmaceutical and chemical industries have money to invest in technology; however, the small and medium pharmaceutical and chemical industries or even independent or unrelated laboratories to large companies are not equipped with the latest technologies. Therefore, varied methods are needed with the purpose of the industry or laboratory choosing the most appropriate to their reality.

An end item that also impacts this multi-dimensional view is cost. The choice of type of analysis has a direct impact on the cost of this final product. So, it is important to know the impact of an analytical decision.

Impact of analytical decisions

Among the methods studied, most of them do not fit the theory of green chemistry, being toxic waste generators, for example the organic solvents as acetonitrile and methanol. Buffer solutions are not toxic to the environment and the operator, but they can decrease the life of equipment and accessories, such as chromatographic columns and this impacts the cost of the analysis.[5,16,20,29,40,53,60] The proposal is to try to change the solvent used by another less toxic or try to decrease the amount of solvent. However, the reality is that analysts and operators do not try to change processes or do not want to improve the process. They test directly, for example, methanol and acetonitrile automatically.

Drugs that are poorly soluble in water can be solubilized first in ethanol (for example) and diluted in water. This is very common in laboratories that work toward green chemistry. The solvent is still used, but it is a less toxic solvent (ethanol, for example) and in a smaller amount (since the water was used as diluent). This contemplates the solvent required for HPLC technology and the solubility of poorly soluble drugs. This is the thought.

During the development of the method considered green there is concern in the choice of solvents with low toxicity (for example, ethanol and water), as well as to use them in low concentrations in addition to the effort to work with reduced samples, through the miniaturization of the samples. If this is not possible, work must be done through on recovery of toxic solvents, as these materials cannot be disposed of directly into the environment.[5,16,20,29,36,48,53,57,59,60]

Decrease the process steps and the pre-treatment of the samples are also a part of the green chemistry, because these activities directly influence in the amount of reagents used, the time of analysis or reaction, the number of materials required and cost involved.[16,27,29] The method of spectrophotometry in the infrared region is an option and a reality for analysis of pharmaceuticals. It can be used for both qualitative and quantitative analyses of raw materials and pharmaceuticals. It is known as a technique of excellence in pharmaceutical analysis. The method of spectrophotometry in the infrared region is also able to indicate the stability of the product to be analyzed by comparing the spectrum of the standard, being considered an indicative method of stability.[3,15,26,28,36,43,59,64]

The choice of equipment should also be important, it is recommended to use those that require the least amount of solvent, less time for analysis, lower energy consumption, lower costs for the company and lower final product prices as for example the HPLC or capillary electrophoresis. In capillary electrophoresis, samples are used around nL and in HPLC it is used around μL.[27–29,59,60] Each method has its advantages and disadvantages. The choice must not be by the most famous method or by the method that everyone is using, but the ideal one for your analysis or for what you want to study. HPLC or capillary electrophoresis? It depends on your objectives. What do you want to investigate at the moment?

These methods should be increasingly encouraged by their advantages and economic benefits. Thus, the universities become reference research centers in the area contributing to achievement of this objective.

Conclusion

Metformin is the drug of choice for the treatment of DM2, disease considered a worldwide epidemic. The wide use of this drug contributes to the development of studies that need carry out their analytical and bioanalytical quantification.

The existing methods in the literature and official compendiums for quantification of metformin in raw material, pharmaceuticals and biological systems can still contemplate more the thought of green chemistry, whether in the choice of solvent, method, amount of sample, number of steps… The improvement of methods of analysis must be constant.

Conflict of interest

The authors declare no conflicts of interest.

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References

[1] Ali, A. R.; Duraidi, I. I.; Saket, M. M.; Abu-Nameh, E. S. Column High-Performance Liquid Chromatographic Method for the Simultaneous Determination of Rosiglitazone and Metformin in a Pharmaceutical Preparation. *J. AOAC Int.* **2009**, *92*, 1, 119–124.

[2] Amini, H.; Ahmadiani, A.; Gazerani, P. Determination of Metformin in Human Plasma by High-Performance Liquid Chromatography. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2005**, *82*, 139–322.

[3] Amorin, S.; Klier, A.; Angelis, L. Quality Control in the Pharmaceutical Industry: Identification of Substances by Infrared Spectroscopy. *Revista Brasileira de Farmácia* **2005**, *94*, 190–198.

[4] Arayne, M. S.; Sultana, N.; Zuberi, M. H. Development and Validation of RP-HPLC Method for the Analysis of Metformin. *Pakistan J. Pharmaceutical Sci.* **2006**, *19*, 3, 231–235.

[5] Armenta S.; Guardia de La M. Green Analytical Chemistry. *Trends Anal. Chem.* **2008**, *27*, 6, 497–511

[6] Brayfield, A. *Martindale: The Complete DrugReference;* 38th ed.; Pharmaceutical Press: London, United Kingdom, **2014**.

[7] BP. *British Pharmacopeia*; The Stationary Office: London, **2017**.

[8] Brazil. *Department of Primary Care. Diabetes Mellitus*; Ministry of Health: Brasília, p.64. II Notebooks of Basic Attention, n.16. **2006**.

[9] Brazilian Health Surveillance Agency. *Brazilian Pharmacopoeia*;5.ed. Atheneu: São Paulo, **2010**.

[10] Brazilian Society of Diabetes. What is diabetes? http://www.diabetes.org.br/o-que-e-diabetes. (accessed Mar 09, **2016**).

[11] Calista, A. A. Therapeutic Conduct for the Treatment of Type 2 Diabetes Mellitus: A Review of the Literature. 45p. (Monograph), State University of Paraíba, Campina Grande, Paraíba, **2012**.

[12] Chen, X.; Gu, Q.; Qiu, F.; Zhong, D. Rapid Determination of Metformin in Human Plasma by Liquid Chromatography-Tandem Mass Spectrometry Method. *J. Chromatogr B Anal. Technol. Biomed. Life Sci.* **2004**, *802*, 2, 377–381.

[13] Cheng, C. L.; Chou, C. H. Determination of Metformin in Human Plasma by High-Performance Liquid Chromatography with Spectrophotometric Detection. *J. Chromatogr B Anal. Technol. Biomed. Life Sci.* **2001**, *726*, 1, 51–58.

[14] Collin, F.; Khoury, H.; Bonnefont-Rousselot, D. B.; Thérond, P.; Legrand, A.; Jore, D.; Gardes-Albert, M. Liquid Chromatographic/Electrospray Ionization Mass Spectrometric Identification of the Oxidation End-Products of Metformin in Aqueous Solutions. *J. Mass Spectrom.* **2004**, *39*, 8, 890–902.

[15] Corrêa, J. C. R.; Salgado, H. R. N. A. Platform for Designing Quantitative Infrared Spectrophotometric Method for Drugs and Pharmaceuticals Analysis: A Rediscover for an Ecological and Safer Technique in the Routine Quality Control Laboratories. *World J. Pharmacy Pharmaceutical Sci.* **2014**, *3*, 2056–2059.

[16] Cue, B. W; Zhang, Ji. Green Process Chemistry in the Pharmaceutical Industry. *Green Chem. Lett. Rev.* **2009**, *2*, 4, 193–211.

[17] Ding, C. G.; Zhou, Z.; Ge, Q. H.; Zhi, X. J.; Ma, L. L. Simultaneous Determination of Metformin and Glipizide in Human Plasma by Liquid Chromatography-Tandem Mass Spectrometry. *Biomed. Chromatogr.* **2007**, *21*, 2, 132–138.

[18] EP. *European Pharmacopoeia*, 9th ed.; Council of Europe, Strasbourg, 2017.

[19] Gabr, R. Q.; Padwal, R. S.; Brocks, D. R. Determination of Metformin in Human Plasma and Urine by High-Performance Liquid Chromatography Using Small Sample Volume and Conventional Octadecylsilane Column. *J. Pharmaceutical Sci.* **2010**, *23*, 4, 486–494.

[20] Galuszka, A.; Migaszewski, Z.; Namiesnik, J. The 12 Principles of Green Analytical Chemistry and the Significance Mnemonic of Green Analytical Practices. *Trends Anal. Chem.* **2013**, *50*, 78–84.

[21] Georgita, C.; Albu, F.; David, V.; Medvedovici, A. Simultaneous Assay of Metformin and Glibenclamide in Human Plasma Based on Extraction-Less Sample Preparation Procedure and LC/ (APCI) MS. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2007**, *854*, 211–218.

[22] Georgita, C.; Sora, I.; Albu, F.; Mounciu, C. M. Comparison of a LC/MS Method with a LC/UV Method for the Determination of Metformin in Plasma Samples. *Farmacia* **2010**, *58*, 2, 158–169.

[23] Gonzalez, O.; Alonso, R. M.; Ferreiros, N.; Weinmann, W.; Zimmermann, R.; Dresen, S. Development of an LC-MS/MS Method for the Quantitation of 55 Compounds Prescribed in Combined Cardiovascular Therapy. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2011**, *879*, 243–252.

[24] Graham, G. G.; Punt, J.; Arora, M. Clinical Pharmacokinetics of Metformin. *Clin. Pharmacokinetics* **2011**, *50*, 2, 81–98.

[25] JP. *Japanese Pharmacopoeia*, 16th ed. Tokyo Society of Japanese Pharmacopoeia: Tokyo, **2011**.

[26] Kogawa, A. C.; Salgado, H. R. N. Development and Validation of Infrared Spectroscopy Method for the Determination of Darunavir in Tablets. *Phys. Chem.* **2013**, *3*, 1–6.

[27] Kogawa A. C.; Aguiar F. A.; Gaitani C. M.; Salgado, H. R. N. Validation of a Stability Indicating Capillary Electrophoresis Method for the Determination of Darunavir in Tablets and Comparison with the of Infrared Absorption Spectroscopic Method. *World J. Pharm. Pharmaceutical Sci.* **2014**, *3*, 6, 283–297.

[28] Kogawa, A. C.; Salgado, H. R. N. Comparative Study Over Methods Developed for Quantification of Darunavir in Tablets by Environmental Friendly Infrared and Capillary Electrophoretic Techniques. *J. Int. Res. Med. Pharmaceutical Sci.* **2015**, *2*, 99–105.

[29] Kogawa, A. C; Salgado, H. R. N. Analytical Methods Need Optimization to Get Innovative and Continuous Processes for Future Pharmaceuticals. *Scholars Acad. J. Pharmacy* **2016**, *5*, 6, 240–244.

[30] Koseki, N.; Kawashita, H.; Niina, M.; Nagae, Y.; Masuda, N. Development and Validation for High Selective Quantitative Determination of Metformin in Human Plasma by Cation Exchanging with Normalphase LC/MS/MS. *J. Pharmaceutical Biomed. Anal.* **2005**, *36*, 5, 1063–1072.

[31] La Roca, M. F.; Sobrinho, J. L. S.; Nunes, L. C. C.; Neto, P. J. R. Development and Validation of Analytical Method: Important Step in the Production of Medicines. *RevistaBrasileira de Farmácia* **2007**, *88*, 4, 177–180.

[32] Li, N.; Cui, M.; Lu, X.; Qin, F.; Jiang, K.; Li, F. A Rapid and Reliable UPLC-MS/MS Method for the Identification and Qualification of Fourteen Synthetic Anti-Diabetic Drugs in Adulterated Chinese Proprietary Medicines and Dietary Supplements. *Biomed. Chromatogr.* **2010**, *24*, 11, 1255–1261.

[33] Liu, A.; Coleman, S. P. Determination of Metformin in Human Plasma Using Hydrophilic Interaction Liquid Chromatography-Tandem Mass Spectrometry. *J. Chromatogr. B Anal. Technolog. Biomed. Life Sci.* **2009**, *877*, 29, 3695–3700.

[34] Lopes, V. P.; Júnior, M. C. S.; Júnior, A. F. S.; Santana, A. I. C. Pharmacology of Type 2 Diabetes Mellitus: Oral Antidiabetics, Insulin and Therapeutic Innovations. *Electron. Pharm Mag.* **2012**, *IX*, 3, 69–90.

[35] Marco, B. A.; Salgado, H. R. N. Characteristics, Properties and Analytical Methods of Cefadroxil: A Review. *Crit. Rev. Anal. Chem.* **2017**, *47*, 93–98.

[36] Marco, B. A.; Salgado, H. R. N. Development and Validation of an Innovative Method for the Determination of Cefadroxil Monohydrate in Capsules. *Phys. Chem.* **2016**, *6*, 67–74.

[37] Marco, B.A.; Natori, J. S. H.; Fanelli, S.; Tótoli, E. G.; Salgado, H.R.N. Characteristics, Properties and Analytical Methods of Amoxicillin: A Review with Green Approach. *Crit. Rev. Anal. Chem.* **2017**. DOI: 10.1080/10408347.2017.1281097.

[38] Marques, M. A.; Soares, A. S.; Pinto, O. W.; Barroso, P. T. W.; Pinto, D. P.; Ferreira-Filho, M.; Werneck-Barroso, W. Simple and Rapid Method Determination for Metformin in Human Plasma Using High Performance Liquid Chromatography Tandem Mass Spectrometry: Application to Pharmacokinetic Studies. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2007**, *852*, 308–316.

[39] Martindale, W. The Complete Drug Reference; Pharmaceutical Press: London, 2007; 35 ed.

[40] McElroy, C. R.; Constantinou, A.; Jones, L. C.; Summerton, L.; Clark, J. H. Towards A Holistic Approach to Metrics for The 21st Century Pharmaceutical Industry. *Green Chem.* **2015**, *17*, 3111–3121.

[41] Mistri, H. N.; Jangid, A. G.; Shrivastav, P. S. Liquid Chromatography Tandem Mass Spectrometry Method for Simultaneous Determination of Antidiabetic Drugs Metformin and Glyburide in Human Plasma. *J. Pharmaceutical Biomed. Anal.* **2007**, *45*, 1, 97–106.

[42] Mol, M. M.; Rojas, G. D. R.; Rosário, G. D.; Rojas N.; Maciel, R. G., Campos, R. A. R.; Nakaoka, V. Y.; Kashiwabara, T. G. B. Diabetes Mellitus type 2 – A Review of the Literature. *Braz. J. Surg. Clin. Res.* **2013**, 4, 61–65.

[43] Moreno, A. H.; Salgado, H. R. N. Development and Validation of the Quantitative Analysis of Ceftazidime in Powder for Injection by Infrared Spectroscopy. *Phys. Chem.* **2012**, *2*, 6–11.

[44] Municipal Health Secretariat Belo Horizonte. Scientific Committee on Drug Use Studies: Therapeutic Information Bulletin. Treatment of type 2 diabetes mellitus at outpatient level. Belo horizonte, **2001**, *920*, 1–17.

[45] Pang, W.; Yang, H.; Wu, Z.; Huang, M.; Hu, J. LC-MS-MS in MRM Mode for Detection and Structural Identification of Synthetic Hypoglycemic Drugs Added Illegally to "natural" Anti-Diabetic Herbal Products. *Chromatographia* **2009**, *70*, 1353–1359.

[46] Parisotto, G.; Marques, M.; Hermesa, A. L.; Floresa, E. M. M.; Ferrão, M. F. Development of Infrared Methodologies Applied for the Quantification of Metformin Hydrochloride in Pharmaceutical Formulations. *Orbital* **2009**, *1*, 38–48.

[47] Patel, D.; Kumar, P.; Dwivedi, J.; Sharma, S. Analytical Methods for Metformin Estimation. *Crit. Rev. Anal. Chem.* **2017**, DOI 10.1080/10408347.2017.1304200.

[48] Pedroso, T. M.; Medeiros, A. C. D.; Salgado, H. R. N. RP-HPLC x HILIC Cchromatography for Quantifying the Ertapenem Sodium with a Look at Green Chemistry. *Talanta* **2016**, *160*, 745–753.

[49] Pernicova, I.; Korbonits M. Metformin-Mode of Action and Clinical Implications for Diabetes and Cancer. *Nature Rev. Endocrinology* **2014**, *10*, 143–156.

[50] Polagani, S. R.; Pilli, N. G.; Gajula, R.; Gandu, V. Simultaneous Determination of Atorvastatin, Metformin and Glimepiride in Human Plasma by LC-MS/MS and its Application to a Human Pharmacokinetic Study. *J. Pharmaceutical Anal.* **2013**, *3*, 1, 9–19.

[51] Pubchem. Pubchem Compound Database. *Metformin* http://pubchem.ncbi.nlm.nih.gov/compound/4091#section=Top. (accessed Dec 09, **2016**).

[52] Radwan, M. A.; Al Taweel, E. S.; Abdulrahman, M.; Aloudah, N. M.; Al Babtain, M. A.; Al-Amri, H. S. Monitoring Metformin in Cardiac Patients Exposed to Contrast Media Using Ultra-High-Performance Liquid Chromatography Tandem Mass-Spectrometry. *Therapeutic Drug Monit.* **2011**, *33*, 6, 742–749, 2011.

[53] Rodrigues D. F.; Salgado H. R. N. Development and Validation of a Green Analytical Method of RP-HPLC for Quantification Cefepime Hydrochloride in Pharmaceutical Dosage Forms: Simple, Sensitive and Economic. *Curr. Pharmaceutical Anal.* **2016**, *12*, 4, 306–314.

[54] Salpeter, S. R.; Greyber, E.; Pasternak, G. A.; Salpeter, E. E. Risk of Fatal and Nonfatal Lactic Acidosis with Metformin use in Type 2 Diabetes Mellitus. The *Cochrane Database Systematic Rev.* **2010**, *4*, 1–34.

[55] Sengupta, P.; Bhaumik, U.; Ghosh, A.; Sarkar, A. K.; Chatterjee, B.; Bose, A.; Pal, T. K. *LC*-MS-MS Development and Validation for Simultaneous Quantitation of Metformin, Glimepiride and Pioglitazone in Human Plasma and its Application to a Bioequivalence Study. *Chromatographia* **2009**, *69*, 1243–1250.

[56] Sorensen, L. K. Determination of Metformin and Other Biguanides in Forensic Whole Blood Samples by Hydrophilic Interaction Liquid Chromatography-Electrospray Tandem Mass Spectrometry. *Biomed. Chromatogr.* **2012**, *26*, 1, 1–5.

[57] Spagnol, C. M.; Isaac, V. L.; Corrêa, M. A.; Salgado, H. R. N. Validation of HPLC-UV Assay of Caffeic Acid in Emulsions. *J. Chromatogr. Sci.* **2016**, *54*, 305–311.

[58] Thevis, M.; Geyer, H.; Schanzer, W. Identification of Oral Antidiabetics and Their Metabolites in Human Urine by Liquid Chromatography/Tandem Mass Spectrometry-A Matter for Doping Control Analysis. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 7, 928–936.

[59] Tótoli E. G.; Salgado H. R. N. Development and Validation of the Quantitative Analysis of Ampicillin Sodium in Powder for Injection by Fourier-Transform Infrared Spectroscopy (FT-IR). *Phys. Chem.* **2012**, *2*, 6, 103–108.

[60] Tótoli, E. G.; Salgado H. R. N. Development and Validation of an Economic, Environmental Friendly and Stability-Indicating Analytical Method for Determination of Ampicillin Sodium for Injection by RP-HPLC. *World J. Pharmacy Pharmaceutical Sci.* **2014**, *3*, 6, 1928–1943.

[61] U.K. Prospective Diabetes Study (UKPDS) Group. Effect of Intensive Blood Glucose Control with Metformin on Complications in Overweight Patients with Type 2 diabetes (UKPDS 34). *The Lancet* **1998**, *352*, 854–865.

[62] USP 39. *The United States Pharmacopei*, 39th ed.; United States Convention: Rockville, 2016.

[63] Verterqvist, O.; Nabbie, F.; Swanson, B. Determination of Metformin in Plasma by High-Performance Liquid Chromatography After Ultrafiltration. *J. Chromatogr. B: Biomed. Sci. Appl.* **1998**, *716*, 299–304.

[64] Vieira, D. C. M.; Ricarte, P. C.; Salgado, H. R. N. Development and Validation of the Quantitative Analysis of Cefuroxime Sodium in Powder for Injection by Infrared Spectroscopy. *Adv. Anal. Chem.* **2012**, *2*, 80–87.

[65] Wang, Y.; Tang, Y.; Gu, J.; Fawcett, J. P.; Bai, X. Rapid and Sensitive Liquid Chromatography-Tandem Mass Spectrometric Method for the Quantitation of Metformin in Human Plasma. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2004**, *808*, 2, 215–219.

[66] Zhang, L.; Tian, Y.; Zhang, Z.; Chen, Y. Simultaneous Determination of Metformin and Rosiglitazone in Human Plasma by Liquid Chromatography/Tandem Mass Spectrometry with Electrospray Ionization: Application to a Pharmacokinetic Study. *J. Chromatogr B: Anal. Technol. Biomed. Life Sci.* **2007**, *854*, 91–98.

[67] Zhang, M.; Moore, G. A.; Lever, M.; Gardiner, S. J.; Kirkpatrick, C. M.; Begg, E. J. Rapid and Simple High-Performance Liquid Chromatographic Assay for the Determination of Metformin in Human Plasma and Breast Milk. *J. Chromatogr B: Anal. Technol. Biomed. Life Sci.* **2002**, *766*, 1, 175–179.

[68] Zhang, W.; Han, F.; Zhao, H.; Lin, Z. J.; Huang, Q.; Weng, N. Determination of Metformin in Rat Plasma by HILIC-MS/MS Combined with Tecan Automation and Direct Injection. *Biomed. Chromatogr* **2011**, *26*, 1163–1169.

[69] Zhong, G. P.; Bi, H.; Zhou, S.; Chen, X.; Huang, M. Simultaneous Determination of Metformin and Glicazide in Human Plasma by Liquid Chromatography-Tandem Mass Spectrometry: Application to a Bioequivalence Study of Two Formulations in Healthy Volunteers. *J. Mass Spectrom.* **2005**, *40*, 11, 1462–1471.