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A green chemistry approach to establish a conductometric technique for quantifying Metformin HCl in pharmaceutical samples and its greenness assessment using an analytical greenness metric calculator

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ABSTRACT

Green analytical chemistry focuses on making analytical processes safer and more environment friendly for the analyst. The primary goals of the proposed research are to develop and validate a conductometric method with green chemistry assistance for the estimation of Metformin HCl (MET), as well as to assess the method's level of greenness using the AGREE-analytical greenness measure tool. The conductometric method for quantification of MET was developed in two steps. Step 1: Preparation of working standard solutions of MET and Step 2: Estimation of electrical conductivity of working standard solutions of MET. During the development, various dilutions of MET were prepared in Millipore water (MW) ranging from 50 to 250 µg/ml. The prepared solutions were subjected to the measurement of electrical conductivity using the conductometer ELICO CM 183EC-TDS analyzer version 2.3 instrument. The created approach was authenticated to regulate its routine capabilities in accordance with the most recent International Council for Harmonisation guidelines for regulatory recommendations. With an r^2 value of 0.999, MET demonstrated linearity concerning amount ranges from 50 to 250 µg/ml. Less than 2% RSD was observed for each set of validation parameters, which was substantially within acceptable limits. The observed recovery levels ranged from 99% to 100%. According to the AGREE metric tool calculation, the suggested method was deemed to be greener and more suitable for analyzing MET in pharmaceutical samples. The proposed research found to show advantages over reported methods in terms of usage of solvents, cost, and time of analysis. The method suggests the usage of MW as a cheap solvent, only simple dilutions and measuring the conductance of the analyte solution makes the method less time-consuming.

INTRODUCTION

Green analytical chemistry (GAC) encourages analytical chemists to think about environmental, human health, and safety issues at every stage of their work. Green analytical process development is essential in the pharmaceutical industries. Till date, various GAC measures were developed to appraise the greenness of analytical techniques. To determine the method's greenness, the "analytical greenness calculator" combines all 12 GAC principles. It is a wide-ranging, analyst-approachable, instructive, and sensitive GAC metric calculator for evaluating analytical methods. The assessment criteria in this procedure are the 12 principles of GAC which are transformed into a common scale of 0–1 and all GAC rules are used to determine the final score. The outcome is a representation that shows the concluding score, performance of the analytical technique for each criterion, and the user-assigned weights (Armenta *et al*., 2008; Pena-Pereira *et al*., 2020; Tobiszewski *et al*., 2015)

A significant element in the product development stage is the quality valuation and assessment of pharmaceuticals. The pharmaceutical industries place a great deal of importance on the development of drug assays and their formulation. The crucial step in pharmaceutical quality control is analytical valuation. A poor analytical evaluation may produce erroneous values and assessment results, which could be dangerous for the stage

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of medicine and product creation. The quality of drugs and formulations can be controlled by using a variety of modern instruments and investigative techniques, such as optical, physical, thermo-analytical, electrochemical, biological, microbiological, titrimetric, radioactive methods, and other analytical methods. The electrochemical methods evaluate the electrochemical characteristics or properties of pharmacological compounds. The conductometric analysis is an analytical tool for quantitative analysis of various analytes, which includes measuring the conductivity of analyte solution. It is widely known that the concentration of analyte and the number of free charges present in the sample affect an electrolytic solution's conductivity. It is also particularly helpful in the analysis of very weak acids and dilute solutions (Sankar, 2010; Siddiqui *et al*., 2013).

The biguanides moiety of the well-known orally accessible antidiabetic drug Metformin (MET) is excellently used in the control of diabetes mellitus (Type-2). It mostly demonstrates its mode of action by reducing glucose secretion. In a few cases, it was said to lower cholesterol, which led to weight loss (El Messaoudi *et al*., 2011; Radosh, 2009). It is advertised and sold in many different dose forms, both alone and in combination with other anti-diabetic drugs. It was created through the reaction of 2-cyanoguanine with dimethylamine hydrochloride in the presence of temperature (Werner and Bell, 1921). It has been revealed to have a few side effects, including lactic acidosis and a few gastrointestinal problems. The use of this medication is both advised and prohibited in those with kidney, liver, lung, or cardiac illnesses (Sonnett *et al*., 2009). MET is *N*, *N*-dimethylimidodicarbonimidic diamide with a compound mass of approximately 129 g/mol (Fig. 1). It is a crystalline powder that ranges from white to off-white, soluble in water, and has a pKa value of 12.4 (Suryawanshi and Palled, 2022).

It is evident for a literature study that only a few spectroscopic, chromatographic, and electrochemical techniques were used to analyze the drug. The described techniques were found to have certain drawbacks, including the usage of expensive instruments, hazardous reagents, and excessive use of organic solvents, expensive reagents, longer processing times, crucial extraction steps, and difficult-to-handle instrumentation. Multiple extraction steps also result in longer processing times. A complex solvent system composition and a higher retention factor are drawbacks of the majority of chromatographic procedures that have been documented (Alessandro *et al*., 1974; Aly and El Rayes, 1983; Barbieri and Gargiulo, 2004; Gul, 2016; Mubeen and Noor, 2009; Suryawanshi *et al*., 2019; Wang *et al*., 2011).

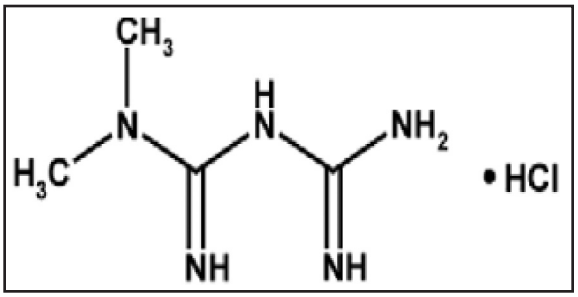

Figure 1. Chemical structure of MET HCl.

The use of conductometric titrations to quantify MET is documented in the literature. In this procedure, titration against silver nitrate was used to quantify the amount of MET. The primary reaction involved in the titration is that between the MET and silver nitrate. Using conductometric, potentiometric, and visual methods, the method's endpoint was examined. The study designed a hypothetical conductance value of the MET when a known amount of titrant is added. In a different approach that has been published, silver-nitrate-based reagents were used to measure the conductivity-metric titration of MET in the marketed formulation. The technique was established based on the chemical interaction among the chloride ions of MET with silver iodide ions giving the precipitate as silver chloride (Sartori *et al*., 2009; Valdivia *et al*., 2019).

Titrimetric procedures are thought to be time-consuming and require the use of additional, expensive substances like silver nitrate. This demonstrates the constraints and drawbacks of methods that have been published. There is a need for the development and validation of a straightforward, financially viable, novel, and a precise electro-analytical method for the valuation of MET in bulk and marketed formulations in order to minimize a few drawbacks of published analytical tools using conductometric titration.

The main goals from the proposed investigation are to develop an inexpensive, quick, robust, sensitive, accurate, reliable, and economical electrochemical technique for estimating MET in marketed preparations and relate its performance to the reported published works of literature.

MATERIAL AND METHODS

Instruments, apparatus, and solvents

The weighing balance of SARTORIUS was used to measure the MET powder, the "Ultrasonic bath Sonicator" was used for the sonication of solutions, the ELICO CM 183EC-TDS analyzer was used to analyze the conductance of the analyte solution and the Direct Q UV aquatic distillation system was used to collect the Millipore Water (MW) for analysis.

Method development

The conductometric method for quantification of MET was developed in two steps. Step 1: Preparation of working standard solutions of MET and Step 2: Estimation of electrical conductivity of working standard solutions of MET. During the development, various dilutions of MET were prepared in MW ranging from 50 to 250 µg/ml. The prepared solutions were subjected to the measurement of electrical conductivity using a conductometer. After the estimation of the electrical conductance of every solution, it was observed that every concentration was found to show a linear response, which is a basic requirement for any analytical method development (i.e., as the concentration increases the electrical conductance increases in linear fashion). The linear response of the method was estimated by constructing a standard calibration curve (Yadav *et al*., 2021).

A standard stock solution of MET

A 50-ml calibrated volumetric flask containing 50 mg of MET was carefully balanced, transported, and filled to the appropriate level using MW as the diluent to create 1,000 µg/ml (Suryawanshi *et al*., 2020).

Working standard solutions of MET

Various volumes were pipetted out from primary stock and transferred separately into 50-ml volumetric flasks, and the volume was marked with MW to yield 50–250 µg/ml of MET (Pancham *et al*., 2020; Uday *et al*., 2021).

Sample preparation and extraction

Weighed and powdered were 20 MET (500 mg label statement) tablets. A fraction measuring 500 mg was weighed and then transferred to a 100-ml volumetric container. MW was utilized to make the mark to 100 ml, then the solution was sonicated for 20 minutes before being strained through Whatman filter paper. To acquire a concentration of 100 µg/ml, dilution was performed using the above-mentioned stock solution. This solution underwent testing to determine its purity level in % (Bossunia *et al*., 2017; Murugesan and Annapurna, 2022).

Method validation

The validation of the analytical method was performed as per the regulatory guidelines for analytical methods (International Council for Harmonisation, 2023).

Selectivity and specificity

The conductance of MW was calculated in the directive to determine the specificity of the technique proposed. The standard amount of MET (100 µg/ml) was produced, and conductance was noted to demonstrate the specificity of the procedure.

Linearity and range

The linearity and range were determined by creating various strengths and evaluating the conductivity. The electrical conductivity of each standard concentration, which contained 50–250 µg/ml of MET, was created. By plotting the accurate quantity of substance against conductance (S), the calibration standard was built, and arithmetic calculations were used to generate data of range and linearity reports.

The limit for detection and estimation

The lowest amount of substance that can be detected but not accurately estimated is known as the detection limit, and it was determined by a statistical method: LOD = 3.3

$$\frac{\sigma}{s}$$

The amount of substance that can be precisely measured and quantified with correctness is known as the quantification limit and it was determined by a statistical method: LOQ = 10

$$\frac{\sigma}{s}$$

where σ = standard deviance and S = slope of the standardization typical curve.

Precision

Measurement in triplicate solutions at higher, middle, and lower concentration levels confirmed the precision in terms of intraday and interday. The conductance of three replicate MET concentrations at three different quantities was measured, as well as the %RSD standards for each obtained conductance. The intraday precision was calculated by running the analysis three times on the same day at three different time intervals. By running the analysis on three different days, the interday precision was determined.

Ruggedness

The ruggedness of the process was done by changing the analyst to test the technique's reproducibility. The electrical conductivity of triplicate solutions at lower, middle, and higher concentration levels was measured and %RSD values for conductance were computed and examined for correctness.

Accuracy

Accuracy was determined using recovery studies, which involved estimating %mean substance recovery at three different levels (150%, 100%, and 50%). Three determinations were performed at each level, and a % mean recovery was calculated. To determine the accuracy of the proposed analytical technique, the standard addition method was referred to.

Conductometric assay

MET tablets (500 mg label statement) were obtained from the market and powdered. A 500 mg powder was weighed accurately and added to a 100-ml volumetric container, and the final capacity was made up to 100 ml with MW and sonicated for 20 minutes before filtering with Whatman sieve paper. The above-mentioned stock solution was diluted to obtain a concentration of 100 µg/ml. This solution was tested to determine its purity percentage. A small amount of methanol was used to extract the exact amount of analyte, and trial studies were conducted.

Table 1. Linearity data of MET HCl by conductometric method.

Concentration µg/ml	Set-1 electrical conductivity (µS)	Set-2 electrical conductivity (µS)	Set-3 electrical conductivity (µS)	Mean electrical conductivity (µS)
50 µg/ml	31.10	30.33	30.20	30.54
100 µg/ml	61.66	61.50	60.90	61.35
150 µg/ml	90.80	91.10	90.70	90.87
200 µg/ml	120.10	120.12	121.12	120.45
250 µg/ml	150.15	149.95	150.10	150.07
r^2	0.9998	0.9998	0.9999	0.9999

Greenness assessment

To systematically assess the greenness of the analytical procedure, we have transformed each of the 12 GAC codes into scores. The following 12 GAC principles are used for assessing the greenness of the method:

1. Direct analytical methods must be used to avoid analyte treatment
2. Use of a limited number of samples and limited sample size
3. *In situ* analysis must be accomplished
4. Incorporation of innovative techniques and methods that saves energy and reduces the use of chemicals
5. Programmed and miniaturized approaches must be designed
6. Avoid the use of derivatization
7. Avoid the generation of large amounts of analytical waste and provide appropriate measures for generated analytical waste
8. Multi-sample analysis approach is preferred
9. Minimum amount of energy should be used
10. Preference should be given to the use of reagents and chemicals manufactured from a renewable source
11. Harmless reagents can be preferred
12. Analyst safety must be considered with more attention

Table 2. Intraday precision data of MET HCl.

Concentration	Time	Conductance (µS)($\bar{x}$)	SD	%RSD
50 µg/ml	Morning	30.62	0.51	1.65
	Afternoon	30.74	0.36	1.18
	Evening	30.86	0.23	0.75
150 µg/ml	Morning	91.03	0.07	0.08
	Afternoon	90.83	0.06	0.07
	Evening	91.02	0.18	0.20
250 µg/ml	Morning	150.78	0.59	0.39
	Afternoon	150.56	0.47	0.31
	Evening	150.77	0.40	0.27

$\bar{x}$ = Mean conductance of three replicates.

Table 3. Interday precision results of MET HCl.

Concentration	Time	Conductance (µS)($\bar{x}$)	SD	%RSD
50 µg/ml	Day-1	31.18	1.12	3.58
	Day-2	30.94	0.16	0.51
	Day-3	30.82	0.17	0.55
150 µg/ml	Day-1	90.76	0.05	0.06
	Day-2	91.02	0.19	0.21
	Day-3	90.97	0.08	0.08
250 µg/ml	Day-1	150.480	0.33	0.22
	Day-2	151.040	0.12	0.08
	Day-3	150.790	0.60	0.40

$\bar{x}$ = Mean of three replicates of conductance.

RESULTS AND DISCUSSION

Method development and validation

In the proposed study, we have chosen MET as an oral anti-diabetic agent that is primarily available in tablet dosage

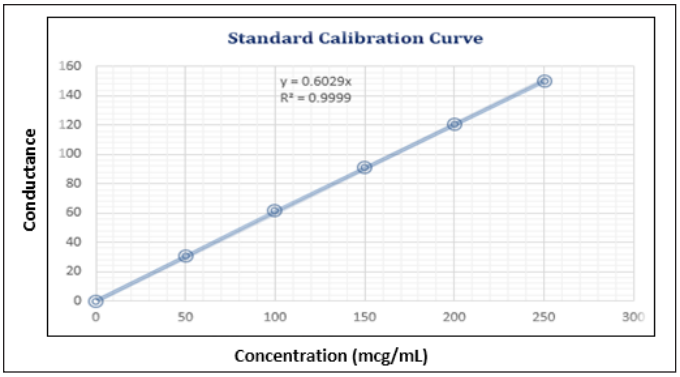

Figure 2. Standard calibration curve of MET HCl.

Table 4. Ruggedness data of MET HCl.

Replicates	Concentration	Change in analyst-1	Concentration	Change in analyst-2
1	50 µg/ml	31.11	150 µg/ml	91.78
2	50 µg/ml	31.80	150 µg/ml	93.80
3	50 µg/ml	30.90	150 µg/ml	92.70
4	50 µg/ml	30.66	150 µg/ml	90.90
5	50 µg/ml	31.11	150 µg/ml	91.05
6	50 µg/ml	30.80	150 µg/ml	90.95
	Mean	31.063	Mean	91.863
	SD	0.401	SD	1.173
	%RSD	1.292	%RSD	1.277

Table 5. Accuracy data of MET HCl.

Sl. No.	Level	Replicate	% Recovery	Mean % Recovery	%SD
1	50%	1	99.90	99.90	0.05
		2	99.95		
		3	99.85		
2	100%	1	100.10	100.04	0.06
		2	100.05		
		3	99.98		
3	150%	1	99.86	99.98	0.15
		2	100.15		
		3	99.94		

Table 6. Assay data of MET HCl in marketed formulation.

Tablet	Drug	Label claim	Sample concentration prepared	% Assay
1	MET	500 mg	100 µg/ml	99.78%

Table 7. Greenness assessment score for conductometric method.

Sl. No.	Principle of green chemistry	Calculated score	Justification
1	Direct analytical techniques should be applied to avoid sample treatment:	0.60	In the proposed analytical method we estimate the study analyte directly without any derivatization and it is a type of at-line analysis. Hence it is given a score of 0.60.
2	Minimal sample size and a minimal number of samples are goals	1.0	In the proposed method in order to prepare the standard solution we require 10 mg of analyte and according to the principle of the researcher uses the sample amount of 100 mg then it is to be assessed as green and the score is given as 1.0.
3	*In situ* measurements should be performed.	1.0	In the proposed method we perform the in-line analysis of MET HCl and hence scoring is given as 1.0.
4	Integration of analytical processes and operations saves energy and reduces the use of reagents	1.0	The proposed method involves a limited number of steps like preparation of standard and sample solutions and the measurement of conductance. It involves simple two steps and hence reduces the energy as well as the additional use of any reagents. According to the GAC principle, the score is given as 1.0 as the proposed procedures involve less than three steps.
5	Automated and miniaturized methods should be selected	0.5	The proposed method is not fully automated and we need to perform manual dilutions as well as measurements. It is considered as the proposed analysis is manual and miniaturized and as per the principle the score is given 0.5.
6	Derivatization should be avoided	1	According to the GAC principle, derivatization should be avoided to reduce the use of extra chemicals. The score is given as 1 as there is derivatization for the proposed method.
7	Generation of a large volume of analytical waste should be avoided and proper management of analytical waste should be provided.	1.0	The generation of a large amount of analytical waste is to be avoided As the waste generated in this procedure is less than 0.1 g/ml.
8	Multianalyte or multiparameter methods are preferred versus methods using one analyte at a time.	0.0	The method analyzes the analysis of multiple samples of the same analyte and hence as per the equation score is calculated as 0.0.
9	The use of energy should be minimized.	1	The score is given 1 as the proposed analytical method consumes <0.1 kWh per sample for the analysis.
10	Reagents obtained from renewable sources should be preferred.	1	The water is used as a solvent and it is obtained from a bio-based source, and hence, the score is 1.
11	Toxic reagents should be eliminated or replaced.	0.059	As the method replaces the use of organic solvents with distilled water it eliminates the use of toxic reagents. Very small amount of methanol has been used in the study for extraction purposes. Based on its requirement per sample analysis of assay and the score has been calculated.
12	The safety of the operator should be increased.	0.8	The safety of the operator is essential while performing the analysis. The proposed research involves the use of water as a solvent and a very less amount of methanol for extraction purposes. Hence one threat is selected as per the guidelines that are toxic to aquatic life. As the methanol and MET HCl, we need to through as waste and which may be not suitable or toxic for aquatic life.
	Final score	0.75	As the final score was found to be more than 0.5 the method is considered greener according to the principles of GAC.

form, with numerous preparations available in the market. A few spectrophotometric, chromatographic assays and electrochemical approaches are reported in the literature to estimate MET formulations. Potentiometric and conductometric titrations are commonly used in reported electrochemical methods. The electrochemical analysis found to exist its limitations and disadvantages. In this research, a novel principle was used to quantify MET, in which we prepared concentrations ranging from 50 to 250 µg/ml and then measured the conductance for every prepared concentration of MET. We observed that as the concentration of analyte increases the conductance value also increases in a linear fashion.

Specificity and selectivity

The technique was found to be selective and specific because the conductance of MW was found to be 1.18 seconds, whereas the conductance of 100 µg/ml MET was found to be 60.66 µS which indicates the selective and specific performance of the method.

Linearity and range

MET demonstrated a linear relationship between electrical conductance (µS) and concentration levels ranging from 50 to 250 µg/ml. Linearity plot calculation yielded an r^2 value of 0.9999. Table 1 displays the statistical linearity and range data. The standard calibration curve, shown in Figure 2, was obtained by plotting the standard amount against the measured conductance of standard solutions.

Detection and quantification limit

MET had detection and quantification limit values of 3.12 and 9.47 µg/ml, respectively. Both outcomes are within the acceptable range.

Table 8. Comparison of the proposed conductometric method with literature methods.

Parameters	Reported/published methods (Sartori *et al*., 2009; Valdivia *et al*., 2019)	Proposed research work method	Conclusion
Development	Conductometric titrimetric methods	Conductometric methods	The newly developed conductometric method is easy to perform with less time and less cost as compared to reported conductometric titrimetric methods.
Solvents and reagents	Diluents and reagents-silver nitrate and Ag(I)	MW	
Performance of method	titrations are involved	Only simple dilutions and measuring the conductance of analyte solution	
Cost with respect to the use of solvents and reagents	Approximately 3,000 to 4,000/- for each 25 g.	0% (As we have used MW)	
Time of analysis	More time is required as it involves the use of titrations	Less time is required as it does not suggest the use of titrations	

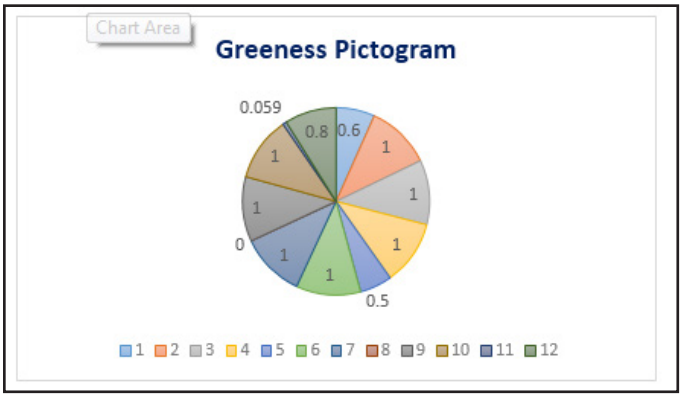

Figure 3. Greenness pictogram of analytical method.

Precision

The analysis reports indicate the preciseness of the suggested technique on similar and altered days. Precision values gained at different concentration levels were less than the 2% RSD limit. Tables 2 and 3 indicate the results of the analysis.

Ruggedness

The ruggedness of the process was tested by different experts and the %RSD values for noted conductance were found to be less than 2%. Table 4 contains the statistics of the ruggedness experiment.

Accuracy

The recovery experiments were carried out at three different levels, namely 100%, 150%, and 50%, and the individual % mean recovery were established between 99% and 100% indicating that the suggested technique is accurate. Table 5 represents the percentage mean recovery values and data of the accuracy experiment.

Conductometric assay

MET tablets (claim 500 mg) were used for the assay, and the comparable weight was measured and diluted to obtain a concentration of 100 µg/ml. Table 6 represents the assay and %purity data of MET quantitative estimation in marketed formulation. The assay value was found to be 99.78%.

Greenness assessment of method using analytical greenness metric tool

The greenness of the method was assessed by giving inputs of the method into the greenness calculator as per the principles of GAC. The principles of GAC, the score calculated for the proposed methodology, and the justification for the inputs have been given in Table 7 and the pictogram is presented in Figure 3.

DISCUSSION

The planned technique was discovered to the usage of MW as the solvent for investigation, and the method does not propose any additional solvents or reagents for the execution of standard and sample preparation. The method involves the measured conductance after preparing various concentrations of analytes in MW. This allows for simple analysis at a low cost and in a short amount of time, which is extremely important and necessary in the pharmaceutical industries that manufacture MET formulations. The suggested process was used to estimate the marketed pharmaceuticals comprising MET in order to assess the applicability and reproducibility during real-time analysis. The suggested research methodology was compared with published literature methods, and the comparison was shown in Table 8.

CONCLUSION

The newly designed and validated method for MET in its powder and tablet dosage form was observed to be novel, cost-effective, easy, and accurate. A simple, accurate, quick, and inexpensive conductometric approach was created and verified using ELICO CM 183EC-TDS analyzer version 2.3. The planned approach was established to employ water as the analysis solvent, and it does not advise the use of any additional solvents or expensive chemicals for executing the dilutions as well as the need for derivatization. The method was found to be green according to green chemistry principles. According to the AGREE metric tool calculation, the suggested method was deemed to be suitable for analyzing MET in pharmaceutical samples.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/ guidelines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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REFERENCES

Alessandro A, Pieri M, Liguori A. Complexometric determination of biguanides in pharmaceutical preparations. G Med Mil, 1974; 124(2–3):279–84.

Aly FA, El Rayes M. Method for the determination of metformin hydrochloride by atomic absorption of its copper complex. Egypt Pharmacol Sci, 1983; 24(1–4):169–75.

Armenta S, Garrigues S, de la Guardia M. Green analytical chemistry. TrAC Trends Anal Chem, 2008; 27(6):497–511.

Barbieri RL, Gargiulo AR. Metformin for the treatment of the polycystic ovary syndrome. Minerva Ginecol, 2004; 56(1):63–79.

Bossunia MTI, Urmi KF, Shaha CK. Quality-by-design approach to stability indicating RP-HPLC analytical method developmentfor estimation of canagliflozin API and its validation. Pharm Methods, 2017; 8(2):92–101.

El Messaoudi S, Rongen GA, de Boer RA, Riksen NP. The cardioprotective effects of metformin. Curr Opin Lipidol, 2011; 22(6):445–53.

Gul W. Metformin: methods of analysis and its role in lowering the risk of cancer. J Bio Equiv, 2016; 08(6):254–9.

Mubeen G, Noor K. Spectrophotometric method for analysis of metformin hydrochloride. Indian J Pharm Sci, 2009; 71(1):100–2.

Murugesan A, Annapurna MM. Simple quantified and validated stability indicating stress degradation studies of oral anti-diabetic agent dapagliflozin by Rp-Hplc method. Int J Appl Pharm, 2022; 14(1):231–7.

Pancham YP, Girish B, Suryawanshi SS. UV-spectrophotometric method for quantification of ascorbic acid in bulk powder. J Pharm Innov, 2020; 9:05–8.

Pena-Pereira F, Wojnowski W, Tobiszewski M. AGREE-analytical GREEnness metric approach and software. Anal Chem, 2020; 92(14):10076–82.

Radosh L. Drug treatments for polycystic ovary syndrome. Am Fam Physician, 2009; 79(8):671–6.

Sankar SR. Text book of pharmaceutical analysis. Rx Publications, India, 2010.

Sartori ER, Suarez WT, Fatibello-Filho O. Conductometric determination of metformin hydrochloride in pharmaceutical formulations using silver nitrate as titrant. Quím Nova, 2009; 32:1947–50.

Siddiqui MR, ALOthman ZA, Rahman N. Analytical techniques in pharmaceutical analysis: a review. Arab J Chem, 2013; 10:1–13.

Sonnett TE, Levien TL, Neumiller JJ, Gates BJ, Setter SM. Colesevelam hydrochloride for the treatment of type 2 diabetes mellitus. Clin Ther, 2009; 31(2):245–59.

Suryawanshi D, Jha DK, Shinde U, Amin PD. Development and validation of a stability-indicating RP-HPLC method of cholecalciferol in bulk and pharmaceutical formulations: analytical quality by design approach. J Appl Pharm Sci, 2019; 9(6):21–32.

Suryawanshi SS, Kavalapure R, Palled MS, Alegaon SG. Development and validation of UV-spectrophotometric method for determination of ciprofloxacin and curcumin in bulk powder. Int J Pharm Sci Res, 2020; 11:1161–6.

Suryawanshi SS, Palled MS. Box-Behnken design assisted optimization and standardization of chromatographic methodology for quality assessment of metformin: analytical quality by design avenue. Indian J Pharm Educ Res, 2022; 56(2s):s152–62.

Tobiszewski M, Marć M, Gałuszka A, Namieśnik J. Green chemistry metrics with special reference to green analytical chemistry. Molecules, 2015; 20(6):10928–46.

Uday TC, Shivabasappa PM, Sanjay SS, Maruti MS. Development and validation of stability indicating UV-spectrophotometric method for the simultaneous estimation of telmisartan and metformin hydrochloride in bulk drugs. Indian J Pharm Educ Res, 2021; 55(2):590–7.

Valdivia AE, Montaño-Osorio C, Vargas-Rodríguez YM. Conductometric titration of metformin hydrochloride: simulation and experimentation. J Chem, 2019; 13:105–11.

Wang XF, Zhang JY, Li L, Zhao XY, Tao HL, Zhang L. Metformin improves cardiac function in rats via activation of AMP-activated protein kinase. Clin Exp Pharmacol Physiol, 2011; 38(2):94–101.

Werner E, Bell J. The preparation of methylguanidine and of dimethyl guanidine by the interaction of di cyano diamide and methylammonium and dimethylammonium chlorides respectively. J ChemSocTrans, 1921; 121:1790–5.

Yadav RK, Maste MM, Suryawanshi SS, Shastri U. Conductometric method development and validation to estimate acamprosate calcium in API and marketed formulation. J Appl Pharm Sci, 2021; 11(11):82–6.

Available via https://www.ema.europa.eu/en/ich-q2r2-validation-analytical-procedures-scientific-guideline (Accessed 16 July 2022).

Available via https://www.intechopen.com/books/phytochemicals-in-human-health/analytical-methods-of-isolation-and-identification (Accessed 08 July 2022).

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