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GREEN ANALYTICAL CHEMISTRY METRICS APPLIED TO PUBLISHED HPLC METHODS FOR PARACETAMOL

MATTHIAS SEIFFERT[1]*, INES FIGUEIREDO[2], RUBEN CASTELLANOS[3]

Affiliation

[1]Department of Pharmaceutical Analysis, Neckar Valley Institute of Pharmaceutical Sciences, Heilbronn, Germany
[2]Department of Quality Assurance, Douro Valley Institute of Pharmaceutical Sciences, Vila Real, Portugal
[3]Department of Analytical Chemistry, Cantabrian Coast Centre for Drug Development, Torrelavega, Spain

*Corresponding author: Matthias Seiffert, m.seiffert@nvips.de
ORCID iD: Matthias Seiffert 0000-0001-2860-4744; Ines Figueiredo 0000-0001-0378-7927; Ruben Castellanos 0000-0001-2756-383X

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Abstract

This short review considers how green analytical chemistry metrics can be applied to published high-performance liquid chromatography (HPLC) methods for paracetamol, and it reports no new data. It summarises the common features of such methods, describes the main assessment tools from the National Environmental Methods Index to AGREE and its sample-preparation companion, and discusses what each tool would be expected to reward or penalise in a typical paracetamol assay. Solvent choice, run time, flow rate and waste handling emerge as the dominant factors. Differences between tools, subjective weighting and incomplete reporting in method papers limit comparability, so scores should be read as guides to improvement and not as rankings.

1. INTRODUCTION

Few drugs are measured as often as paracetamol. It is in tablets, syrups, suppositories, combination cold remedies and, increasingly, in wastewater, so analysts are never short of reasons to run an assay. HPLC with ultraviolet detection is the workhorse for most of this work, and the literature on it is large [1, 2]. The environmental cost of all those runs is less often discussed. A single method may look modest, yet a quality-control laboratory can use many litres of organic solvent a year on routine assays alone [3, 4].

Green analytical chemistry grew out of the broader green chemistry movement and tries to reduce the hazards of analytical work without sacrificing quality [5, 6, 7, 8]. Early papers listed principles. Later work asked how to measure progress, and a series of metrics followed, each turning a method description into a pictogram or a score [9, 10]. This article reviews how those tools can be applied to published HPLC methods for paracetamol, what they tend to reward, and where they disagree. No laboratory work was done, and the discussion draws only on published literature.

The pressure for change comes from several directions at once. Laboratories face rising solvent costs and disposal charges, regulators and funding bodies increasingly ask about environmental impact, and younger analysts often expect sustainability to be part of method design [7, 11]. Yet much of the routine chromatography of paracetamol still follows conditions that were set decades ago and have never been reconsidered. That mismatch between what is possible and what is done is the starting point for the assessment exercise described here [1, 3].

Regulatory pressure adds a further push. Validation guidelines such as ICH Q2(R1) say little about environmental impact, and a method can meet every criterion for accuracy, precision and linearity while using generous amounts of solvent [12]. Pharmacopoeial monographs for paracetamol also tend to rely on established conditions, which can slow the adoption of greener alternatives [1, 12]. A cultural factor may also be at work: analysts trust methods that have a long history, and the perceived risk of change is often larger than the real one.

2. PARACETAMOL AND ITS HPLC METHODS

Paracetamol is a simple molecule, a para-substituted phenol with an acetamido group, and it absorbs ultraviolet light strongly in the region of 240 to 250 nm, which makes detection straightforward [1]. It is well absorbed after oral dosing and cleared mainly by glucuronidation and sulfation, with a small oxidative fraction that becomes important in overdose [13, 14, 15]. These properties explain why assay methods are so varied: they serve dosage-form testing, bioanalysis, impurity profiling and environmental monitoring, each with different demands on sensitivity and selectivity [1].

Published reversed-phase methods follow a recognisable pattern. A C18 column of 150 to 250 mm length and 4.6 mm internal diameter is typical, run at about 1 mL/min with an isocratic mobile phase of water or buffer mixed with methanol or acetonitrile, and detection by ultraviolet absorbance [1, 2]. Run times range from a few minutes for simple tablet assays to much longer for methods that must separate paracetamol from its impurities or from co-formulated drugs. Pharmacopoeial and validation guidance sets the quality targets such methods must meet, and green considerations are usually added afterwards, if at all [12].

Newer work has moved towards shorter columns and smaller particles. Ultra-high-pressure systems reduce analysis time and solvent use for the same separation, as the early reviews of the technology made plain [16]. Others have replaced acetonitrile with ethanol or methanol, trimmed the buffer, or used micellar or aqueous-rich mobile phases. These changes do not always appear in the title of a paper, which is one reason a systematic scoring exercise is needed to see how much real progress has been made [3, 4, 17].

Detection and sample handling vary by purpose. Tablet assays need little more than dissolution, filtration and dilution, which keeps sample preparation simple and relatively green. Bioanalytical methods for plasma or urine usually add protein precipitation or extraction, and these steps bring extra solvent, consumables and time [1, 18]. Environmental work on wastewater often requires solid-phase extraction to reach the low concentrations involved [19, 20]. The greenness of the whole procedure therefore depends as much on what happens before the column as on the chromatography itself, a point that older metrics tended to underplay.

Overdose is the main clinical reason for sensitive paracetamol assays in plasma. Timed concentrations guide treatment decisions after acute ingestion, so speed and

reliability count for more than economy of solvent in that setting [14, 15]. Any move towards greener bioanalysis therefore has to preserve turnaround time and accuracy first, and only then look at waste. Rapid methods based on short columns could in principle serve this need and reduce solvent at the same time [16].

Validation requirements limit how freely a method can be changed. Specificity, linearity, accuracy, precision and robustness must all be demonstrated for the intended use, and a change in solvent or column normally triggers at least partial revalidation [12]. For laboratories running regulated release testing, that cost is real. The greener route is easiest to take when a method is being developed from the start, since the green criteria can then be built in alongside the analytical ones.

3. GREENNESS ASSESSMENT TOOLS

The twelve principles of green analytical chemistry, formulated by Gałuszka and colleagues, provide the conceptual base for most modern tools [6]. They call for direct analysis where possible, minimal sample size, in situ measurement, integration of steps, automation, avoidance of derivatisation, reduction of waste, multi-analyte methods, lower energy use, renewable reagents, elimination of toxic reagents and operator safety. Earlier reviews had framed similar goals around solvent reduction and miniaturisation [11, 21, 22]. The principles are qualitative, so they cannot compare two methods that each satisfy a few of them.

The National Environmental Methods Index (NEMI) was one of the first practical tools. It uses a four-quadrant pictogram that is filled in when a method avoids persistent, bioaccumulative and toxic reagents, avoids listed hazardous chemicals, avoids strongly corrosive conditions, and generates little waste [10]. The approach is quick and visual, but it is binary. A method that uses a large volume of a moderately hazardous solvent can score the same as one that uses a trace, which limits its power to separate HPLC procedures that all rely on similar mobile phases [9, 10].

The Analytical Eco-Scale takes a more quantitative route. Penalty points are subtracted from a base of 100 for the amount and hazard of each reagent, for energy consumption, for occupational hazards and for waste. A final score above 75 is regarded as excellent, above 50 as acceptable, and lower values as inadequate [23]. It is simple to calculate and sensitive to solvent volume, but it depends on the reagent hazard data used and does not show where in the procedure the burden arises [9].

A practical issue with any pictogram is software support. Free tools exist for AGREE and AGREEprep, which calculate the score as the user answers a series of questions about the procedure [18, 24]. This lowers the barrier to use and improves consistency, but it can also encourage uncritical acceptance of whatever number appears. The answers still depend on the assessor's reading of the experimental section, and two people can answer the same question differently when a paper is vague about reagent amounts or waste handling [9, 10].

The Green Analytical Procedure Index (GAPI) addressed that gap by splitting a method into stages, from sample collection and preservation through preparation to final determination, and colouring each cell green, yellow or red [25]. Its extension, ComplexGAPI, adds fields for the pre-analytical synthesis or preparation of reagents and materials [26]. These pictograms show at a glance which step is the weak point, though they remain semi-quantitative and leave room for different readers to score the same paper differently.

AGREE moved the field towards a single numerical result. Each of the twelve principles is converted to a score between zero and one, weights can be adjusted, and the overall value appears at the centre of a circular pictogram whose segments are coloured by performance [24]. A companion tool, AGREEprep, applies a similar logic to sample preparation, which matters for paracetamol in biological or environmental matrices [18]. Other approaches include the RGB model, which balances greenness against analytical performance and practicality (red, green and blue), and the analytical method volume intensity (AMVI), which is specific to HPLC and expresses the

total volume of mobile phase consumed relative to the analysis performed [27, 28].

Several reviews have compared these tools side by side, and the shared conclusion is that no single metric is sufficient. Each captures a different facet, uses different data and gives a different emphasis to energy, waste and toxicity [9, 10]. Using two or three together, for example a quantitative score and a stage-by-stage pictogram, is the pragmatic recommendation. The tools are summarised in table 1 together with the main chromatographic and solvent considerations that bear on paracetamol methods, and the distribution of entries is shown in fig. 1.

Table 1: Assessment tools and method features relevant to green HPLC of paracetamol

Tool or factor	Feature relevant to paracetamol HPLC	Ref.
NEMI four-quadrant pictogram	Binary criteria for toxicity, hazard, corrosivity and waste; limited power to separate similar HPLC methods.	[9, 10]
Analytical Eco-Scale penalty points	Points subtracted from 100 for reagents, energy and waste; scores above 75 rated excellent.	[23]
GAPI stage-by-stage	Colour-coded cells show whether sample handling or final determination is the weak point.	[25]
ComplexGAPI	Adds pre-analytical steps such as reagent and material preparation.	[26]
AGREE twelve principles	Scores each principle from zero to one with adjustable weights and a single overall value.	[24]
AGREEprep	Dedicated assessment of sample preparation, relevant to plasma and environmental samples.	[18]
AMVI HPLC specific	Relates mobile-phase volume consumed to the analytical work performed.	[27]
Column and flow choices	Shorter columns and smaller particles cut run time and eluent use at equal separation.	[4, 16]
Acetonitrile solvent supply	Effective eluent but toxic and subject to supply problems; penalised by solvent guides.	[17, 29, 30]
Ethanol and methanol	Generally rated more favourably than acetonitrile, with trade-offs in viscosity and selectivity.	[30, 31]

Solvent selection guides deserve separate mention because they feed directly into the scores. The guides published by pharmaceutical companies rank common solvents on safety, health, environmental and waste-handling criteria, and they tend to agree that ethanol and water are preferred, methanol is usable, and acetonitrile is a problem solvent [29, 30, 31]. Frameworks for the environmental assessment of solvents provide the underlying numerical data, such as life-cycle energy and emissions to air and water [32]. Where an analytical tool asks only about hazard, a solvent guide can supply the missing life-cycle perspective.

Underlying all of these frameworks is the older idea of mass-based efficiency measures. The E factor, which relates the mass of waste to the mass of product, was introduced for synthetic chemistry and shaped how process chemists think about waste [33]. Analytical work has no product to speak of, so the concept has been adapted, for example through waste per analysis. Frameworks that grade solvents on safety, health and environmental criteria were developed in a similar spirit [32].

4. APPLYING THE METRICS TO HPLC

Consider a typical isocratic paracetamol assay: a 4.6 mm column, a flow of 1 mL/min, a run of ten minutes and a mobile phase that is roughly one third organic solvent. That method consumes about ten millilitres of eluent per injection, of which perhaps three millilitres is organic solvent. Multiplied by calibration standards, replicate injections and system suitability, a single batch analysis can yield well over 100 mL of waste. Both the Eco-Scale and AGREE would register this, because waste and reagent volume feature in their calculations [23, 24, 27].

Where would such a method lose points? In GAPI, the sample preparation stage for a tablet assay is usually green or yellow, since it involves dissolving and diluting in the

mobile phase, but the determination stage turns yellow or red because of solvent hazard, waste volume and the lack of waste treatment [25]. In AGREE, principles on sample treatment and sample size score well, whereas those covering waste, energy and the toxicity of reagents tend to pull the total down [24]. Methods that are off-line, with no automation and no integration of steps, lose points on several principles at once [6, 24].

Not every method can simply swap its solvent. Paracetamol is quite polar and elutes early on C18 columns, so mobile phases with a high aqueous fraction are common, which already works in favour of greenness [1, 2]. Problems arise when impurities such as 4-aminophenol must be resolved from the main peak, since the more demanding separation may call for gradient elution, ion-pairing or longer runs. In those cases a greener solvent has to be tested against resolution criteria, and published comparisons show that such substitution is often feasible but needs reoptimisation of the whole separation [3, 4, 17].

Waste treatment offers a quiet opportunity. Most of the tools give credit when a method includes a plan for waste, such as collection, recycling or degradation, and many HPLC papers say nothing at all on the subject [23, 24, 25]. Solvent recovery from isocratic effluent is technically feasible in principle, though contamination by buffer and analyte limits the quality of what is recovered. Simply segregating halogen-free organic waste from aqueous waste is a modest step, but a reportable one, and it can shift a score in tools that reward waste management [4, 24].

Acetonitrile is the usual flashpoint. It is a very effective solvent for chromatography, yet it is a by-product of acrylonitrile manufacture, supply has been unpredictable, and it is toxic, which most solvent selection guides penalise [17, 29, 30]. Methanol scores somewhat better on supply and worse on toxicity, and ethanol is generally the preferred choice when it can deliver adequate selectivity and pressure [30, 31]. Because the three solvents differ in viscosity and elution strength, switching is not trivial, so the greenness gain has to be weighed against the effort of revalidation under the relevant guideline [12, 17].

Reading across the tools helps to explain why they sometimes disagree. NEMI would give the same pictogram to two isocratic methods that differ several-fold in eluent volume, whereas the Eco-Scale would separate them by penalty points and AMVI by volume per analysis [10, 23, 27]. GAPI would show the same weak determination step in both, and AGREE would place them at different positions on a continuous scale [24, 25]. The differences are not errors. Each tool simply answers a slightly different question, and the best use is to ask which question matters for the decision at hand.

Operating conditions often have more influence than the choice of solvent. Reducing a run from fifteen minutes to five cuts solvent use by two thirds, and shortening the column or lowering the flow rate does something similar. The practical route is to use shorter columns with smaller or core-shell particles, which keep efficiency at lower volumes [4, 16]. AMVI captures this directly, since it relates consumption of mobile phase to the number of analytical operations, and it was designed specifically to benchmark HPLC procedures in this way [27].

Sample throughput changes the picture further. A method that looks wasteful for a single injection may be economical per analyte if it measures several compounds, or if an autosampler allows unattended overnight runs on a shared mobile phase [24, 27]. Method transfer to other laboratories can undo such gains if the receiving site lacks the same equipment.

Energy is the least visible contributor. A pump, column oven, autosampler and detector together draw a modest amount of power, but a long gradient with a heated column and a cooled autosampler can add up over a working day. The Eco-Scale assigns penalty points once consumption per sample exceeds set thresholds, and AGREE gives a separate principle to energy [23, 24]. Methods run at ambient temperature with short analysis times are therefore favoured, although most papers do not report instrument power and assessors must estimate it from typical values [2, 9].

Other design points are easier to overlook. Buffer salts and ion-pairing agents add hazards of their own, and phosphate buffers that are tolerated in the laboratory complicate waste disposal. Derivatisation is rarely needed for paracetamol, which is a point in its favour under the principles of green analytical chemistry [1, 6]. Multi-analyte methods, such as those that determine paracetamol with caffeine or other co-formulated drugs, improve the information obtained per run and so may score better per analyte even if the run itself is longer [6, 24].

5. WHY GREENNESS MATTERS FOR PARACETAMOL

The case for care is stronger than it first appears. Pharmaceuticals, including common analgesics, are detected in surface waters and wastewater, and the environmental fate of drugs has been studied since the late 1990s [19, 20]. Analytical laboratories contribute only a small part of this burden, but they are one of the few parts a profession can change by its own choices. A sector that analyses a drug so often has a particular reason to ask whether each analysis is as lean as it could be [3, 4].

There is also a practical argument. Reducing solvent use lowers purchase and disposal costs, shortens run times, and often improves laboratory safety. Industrial groups have reported that greener choices can be economical as well as responsible [3, 27]. That alignment of interests is a useful point to make when introducing new practices, because it avoids the perception that sustainability is imposed at the expense of quality. It also suggests that incentives for greener methods can come from within analytical groups rather than regulation [7, 11].

Education has a role as well. Students learn paracetamol assays early in analytical courses because the molecule is stable, inexpensive and easy to detect, so the habits formed on this analyte may carry over to later work. Teaching laboratories can compare a conventional acetonitrile method with a shorter ethanol-based one and score both with a simple tool, which gives a concrete lesson in trade-offs [3, 7, 11]. Students can also be asked to calculate the volume of solvent their own assay generated over a term, which makes the cost visible.

6. LIMITATIONS AND FUTURE DIRECTIONS

Metrics are only as good as the information fed into them. Many HPLC papers do not state waste volumes, instrument energy use or the preparation of standards in enough detail, so the person scoring must guess. Different assessors may then reach different results for the same paper [9, 10]. Weighting is another source of disagreement: whether toxicity of a solvent should count for more than the volume used is a value judgement, and the tools do not settle it. Scores from different tools should not be mixed in a league table [24, 28].

Another limitation is that greenness scores say nothing about the quality of the chemistry. A fast, low-solvent method that fails to resolve a degradation product is worse than useless, since it gives a false sense of control over a pharmaceutical product. Validation parameters and greenness therefore have to be reported together, and the Q2(R1) characteristics remain the entry ticket for any method regardless of its colour on a pictogram [12, 28]. The better papers in the field already do this.

Finally, the exercise described here is hypothetical in an important respect. The article applies the tools to typical choices rather than to a defined set of papers, so its general statements should be tested by assessing a documented sample of published methods with two independent assessors and reporting their agreement [9, 10]. Such an audit would reveal how often reported details are sufficient for scoring and whether apparent greenness reflects real improvement or only selective reporting [24, 25].

Greenness is also not the only consideration. A method that is slightly less green but more sensitive or robust may be the better choice for an impurity assay or a bioanalytical study, and the RGB model explicitly asks analysts to balance these demands [28]. Future work might include routine reporting of a greenness score with each new method, shared templates that record the data the tools need,

and attention to life-cycle effects such as column manufacture and solvent supply [9, 10]. Such practices would make comparisons across papers much more honest [18].

7. CONCLUSION

Published HPLC methods for paracetamol are well suited to greenness assessment because they share a small set of design choices: a C18 column, an isocratic mixture of water with methanol or acetonitrile, ultraviolet detection and a run measured in minutes. The metrics reviewed here would be expected to respond mainly to solvent identity, solvent volume, run time and the handling of waste, and these are exactly the features that analysts can alter without changing the chemistry of the separation [17, 23, 24, 27].

No single tool is adequate. A quantitative score, a stage-by-stage pictogram and an HPLC-specific measure such as AMVI give complementary views, and all depend on authors reporting the details that the calculations require [9, 10, 25]. Used with that in mind, the metrics are a useful prompt for improvement, such as shorter columns, ethanol where feasible, and less waste per batch, rather than a means of ranking papers or laboratories [6, 28].

8. ABBREVIATIONS

AGREE-Analytical GREEnness metric approach, AMVI-Analytical method volume intensity, GAPI-Green Analytical Procedure Index, HPLC-High-performance liquid chromatography, ICH-International Council for Harmonisation, NEMI-National Environmental Methods Index, RGB-Red-green-blue model for method evaluation, UV-Ultraviolet

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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