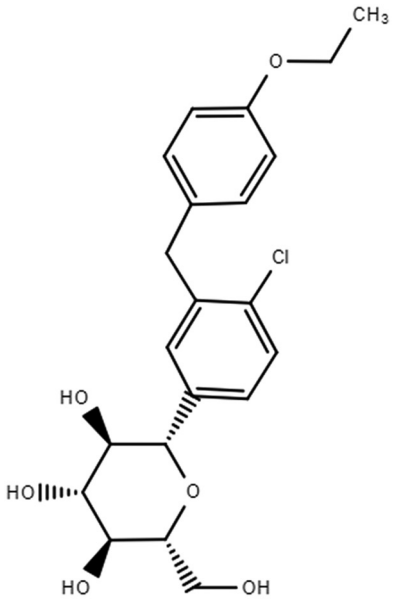
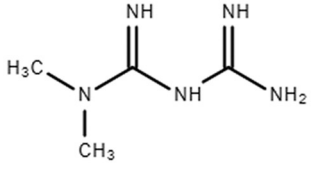
Supplementary material



(a)



(b)

Figure S1: Chemical structure of (a) MET and (b) DAP.

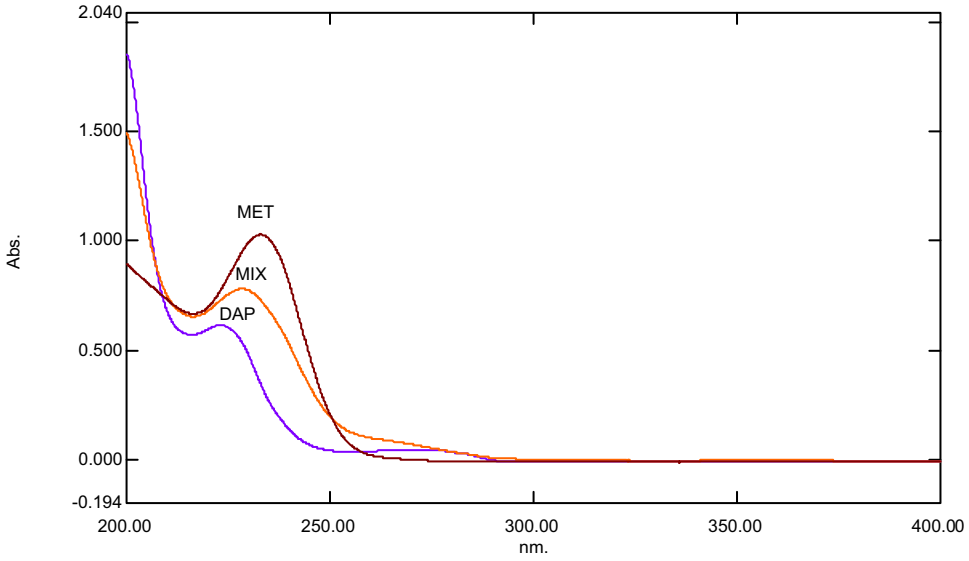


Figure S2: Zero-order absorption spectra of binary combination, MET, and DAP at 10 μg·mL^{-1} with solvent used as blank.

Analytical Greenness report sheet

13/06/2024 09:19:03

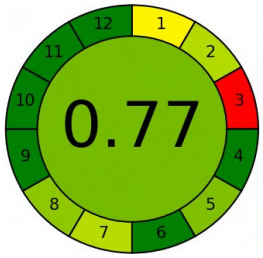
Criteria	Score	Weight
1. Direct analytical techniques should be applied to avoid sample treatment.	0.48	2
2. Minimal sample size and minimal number of samples are goals.	0.65	2
3. If possible, measurements should be performed in situ.	0.0	2
4. Integration of analytical processes and operations saves energy and reduces the use of reagents.	1.0	2
5. Automated and miniaturized methods should be selected.	0.75	2
6. Derivatization should be avoided.	1.0	2
7. Generation of a large volume of analytical waste should be avoided, and proper management of analytical waste should be provided.	0.69	2
8. Multi-analyte or multi-parameter methods are preferred versus methods using one analyte at a time.	0.84	2
9. The use of energy should be minimized.	1.0	2
10. Reagents obtained from renewable sources should be preferred.	1.0	2
11. Toxic reagents should be eliminated or replaced.	1.0	2
12. Operator's safety should be increased.	1.0	2

(a)

Figure S3: AGREE (a) and (b) and AGREEprep (c) and (d) applications for evaluating the UPLC and UV techniques.

Analytical Greenness report sheet

13/06/2024 09:26:02



Criteria	Score	Weight
1. Direct analytical techniques should be applied to avoid sample treatment.	0.48	2
2. Minimal sample size and minimal number of samples are goals.	0.65	2
3. If possible, measurements should be performed in situ.	0.0	2
4. Integration of analytical processes and operations saves energy and reduces the use of reagents.	1.0	2
5. Automated and miniaturized methods should be selected.	0.75	2
6. Derivatization should be avoided.	1.0	2
7. Generation of a large volume of analytical waste should be avoided, and proper management of analytical waste should be provided.	0.64	2
8. Multi-analyte or multi-parameter methods are preferred versus methods using one analyte at a time.	0.72	2
9. The use of energy should be minimized.	1.0	2
10. Reagents obtained from renewable sources should be preferred.	1.0	2
11. Toxic reagents should be eliminated or replaced.	1.0	2
12. Operator's safety should be increased.	1.0	2

(b)

Figure S3: (*Continued*)

AGREEprep

Analytical Greenness Metric for Sample Preparation

13/06/2024 09:30:31

#	Criterion	Score	Weight
1.	**Sample preparation placement** Sample preparation placement: Ex situ	0.0	1
2.	**Hazardous materials** Mass [g] or volume [mL] of problematic materials: 0	1.0	5
3.	**Sustainability, renewability, and reusability of materials** Only sustainable and renewable materials are used SEVERAL TIMES	1.0	2
4.	**Waste** Mass [g] or volume [mL] of waste: 1	0.63	4
5.	**Size economy of the sample** Mass [g] or volume [mL] of the sample: 1	0.67	2
6.	**Sample throughput** Hourly sample throughput: 20	0.71	3
7.	**Integration and automation** No. of sample prep. steps: 2 steps or fewer; degree if automation: Semi-automated systems	0.5	2
8.	**Energy consumption** Approximate energy consumption per analysis [W]: 0.1	1.0	4
9.	**Post-sample preparation configuration for analysis** Liquid chromatography, gas chromatography with quadrupole detection, etc.	0.25	2
10.	**Operator's safety** No. of distinct hazards: No hazards or no exposure	1.0	3

(c)

Figure S3: (*Continued*)

AGREEprep

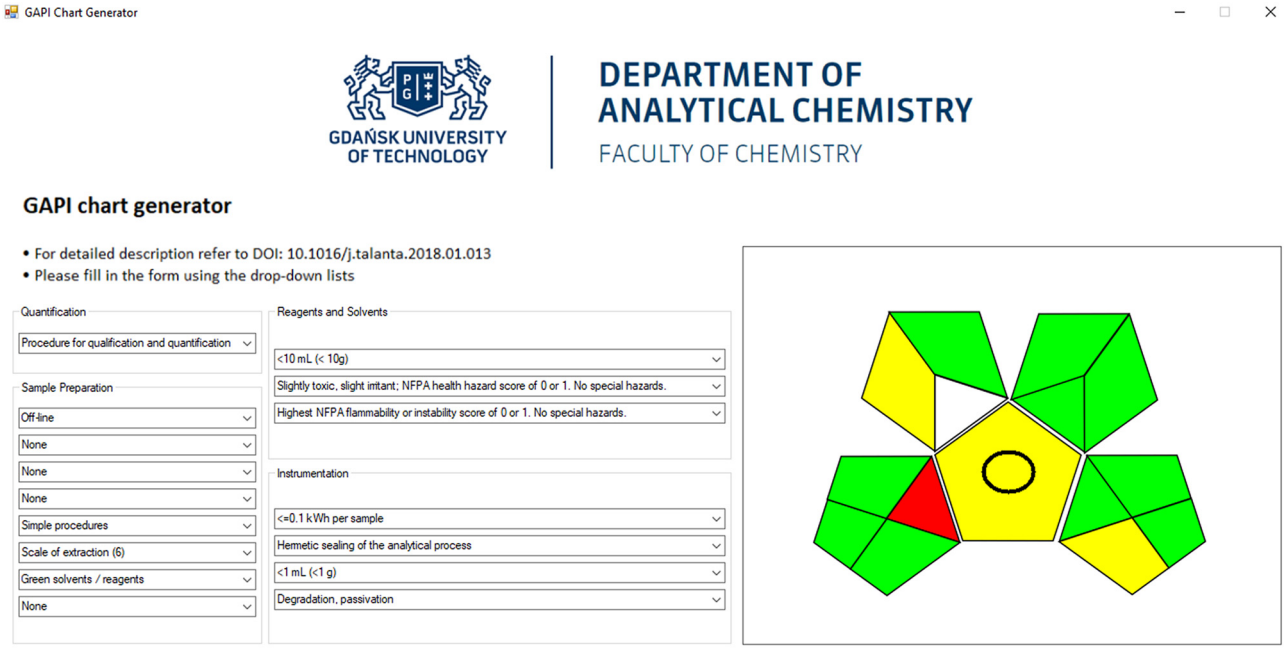
Analytical Greenness Metric for Sample Preparation

13/06/2024 10:10:48

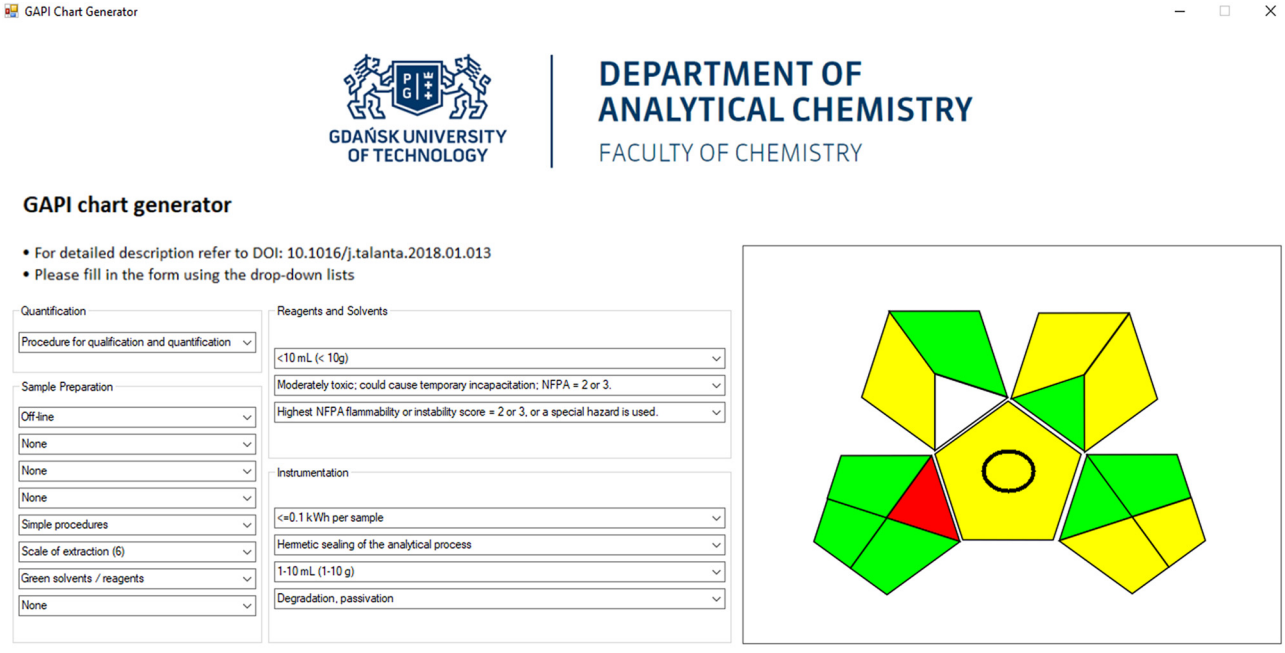
#	Criterion	Score	Weight
1.	**Sample preparation placement** Sample preparation placement: Ex situ	0.0	1
2.	**Hazardous materials** Mass [g] or volume [mL] of problematic materials: 0	1.0	5
3.	**Sustainability, renewability, and reusability of materials** Only sustainable and renewable materials are used SEVERAL TIMES	1.0	2
4.	**Waste** Mass [g] or volume [mL] of waste: 3	0.45	4
5.	**Size economy of the sample** Mass [g] or volume [mL] of the sample: 1	0.67	2
6.	**Sample throughput** Hourly sample throughput: 12	0.58	3
7.	**Integration and automation** No. of sample prep. steps: 2 steps or fewer; degree if automation: Semi-automated systems	0.5	2
8.	**Energy consumption** Approximate energy consumption per analysis [W]: 0.1	1.0	4
9.	**Post-sample preparation configuration for analysis** Spectrophotometry, surface analysis techniques, voltammetry, potentiometry, etc.	0.75	2
10.	**Operator's safety** No. of distinct hazards: No hazards or no exposure	1.0	3

(d)

Figure S3: (*Continued*)

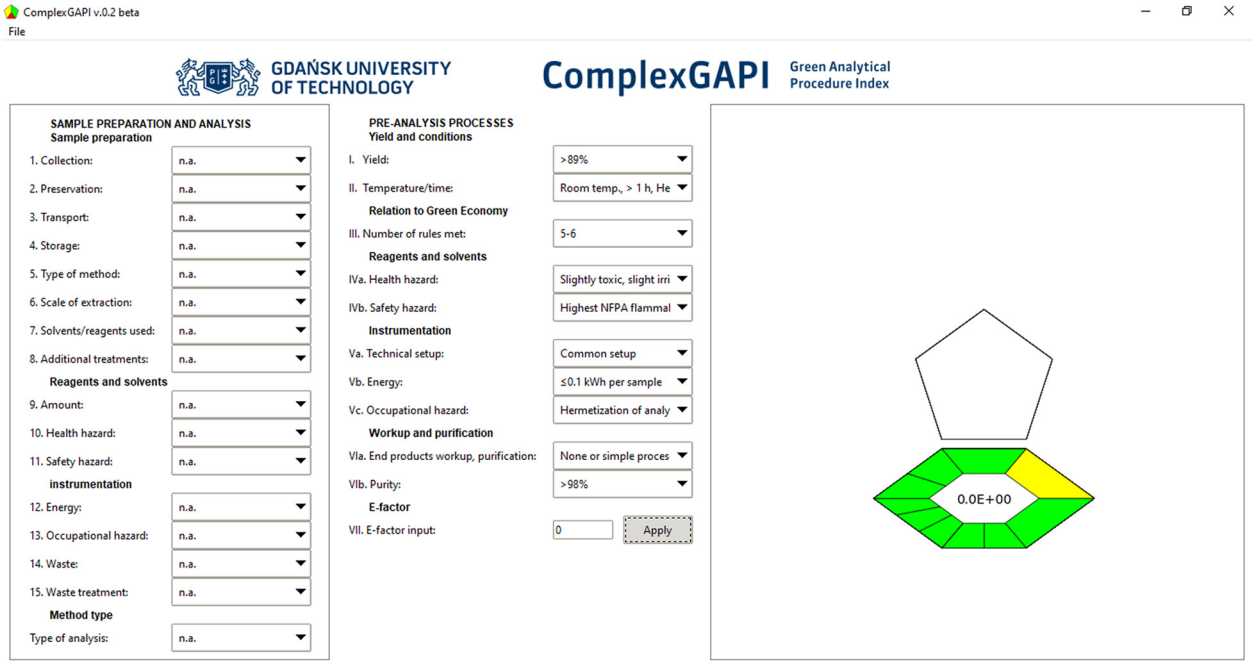


(a)

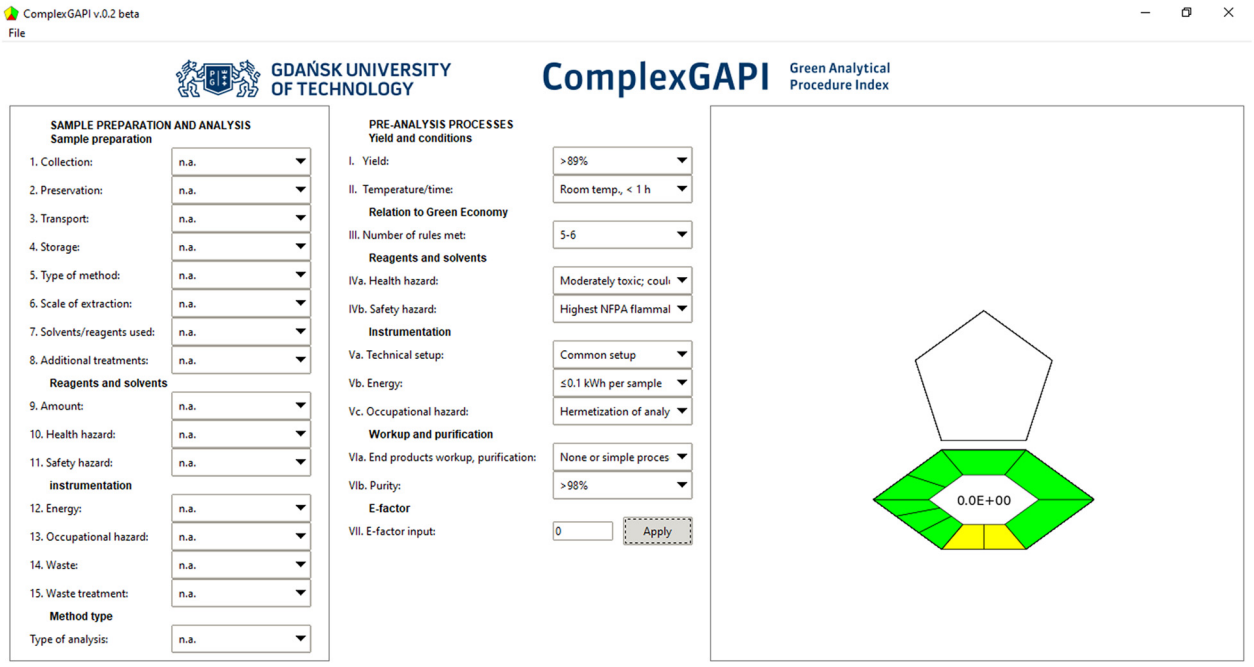


(b)

Figure S4: GAPI (a) and (b), ComplexGAPI (c) and (d), and BAGI (e) and (f) applications for evaluating the UPLC and UV techniques.

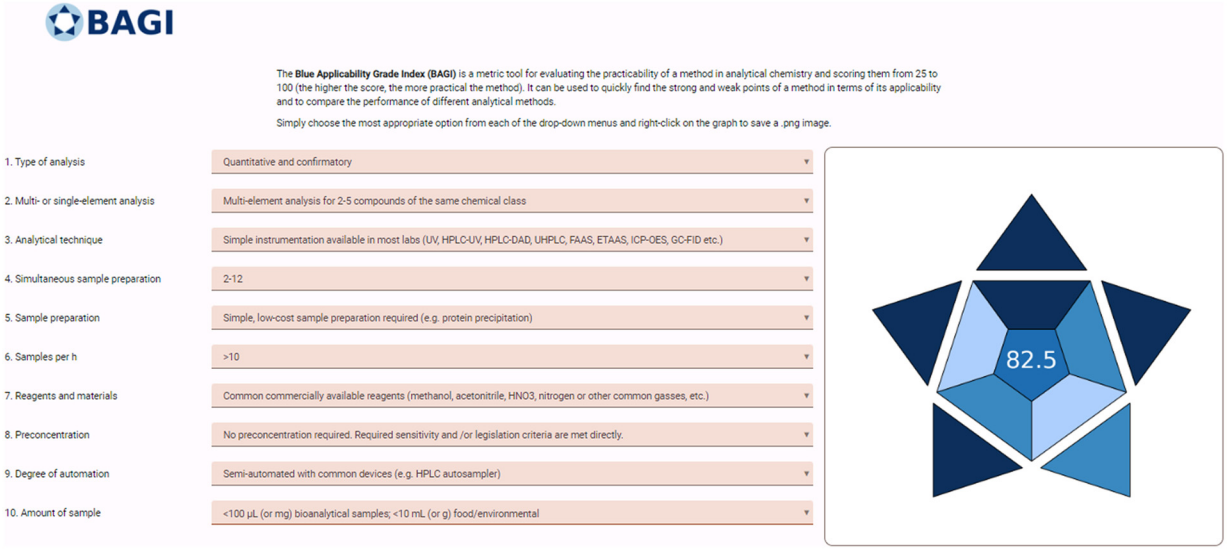


(c)

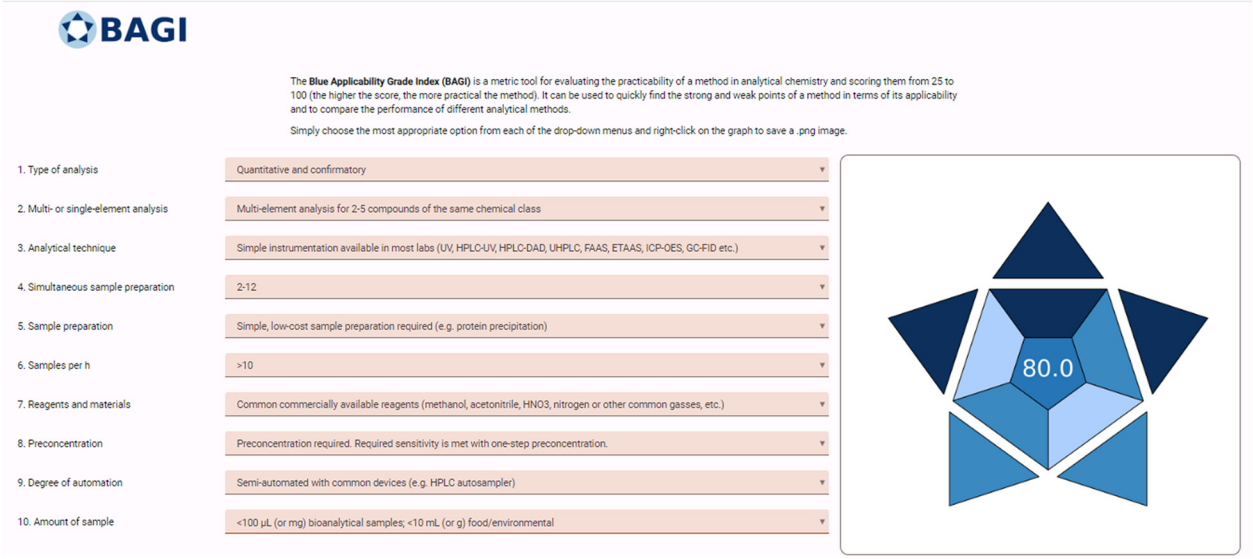


(d)

Figure S4: (*Continued*)



(e)

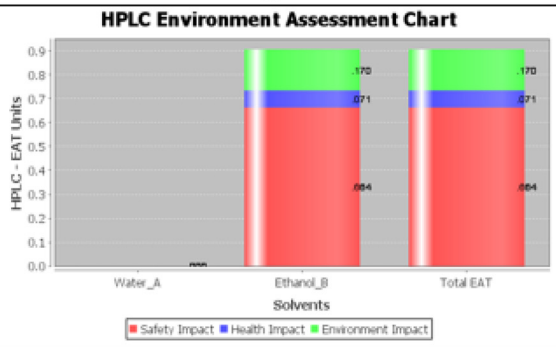


(f)

Figure S4: (*Continued*)

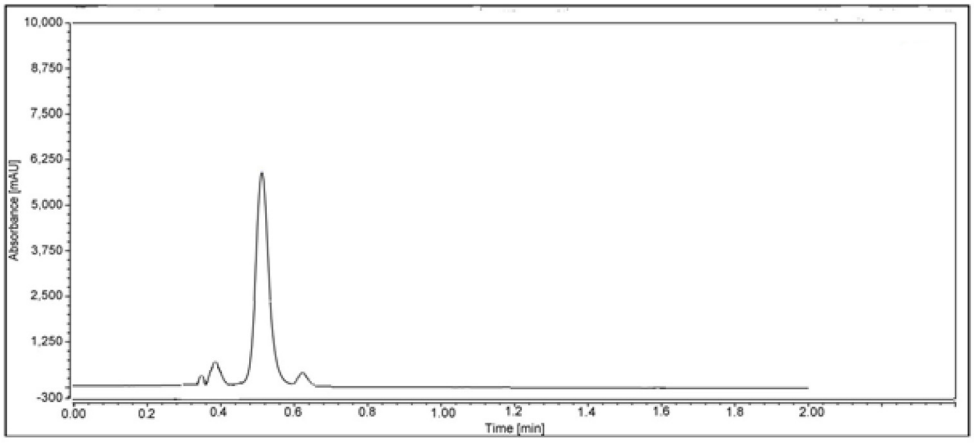
	AMGS	Proposed Method		Figure
Instrument Conditions	Technique	UPLC		
	Number of analytes of interest	2		
	Number of injections/runs for one full analysis	15		
	Flow Rate (mL/min)	0.5		
	Run time (min/injection)	2		
Solvent	Purified water and ethanol (mL)	210		
Sample	Sample prep volume (mL)	100		
	Number of sample preps	2		
Standards	Stock standard prep volume (mL)	100		
	Number of stock standard preps	1		
Standard Diluent	Working Standard prep volume (mL)	10		
	Number of stock standard preps	1		
System Suit Test (SST) volume (mL)	SST prep volume (mL)	10		
	Number of SST preps	1		
Method	Instrument Energy Score	**21.44**	**(7.39%)**	
	Solvent Energy Score	**175.13**	**(60.33%)**	
	Solvent EHS Score	**93.71**	**(32.28%)**	
Greenness Score		**290.28**		

(a)

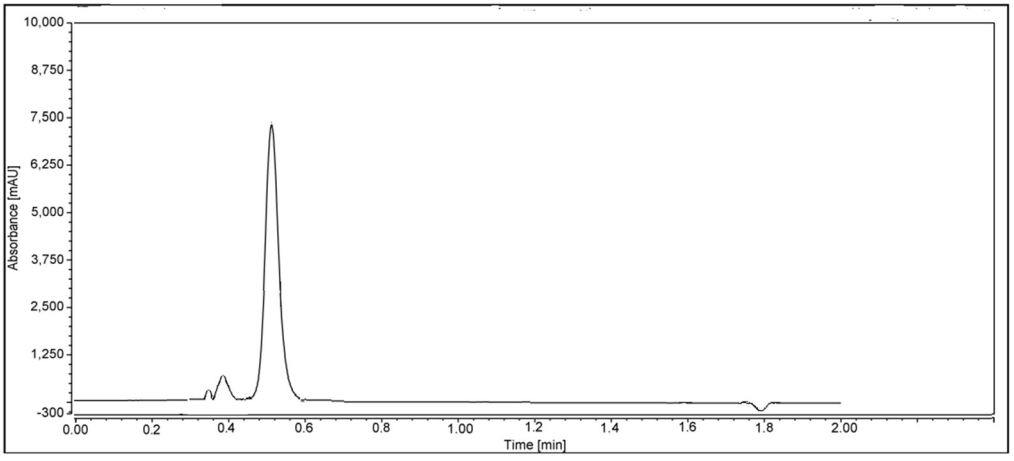
Calculation SHE	Proposed Method	Figure
Sample Pre-Treatments	None	
Mobile phase A	Phosphate buffer (55%)	
Mobile phase B	Ethanol (45%)	
Flow rate	0.5 mL/min	
Run time	2 min	
Safety Impact	0.664	
Healthy Impact	0.071	
Environment Impact	0.17	
Total HPLC-EAT score	0.905	

(b)

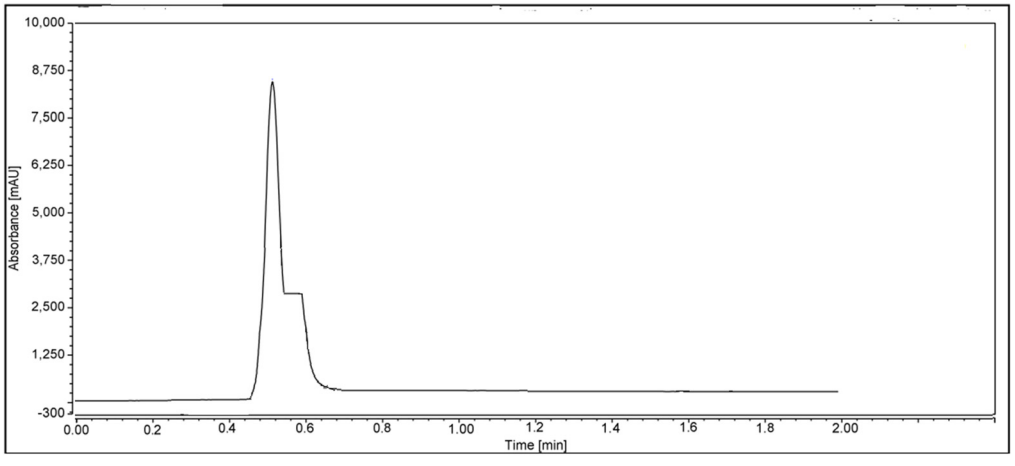
Figure S5: (a) AMGS and (b) HPLC-EAT metrics for evaluation of the UPLC approach.



(a)

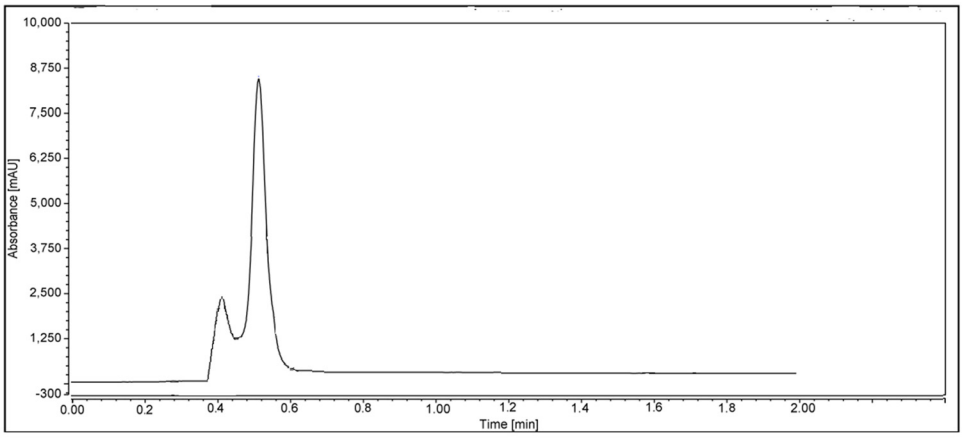


(b)

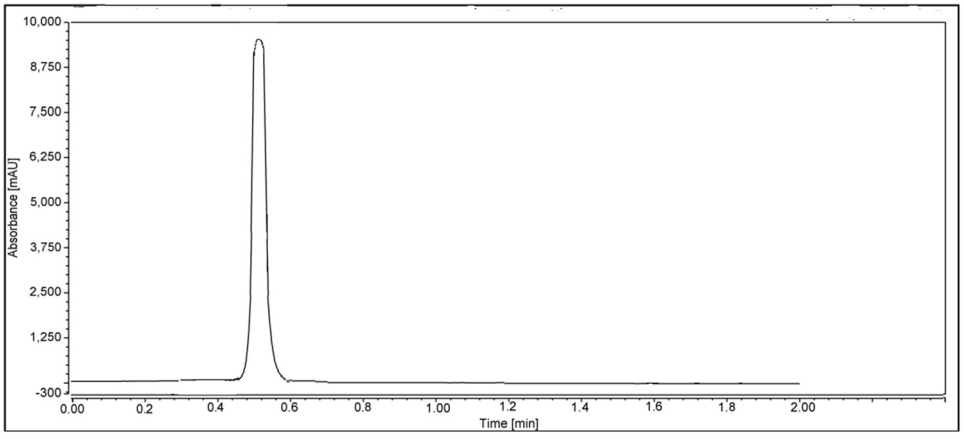


(c)

Figure S6: UPLC charts of (a) placebo and blanks for (b) diluent, (c) acid, (d) base, and (e) oxidation.



(d)



(e)

Figure S6: (*Continued*)

Table S1: Intra- and inter-day precision, robustness, and stability of the analytical solution of the recommended UPLC and UV methods

Parameter	UPLC		UV		Limit (%)
	MET	DAP	MET	DAP	
Day to Day	0.7	0.5	0.3	0.4	**RSD**
Analyst to Analyst	1.1	0.9	0.5	0.8	≤ **2.0%**
Column to Column	0.9	0.8	—	—	
Flow rate change (±0.1 $mL \cdot min^{-1}$)	0.4	0.6	—	—	
pH changes of mobile phase (±0.05)	0.8	0.9	—	—	
Organic solvent change (±2%)	0.3	0.4	—	—	
Fresh sample	0.2	0.1	0.3	0.4	
Stored sample in fridge	0.7	0.5	0.8	0.6	
Stored sample in autosampler	0.6	0.7	—	—	
Stored Sample at room temperature	0.8	0.9	1.2	0.9	

Table S2: Assay of MET and DAP in the film-coated tablet employing the recommended methods

Dosage form	UPLC		UV		Limit
	Assay (%)				
Forminodab XR	MET	DAP	MET	DAP	90–110%
10/1,000 mg FCT	99.89	100.58	99.28	101.43	
	100.43	101.47	100.95	100.37	
	98.98	99.78	102.27	102.76	
	97.87	98.93	100.69	100.86	
	101.12	99.28	101.37	99.49	
	102.09	101.27	103.87	100.57	
Mean ± RSD	100.06	100.22	101.41	100.91	
	± 1.51	± 1.05	± 1.53	± 1.10	

Table S3: Results of system suitability parameters of the recommended UPLC method

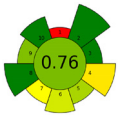
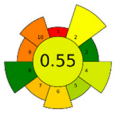
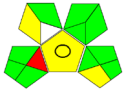
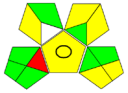
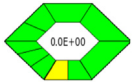
Item	UPLC		Reference values
	MET	DAP	
Tailing factor	1.4	1.2	$T \leq 2.0$
Injection precision	0.4	0.5	RSD ≤ 2%
Number of theoretical plates (N)	3,442	2,594	$N > 2{,}000$
Resolution	4.8	—	Rs >1.5
Retention time (R_t)	0.5	0.8	RT window ≤ 10%

Table S4: The distinction between the recovery outcomes of the published procedures and the recommended approaches for quantitative DAP and MET drugs

Method	Application	Mobile phase/Solvent	Flow rate	Run time	Waste[a]	Recovery (%)
UPLC and MCR (The suggested methods)	Green and White appraisal for UPLC and MCR techniques	Mobile Phase: Phosphate buffer and ethanol (55:45, v/v) adjusted to pH 7.0. Solvent: Purified water and ethanol at a ratio of (70:30, v/v) for UPLC. Ultra-pure water for UV	0.5 mL·min^{-1}	2.0 min	1.0 g/ sample	99.5–100.9% for DAP and 99.9–100.3% for MET
[1]	First Derivative Spectrophotometric method for determining DAP in the presence of MET	Solvent: 0.1 N HCl for UV.	Not Applicable	Not Applicable	3.0 g/ sample	98.9–100.4% for DAP
[2]	Ratio difference spectroscopy Derivative Ratio Spectrum-Zero crossing	Solvent: distilled water for UV.	Not Applicable	Not Applicable	3.0 g/ sample	98.4–100.9% for DAP and 97–101% for MET
[3]	Simultaneous equation method	Solvent: Methanol: water (80:20, v/v) for UV	Not Applicable	Not Applicable	3.0 g/ sample	98.7–99.1% for DAP and 98.7–99.4% for MET
[4]	UPLC	Mobile Phase: Orthophosphoric acid (pH 3.00) and acetonitrile (55:45%, v/v) Solvent: water: acetonitrile (50:50%, v/v) for UPLC	0.2 mL·min^{-1}	5.0 min	1.0 g/ sample	98.77–99.57% and 99.15–101.2% for DAP and MET
[5]	UHPLC	Mobile Phase: A mixture of potassium dihydrogen phosphate buffer, pH (3.5)—acetonitrile (50:50, v/v). Solvent: Methanol for UPLC	0.4 mL·min^{-1}	10 min	4.0 g/ sample	98.77–99.57% and 99.15–101.2% for DAP and MET

[a]Waste = (run time × flow rate) for UPLC methods or Size economy of the sample in UV methods.

Table S5: Enhancing comparative analysis with existing methods for ecological appraisal

Method	Proposed UPLC method	Proposed UV method	Reported method [1]	Reported method [2]	Reported method [3]	Reported method [4]	Reported method [5]
AGREE							
AGREEprep							
GAPI							
ComplexGAPI							
BAGI							

References

[1] Antakli S, Kabbani R, Labban R. Analytical spectrometric study for determining dapagliflozin propanediol monohydrate individually or in presence of metformin hydrochloride in Tablets formulation. J Adv Chem. 2020;17:80–7. doi: 10.24297/jac.v17i.8812.

[2] Sen DB, Jatu S, Maheshwari RA, Zanwar AS, Velmurugan R, Sen AK. New Eco-friendly UV-spectroscopic Methods for Simultaneous Assessment of Dapagliflozin, Saxagliptin and Metformin in Ternary Mixture. Indian J Pharm Educ Res. 2023;57(2):559–69. doi: 10.5530/ijper.57.2.69.

[3] Suman SS, Chaubey R. Simultaneous spectrophotometric estimation of metformin, saxagliptin and dapagliflozin in marketed formulations. J Pharm Res Int. 2021;33(61B):167–73. doi: 10.9734/jpri/2021/v33i61B35495.

[4] Vyas AJ, Jadav CD, Patel KJ, Patel R, Vadile HM, Patel AB, et al. Diode array detector based RP-UPLC method for simultaneous estimation of dapagliflozin propanediol monohydrate and metformin. Res J Pharm Technol. 2024;17(3):991–6. doi: 10.52711/0974-360X.2024.00153.

[5] Zaghary WA, Mowaka S, Hendy MS. Kinetic degradation study of dapagliflozin coupled with UHPLC separation in the presence of major degradation product and metformin. Chromatographia. 2019;82:777–89. doi: 10.1007/s10337-019-03702-3.