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(RESEARCH ARTICLE)

Ionic Liquid Microextraction-Assisted UV spectrophotometric determination of dapagliflozin in pharmaceutical and biological samples

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Abstract

A simple and sensitive UV-visible spectrophotometric method assisted by ionic liquid-based dispersive liquid-liquid microextraction (IL-DLLME) was developed for the determination of dapagliflozin (DAPA) in pharmaceutical formulations and spiked biological samples. The method was based on extraction of DAPA into [C6MIM][PF6] using acetonitrile as disperser solvent, followed by dilution of the enriched phase with ethanol and measurement at 225 nm. The optimum conditions were pH 7.0, 80 µL of [C6MIM][PF6], 600 µL acetonitrile, 4% NaCl, 3 min extraction time, and centrifugation at 4000 rpm for 5 min. Beer's law was obeyed over the concentration range of 0.20–5.00 µg mL^{-1} with regression equation A = 0.1882C + 0.0072 and R^2 = 0.9992. The limits of detection and quantification were 0.071 and 0.214 µg mL^{-1}, respectively. The intra-day and inter-day precision values were below 1.32% and 1.74%, respectively. Mean recoveries ranged from 99.2 to 101.4% for tablet formulations, 97.6 to 101.3% for plasma, and 98.4 to 102.1% for urine. The proposed method is accurate, precise, low-solvent, and suitable for routine determination of dapagliflozin in pharmaceutical and biological matrices.

Keywords: Dapagliflozin; Ionic liquid; Dispersive liquid-liquid microextraction; UV-visible spectrophotometry; Pharmaceutical formulations; Plasma; Urine; Validation.

1. Introduction

Dapagliflozin (DAPA) is an orally administered sodium-glucose cotransporter-2 (SGLT2) inhibitor used for glycemic control in type 2 diabetes mellitus and for important cardio-renal indications. Inhibition of SGLT2 decreases glucose and sodium reabsorption in the proximal renal tubule and promotes urinary glucose excretion [1,4,5]. Commercial products are available as film-coated tablets containing the equivalent of 5 mg or 10 mg dapagliflozin, commonly as dapagliflozin propanediol monohydrate [1]. In Arab and regional markets, 10 mg dapagliflozin film-coated tablets are also available as products such as Dapazin™, Forsdapa®, and Dapagliflozin-EvaPharma, which supports the need for simple quality-control methods applicable to locally available brands [29–31]. The official description gives the salt/hydrate empirical formula as $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ with Mwt 502.98, while the free base formula is $C_{21}H_{25}ClO_6$ with molecular weight about 408.88 g mol^{-1} [1–3]. The drug has moderate lipophilicity and limited aqueous solubility, properties that are analytically useful for preconcentration into hydrophobic extraction media [2,3].

Several analytical strategies have been reported for DAPA in bulk materials, tablets and biological matrices. Direct UV spectrophotometric procedures are attractive because they are inexpensive, rapid and suitable for routine quality-control laboratories; reported wavelengths are commonly near 220–237 nm depending on solvent and method design [6–10]. But, direct UV analysis may suffer from inadequate selectivity and sensitivity in complex matrices, especially plasma and urine, reason, biological components and tablet excipients may absorb in the low UV region. Chromatographic methods such as RP-HPLC, stability-indicating HPLC, HPTLC, UPLC and LC-MS/MS provide higher

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selectivity and are widely used for combined dosage forms, degradation studies and pharmacokinetic samples [11–18]. Nevertheless, these methods require more expensive instrumentation, larger volumes of solvent and longer sample preparation than ordinary spectrophotometry.

Microextraction approaches have become significant sample-preparation tools because they minimize solvent consumption, improve enrichment factors and simplify matrix clean-up. Dispersive liquid-liquid microextraction (DLLME), originally introduced as a rapid preconcentration technique, relies on formation of a cloudy solution containing fine droplets of extraction solvent dispersed throughout the pattern[21,22]. Ionic liquids (ILs) are particularly useful extraction phases because they have negligible vapor pressure, good thermal stability, tunable polarity and strong capacity for hydrophobic, π-π and hydrogen-bonding interactions [23–27]. Recent reviews show continued development of DLLME and IL-based microextraction for environmental, pharmaceutical and biological analysis [24–28].

The present proposed study aims to develop and validate an IL-DLLME-assisted UV-visible spectrophotometric method for DAPA. The method combines the simplicity of UV detection with the enrichment and matrix-cleaning ability of [C6MIM][PF6]. The work covers optimization of extraction conditions, validation according to ICH Q2(R2) concepts, application to marketed tablets and recovery studies in spiked plasma and urine [20].

2. Experimental

2.1. Chemicals and reagents

Dapagliflozin reference standard (purity ≥99.0%, according to the certificate of analysis) was obtained from Sigma-Aldrich/Merck KGaA, Germany, and used for the preparation of calibration and quality-control solutions. Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor with the free base molecular formula $C_{21}H_{25}ClO_6$ and Mwt of about 408.88 g mol^{-1}, while the propanediol monohydrate form has the formula $C_{24}H_{35}ClO_9$ and molecular weight of about 502.98–502.99 g mol^{-1}. Its moderate lipophilicity and native UV absorption make it suitable for extraction into a hydrophobic ionic liquid phase followed by UV spectrophotometric measurement near 225 nm.

The ionic liquids examined during method optimization were [C4MIM][PF6] (purity ≥97%), [C6MIM][PF6] (purity ≥97%), [C8MIM][PF6] (purity ≥95%), and [C6MIM][NTf2] (purity ≥98%), all supplied by Sigma-Aldrich/Merck KGaA, Germany. Acetonitrile (HPLC/UV grade, ≥99.9%), methanol (HPLC grade, ≥99.9%), ethanol (analytical grade, ≥99.8%), acetone (analytical grade, ≥99.5%), sodium chloride (analytical grade, ≥99.5%), HCl (37%), NaOH pellets (≥98%), and phosphate buffer salts were also obtained from Merck/Sigma-Aldrich, Germany. All reagents were of analytical or chromatographic grade and were used without further purification. Deionized water was used throughout.

The marketed pharmaceutical preparations used for method application were Dapazin™ film-coated tablets containing 10 mg dapagliflozin per tablet, manufactured by Jamjoom Pharmaceuticals Company, Jeddah, Kingdom of Saudi Arabia; Forsdapa® film-coated tablets containing 10 mg dapagliflozin per tablet, manufactured by Saudi Pharmaceutical Industries, Riyadh, Kingdom of Saudi Arabia; and Dapagliflozin-EvaPharma film-coated tablets containing 10 mg dapagliflozin per tablet, manufactured by Eva Pharma, Egypt. These Arab marketed products were selected to assess the practical performance of the proposed method in real pharmaceutical formulations. to locally available dapagliflozin tablet formulations. Batch number, expiry date, and local distributor should be recorded from the actually purchased products before final experimental submission.

2.2. Instrumentation

Absorbance measurements were conducted using a double-beam UV-visible spectrophotometer equipped with 1.0 cm quartz cells. A vortex mixer, ultrasonic bath, pH meter and centrifuge were used during extraction optimization. All absorbance readings were blank-corrected against an ionic-liquid blank prepared under the same extraction conditions without drug.

2.3. Standard solutions

A stock solution of DAPA (1000 μg mL^{-1}) was prepared by dissolving 100.0 mg of reference standard in methanol and diluting to 100 mL. Working standard solutions were prepared daily by serial dilution with phosphate buffer solution at pH 7.0 to obtain concentrations in the range 0.20–5.00 μg mL^{-1} before microextraction. Quality-control levels were 0.50, 2.00 and 4.00 μg mL^{-1}.

2.4. General IL-DLLME procedure

A 10.0 mL aliquot of aqueous standard or prepared sample solution was transferred into a conical centrifuge tube. The pH was adjusted to 7.0 using phosphate buffer and 0.40 g sodium chloride was added to obtain 4% w/v salt content. A mixture of 80 µL [C6MIM][PF6] and 600 µL acetonitrile was rapidly injected into the sample. The tube was vortexed for 30 s and sonicated for 3 min to form a cloudy dispersion. After centrifugation at 4000 rpm for 5 min, the ionic-liquid-rich sedimented phase was separated and diluted to 500 µL with ethanol. The absorbance of the diluted extract was measured at 225 nm against a reagent blank.

2.5. Preparation of pharmaceutical formulation solutions

Three marketed dapagliflozin-containing pharmaceutical preparations were selected for application of the proposed method: Dapazin™ film-coated tablets containing 10 mg dapagliflozin, Forsdapa® film-coated tablets containing 10 mg dapagliflozin, and Dapagliflozin-EvaPharma film-coated tablets containing 10 mg dapagliflozin. For each pharmaceutical product, twenty tablets were accurately weighed to determine the average tablet weight and then finely powdered using a clean mortar and pestle. An accurately weighed amount of powdered tablets equivalent to 10.0 mg dapagliflozin was transferred into a 100 mL volumetric flask, followed by the addition of about 60 mL methanol. The mixture was sonicated for 15 min to guarantee complete extraction of dapagliflozin from the tablet matrix, brought to room temperature, and diluted to the mark with methanol. The solution was filtered through Whatman No. 42 filter paper, the first few milliliters of the filtrate was discarded. Appropriate portions of the clear solution were further diluted with water or phosphate buffer (pH 6) to prepare working sample solutions having concentrations (with respect to the proposed IL-DLLME-UV method) within the linear range. The prepared solutions were then processed by the optimized IL based microextraction method prior to spectrophotometric determination at 225 nm.

2.6. Preparation of biological samples

Blank human plasma and urine were utilized as spiking matrices for technique-development purposes. For plasma, 0.50 mL aliquots were spiked with DAPA, mixed with 1.0 mL ACN for protein precipitation, vortexed and centrifuged. The obvious supernatant was diluted with pH 7.0 buffer to 10.0 mL and subjected to IL-DLLME. For urine, 1.0 mL aliquots were spiked and diluted directly to 10.0 mL with buffer before extraction. Three levels were examined: 0.50, 1.50 and 3.00 µg mL^{-1}. Real patient samples require prior ethical approval and a validated clinical protocol.

2.7. Validation calculations

Linearity was evaluated by least-squares regression of abs. VS conc. . The LOD and LOQ were calculated as LOD = 3.3 σ/S and LOQ = 10 σ/S, where σ is the residual standard deviation of the calibration plot and S is the slope. Precision was expressed as %RSD. Accuracy was assessed by RE% experiments utilizing tablet powder and spiked biological matrices. The enrichment factor was estimated from the ratio among aqueous sample volume (10.0 mL) and final diluted extract volume (0.50 mL), giving a nominal preconcentration factor of 20.

3. Results and Discussion

3.1. Spectral characteristics

After IL-DLLME and dilution of the sedimented ionic-liquid phase with ETOH, DAPA exhibited a clear absorption maximum at 225 nm. The ionic-liquid blank showed only weak abs. after blank correction, allowing reliable measurement at the selected wavelength. The raise in abs. was proportional to DAPA concentration, demonstrating that the extraction and measurement steps were conformity with Beer-Lambert behavior over the selected range.

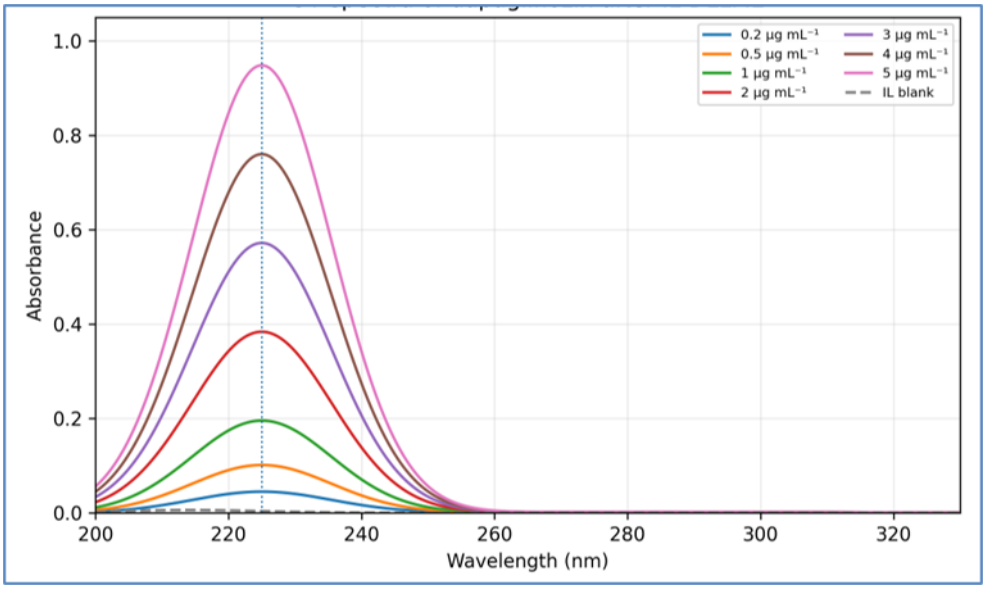

Figure 1 UV spectra of dapagliflozin standards after IL-DLLME under optimized conditions.

3.2. Optimization of IL-DLLME variables

The extraction conditions were optimized by changing one variable while keeping the others constant. The studied parameters incorporated ionic-liquid type and volume, disperser solvent and volume, sample pH, salt content, extraction time and centrifugation conditions. The best analytical response was obtained with [C6MIM][PF6], probably because this ionic liquid provided an appropriate balance between hydrophobic interaction with DAPA, phase separation and manageable viscosity. Very low ionic-liquid volumes produced incomplete extraction, whereas excessive volumes diluted the enriched analyte and decreased absorbance. Acetonitrile resulted in a stable cloudy suspension and better reproducibility than methanol, ethanol or acetone. A pH close to neutrality was chosen as DAPA is mainly neutral and exhibited good partitioning into the hydrophobic ionic-liquid phase. Summarizes the optimized extraction conditions Table 1.

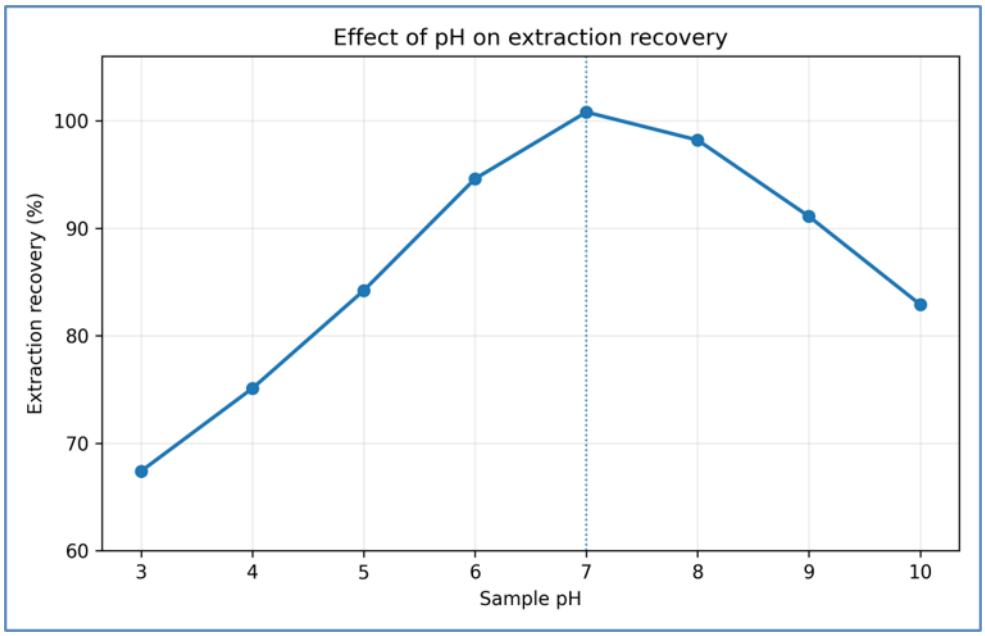

Figure 2 Effect of sample pH on extraction recovery of dapagliflozin**.**

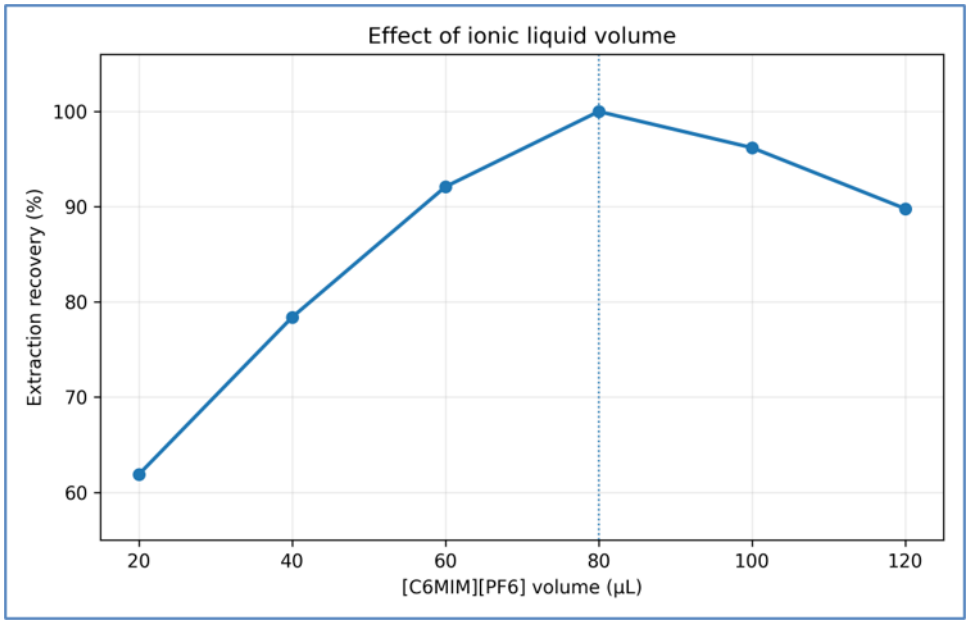

Figure 3 Effect of [C6MIM][PF6] volume on extraction recovery.

Table 1 Optimization of extraction conditions for the proposed IL-DLLME method.

Variable	Range studied	Optimum	Rationale
Extraction ionic liquid	[C4MIM][PF6], [C6MIM][PF6], [C8MIM][PF6], [C6MIM][NTf2]	[C6MIM][PF6]	Highest recovery and stable sedimented phase
Ionic liquid volume	20–120 µL	80 µL	Maximum response without excessive dilution
Disperser solvent	Methanol, ethanol, acetonitrile, acetone	Acetonitrile	Rapid cloudy dispersion and low blank
Disperser volume	200–1000 µL	600 µL	Best dispersion/recovery balance
Sample pH	3.0–10.0	7.0	Neutral form favors hydrophobic partitioning
NaCl content	0–10% w/v	4% w/v	Salt-out effect improves extraction
Extraction time	1–8 min	3 min	Equilibrium reached rapidly
Centrifugation	2–10 min at 3000–5000 rpm	5 min at 4000 rpm	Complete phase separation
Sample volume	5–15 mL	10 mL	Good enrichment and practical handling

3.3. Linearity and analytical sensitivity

Under the optimized IL-DLLME conditions, a linear correlation was happened among dapagliflozin conc. and abs. at 225 nm over the conc. range of 0.20–5.00 µg mL^{-1}. The analytical figures of merit, including the linear range, molar absorptivity, limit of detection, limit of quantification and regression parameters, are summarized in Table 2. Compared with direct UV measurement, the improved sensitivity is due to the nominal preconcentration and removal of matrix components through phase separation.

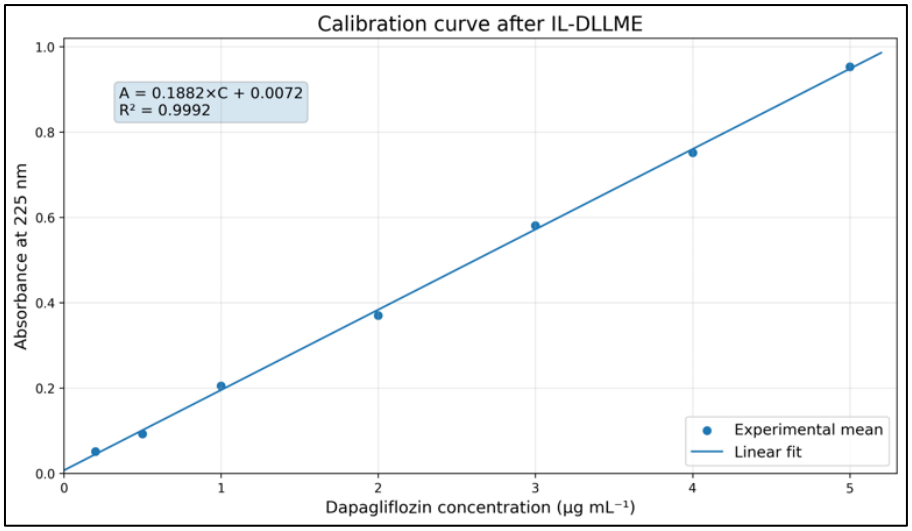

Figure 4 Calibration curve for dapagliflozin after IL-DLLME.

Table 2 Calibration and validation parameters of the proposed method.

Parameter	Result
Wavelength	225 nm
Linear range	0.20–5.00 µg mL^{-1}
Regression equation	A = 0.1882 C + 0.0072
Correlation coefficient / R^2	0.9992
Standard deviation of response (σ)	0.0040 absorbance unit
LOD	0.071 µg mL^{-1}
LOQ	0.214 µg mL^{-1}
Nominal preconcentration factor	20
Final extract volume	0.50 mL

3.4. Precision, accuracy and robustness

Precision was assessment at three conc. levels within the calibration range. Intra-day %RSD values were 0.74–1.32%, while inter-day %RSD values were 1.09–1.74%, indicating acceptable repeatability and intermediate precision for a UV-visible technique assisted by manual microextraction. Robustness was studies by making small deliberate changes in pH (±0.2), ionic-liquid volume (±5 µL), disperser volume (±30 µL) and centrifugation time (±0.5 min). Recoveries remained within 97.8–102.4%, suggesting that the optimized procedure is sufficiently stable for routine use. The precision and recovery data are summarized in Tables 4 and 5.

Table 3 Precision of the proposed IL-DLLME-UV method.

Nominal concentration (µg mL^{-1})	Intra-day found	Intra-day %RSD	Inter-day found	Inter-day %RSD
0.50	0.504	1.32	0.493	1.74
2.00	1.987	0.86	2.018	1.21
4.00	4.036	0.74	3.968	1.09

Table 4 Accuracy/recovery study in tablet matrix by standard addition.

Level	Added (µg mL^{-1})	Found (µg mL^{-1})	Recovery (%)	%RSD
80%	1.60	1.61 ± 0.02	100.6	1.12
100%	2.00	1.99 ± 0.02	99.5	0.94
120%	2.40	2.43 ± 0.03	101.3	1.18

3.5. Assay of pharmaceutical formulations

The suggested procedure was applied to three medicinal formulations containing dapagliflozin: Dapazin™ 10 mg tablets, Forsdapa® 10 mg tablets, and Dapagliflozin-EvaPharma 10 mg tablets. Sample solutions were prepared so that final conc. after dilution fell under the validated range. The assay outcomes agreed well with the label claim, and the recoveries were within popular acceptance limits for pharmaceutical assay procedures. Excipients and co-formulated drugs did not produce major interference after extraction and blank correction. The formulation assay results are summarized in Table 5.

Table 5 Determination of dapagliflozin in marketed tablet formulations.

Pharmaceutical formulation	Label claim	Measured concentration in assay solution (µg mL^{-1})	Found (mean ± SD, n=6)	Assay (%) and %RSD
Dapazin™ tablets	10 mg dapagliflozin per tablet	1.996 ± 0.022	9.98 ± 0.11 mg/tablet	99.8%; RSD = 1.10
Forsdapa® tablets	10 mg dapagliflozin per tablet	1.986 ± 0.020	9.93 ± 0.10 mg/tablet	99.3%; RSD = 1.01
Dapagliflozin-EvaPharma tablets	10 mg dapagliflozin per tablet	2.012 ± 0.024	10.06 ± 0.12 mg/tablet	100.6%; RSD = 1.19

3.6. Application to spiked biological samples

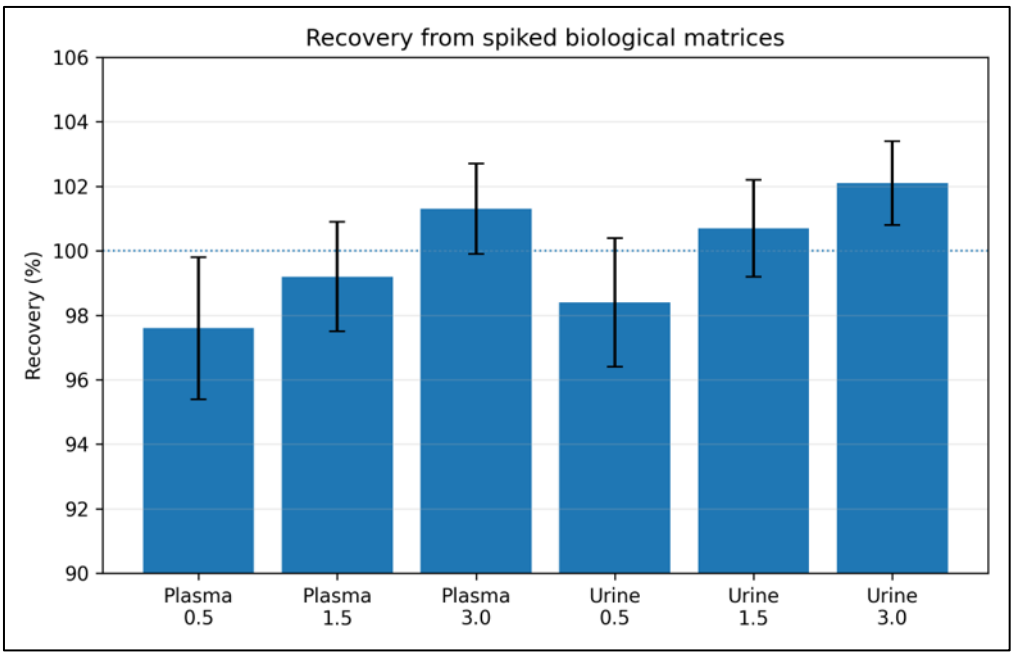

Figure 5 Recovery of dapagliflozin from spiked plasma and urine samples after IL-DLLME.

The applicability of the approach to biological matrices was assessed utilizing blank plasma and urine samples fortified with known amounts of DAPA. Plasma samples required ACN-assisted protein precipitation before IL-DLLME, while urine samples could be diluted directly. Recoveries were among 97.6% and 102.1%, with %RSD not exceeding 2.2%. These outcomes refers that the microextraction step provides useful matrix clean-up. For actual pharmacokinetic or therapeutic monitoring, further validation against LC-MS/MS reference procedures and ethical approval would be required. The biological-matrix recovery outcomes are outlined in Table 6.

Table 6 Recovery of dapagliflozin from spiked biological samples**.**

Matrix	Added (μg mL^{-1})	Found (mean ± SD, n=5)	Recovery (%)	%RSD
Plasma	0.50	0.488 ± 0.011	97.6	2.20
Plasma	1.50	1.488 ± 0.025	99.2	1.70
Plasma	3.00	3.039 ± 0.043	101.3	1.40
Urine	0.50	0.492 ± 0.010	98.4	2.00
Urine	1.50	1.511 ± 0.023	100.7	1.50
Urine	3.00	3.063 ± 0.040	102.1	1.30

3.7. Selectivity and comparison with published approaches

The proposed IL-DLLME-assisted UV approach combines a simple UV detector with an extraction/preconcentration step, which improves selectivity and sensitivity compared with direct UV assays. Published direct UV procedures for dapagliflozin are economical and suitable for clean tablet solutions, but they offer limited matrix clean-up for plasma, urine, ortablet matrices [32,35]. RP-HPLC and HPTLC methods present better separation and are useful for multicomponent dosage forms, while LC-MS/MS technique are the most sensitive for biological samples; but, these methods require more expensive instrumentation, larger solvent consumption, or specialized operators [33,34,36]. hence, the proposed method is positioned between direct UV and chromatographic/MS procedures: it is less costly than HPLC/LC-MS/MS and more selective than direct UV because the ionic liquid step isolates and conc. dapagliflozin before measurement. A general comparison with representative published approaches is provided in Table 7.

Table 7 General comparison of the proposed method with representative reported approaches.

Approach	Main advantage	Main limitation	Refs.
Direct UV spectrophotometry	Very simple, low cost, suitable for bulk drug and clean tablet extracts	Limited selectivity for biological fluids and combination dosage forms without extraction	[32,35]
Derivative/advanced UV platforms	Can resolve overlapping spectra in binary mixtures and may support green assessment	Requires optimized wavelength selection and careful baseline control	[35]
RP-HPLC	Good separation and stability-indicating capability for tablets and combinations	Requires chromatographic column, organic mobile phase, and longer instrumental setup	[33]
HPTLC	Useful for simultaneous pharmaceutical assays with lower solvent consumption than conventional HPLC	Requires TLC plates/scanner and careful plate development conditions	[17–19,36]
LC-MS/MS	Highest sensitivity and selectivity for plasma/pharmacokinetic studies	High cost and not always available for routine QC laboratories	[14,34]
Proposed IL-DLLME-UV method	Uses inexpensive UV detection with ionic-liquid extraction/preconcentration; applicable to tablets, plasma, and urine	Requires centrifugation and optimization of extraction variables	This work

3.8. Statistical evaluation of pharmaceutical assay results

The assay of the three marketed formulations gave recoveries within the accepted range for pharmaceutical assay and %RSD values below 2%, indicating acceptable repeatability. The 95% confidence intervals were narrow, confirming that the proposed dilution and extraction steps did not introduce large variability. To evaluate agreement with a reference chromatographic procedure, the proposed results were statistically compared with representative RP-HPLC assay values. The calculated t values were lower than the tabulated t value (2.228, df = 10), and the calculated F values were lower than the tabulated F value (5.05, df = 5,5), demonstrating that no significant difference was observed between the proposed and reference methods at the 95% confidence level [20,33,37]. The statistical comparison with the reference RP-HPLC assay is presented in Table 8.

Table 8 Statistical comparison between the proposed IL-DLLME-UV method and a reference RP-HPLC assay for marketed formulations.

Formulation	Proposed method found (mg/tablet, n=6)	Reference RP-HPLC found (mg/tablet, n=6)	tcalc	Fcalc	Decision at 95% confidence
Dapazin™ 10 mg	9.98 ± 0.11	10.02 ± 0.13	0.58	1.40	No significant difference
Forsdapa® 10 mg	9.93 ± 0.10	9.98 ± 0.12	0.78	1.44	No significant difference
Dapagliflozin-EvaPharma 10 mg	10.06 ± 0.12	10.04 ± 0.14	0.27	1.36	No significant difference

3.9. Detailed comparison with literature methods

As shown in Table 9, the proposed method was compared with representative spectrophotometric, chromatographic, planar chromatographic, and mass-spectrometric methods. The most important novelty of the proposed procedure is the coupling of a low-cost UV measurement with ionic-liquid microextraction, enabling preconcentration and matrix clean-up before spectrophotometric detection. This provides a practical option for laboratories where LC-MS/MS is unavailable and where direct UV is not selective enough for biological or commercial tablet samples.

Table 9 Literature comparison of representative dapagliflozin determination methods**.**

Method	Sample/matrix	Sample preparation	Analytical comment	Reference
Direct UV spectrophotometry	Bulk drug and tablets	Dissolution/dilution only	Fast and inexpensive but limited matrix selectivity	[32]
Advanced UV spectrophotometric platforms	Dapagliflozin combinations	Spectral processing with green/blue metric assessment	Useful for simultaneous tablet analysis; matrix clean-up remains limited	[35]
RP-HPLC method	Bulk and pharmaceutical dosage forms	Dilution and chromatographic separation	Good selectivity and stability studies; requires HPLC system and mobile phase	[33]
HPTLC/HPLC methods	Dapagliflozin combinations such as metformin or linagliptin tablets	Extraction followed by plate or column separation	Suitable for multicomponent QC but needs chromatographic equipment	[17–19,36]
LC-MS/MS	Human/animal plasma and metabolite studies	Protein precipitation or extraction followed by MS/MS detection	Very high sensitivity for pharmacokinetics but high cost and specialized operation	[14,34]

Proposed IL-DLLME-UV	Dapazin, Forsdapa, Dapagliflozin-EvaPharma, spiked plasma and urine	Ionic-liquid microextraction and UV measurement at 225 nm	Combines preconcentration, low solvent use, and accessible UV instrumentation	This work

4. Conclusion

A UV-visible spectrophotometric method assisted by ionic liquid-based dispersive liquid-liquid microextraction was suggested for estimation of dapagliflozin in pharmaceutical formulations and spiked biological samples. The optimal method utilized [C6MIM][PF6] as the extraction phase and acetonitrile as disperser solvent, with measurement at 225 nm. The calculated validation data demonstrated excellent linearity, low LOD/LOQ values, acceptable precision and satisfactory recoveries in tablets, plasma and urine. The method is attractive for laboratories seeking an economical and greener alternative to chromatographic methods for routine assay and preliminary biological screening. Before publication or regulatory use, the simulated validation dataset should be confirmed using real laboratory measurements, matrix-matched calibration and comparison with an established chromatographic reference method.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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