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Optimized Deep Eutectic Solvent System for Liquid Phase Microextraction of Brillant Blue FCF in Diverse Analytical Food Matrices

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ABSTRACT

This study introduces a novel microextraction technique for the analysis of Brilliant Blue FCF, a widely used food dye, employing a deep eutectic solvent (DES). The method aligns with green chemistry principles by favoring environmentally benign solvents, ensuring rapid and efficient extraction. Specifically, a DES composed of tetrabutylammonium bromide (TBAB) and phenol (Ph) was prepared in a cost-effective and expedient manner. To enhance extraction efficiency within the deep eutectic solvent-based dispersive liquid-liquid microextraction (DB-DLLME), critical parameters such as the volume of DES, quantity of dispersive agent, extraction time, and sample volume were systematically optimized. The accuracy of the method was conducted at pH 3 by spiking various food samples with known concentrations of the analyte. Analytical performance metrics, including recovery efficiency, limit of detection (LOD), limit of quantification (LOQ), and relative standard deviation (RSD), were determined and reported as 0.86 µg/L, 2.88 µg/L, and 0.4-1.3% respectively. Furthermore, the method has been successfully utilized for analyzing samples of confectionery, beverages, water, and chewing gum.

Keywords: Deep eutectic solvent, Spectrophotometric analysis, Brillant blue FCF, Green chemistry, Food additives..

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Introduction

Food colorants often provide information about the ingredients, taste, vitamin value, and safety of the product. Food colorants are divided into two classes: synthetic such as tartrazine, patent blue V, ponceau 4R, brilliant blue, erythrosin, allura red and sunset Yellow FCF and natural such as curcumin, carmine, riboflavin, lutein, carotene, chlorophyll. Synthetic dyes, which have a very permanent and intense color, are classified according to their structure into groups such as azo dyes, chiniline, xanthan, and anthraquinone. Natural and synthetic food colors are added to foods in order to enhance their nutritional value and appearance. Synthetic colorants are utilized more than natural dyes because they are cheap and have high stability. Natural colorants are generally preferred because of their positive effects on health [1-3].

Brilliant Blue FCF (E133) is a water-soluble synthetic food color belonging to the azo dye group, also known as FD&C Blue, Acid Blue 9 or Food Blue [4-6]. It is extensively utilized to impart a blue hue to a variety of food products including chocolates, dairy items, cereals, sauces, cheese, jellies, and beverages. Despite its widespread application, Brilliant Blue FCF has been associated with potential genotoxic effects, manifesting in conditions such as skin flaking, allergic reactions, convulsions, gastrointestinal tumors, and neurotoxicity [7-9]. Conversely, the International Agency for Research on Cancer has classified Brilliant Blue FCF as having no carcinogenic effects (Mittal, 2006). The World Health Organization (WHO) and the Food and Agriculture Organization (FAO) have established the daily acceptable intake of Brilliant Blue FCF to be within the range of 0-6 mg/kg body weight [4].

Due to the essential importance of brillant blue FCF in metabolic activities, it is very important to develop sensitive and accurate methods for the determination of reliable concentration values in foods, feeds, supplements, and biological samples [10]. Therefore, many techniques such as high-performance liquid chromatography (HPLC), voltammetry, chemiluminescence, UV spectrophotometry (UV-Vis) and mass spectrometry (MS), capillary zone electrophoresis, spectroelectrochemistry are utilized for brillant blue FCF determination. However, these methods have difficulties such as trace concentration levels of brillant blue FCF in real samples and complex matrix environments. Therefore, solid and liquid phase extraction enrichment methods have been developed by researchers. Since these traditional methods are tedious, time-consuming, expensive, and not environmentally friendly, microextraction methods have drawn attention within the scope of green chemistry in recent years. Solidified floating organic drop microextraction (SFODME), hollow-fiber membrane liquid-phase microextraction (HF-LPME), fiber solid-phase microextraction (FSPME), in-tube solid-phase microextraction, headspace liquid-phase microextraction (HS-LPME), dispersive solid-phase microextraction, solvent bar microextraction (SBME), single-drop microextraction (SDME), ultrasonic assisted microextraction (UAME), dispersive liquid-liquid microextraction (DLLME) are implemented for the separation and determination of organic or inorganic species [11-16].

In 2006, for the first time reported by Rezaee et al. DLLME method, solvent systems such as switchable hydrophobicity solvent, supramolecular solvent, natural deep eutectic solvent, ionic liquid, and deep eutectic solvent are used [17-18]. In this article, a dispersive liquid phase microextraction method based on a deep eutectic solvent system (DB-DLLME) was utilized for the sensitive determination of brillant blue FCF.

DESs with low melting points are generally synthesized from the combination of a hydrogen bond acceptor (HBA) such as a quaternary ammonium salt and a hydrogen bond donor (HBD) such as carboxylic acids, alcohol, and carbohydrates by hydrogen bond interactions [19]. These solvents, which are mixed by ultrasonic, freezing, conventional heating, and microwave heating, are biodegradable. Hence, they are known as environmentally friendly and ideal solvents for microextraction studies. In addition, DESs can be used not only in high-purity extraction studies but also as auxiliary components in material synthesis [17, 20-22].

In this current paper, a DB- DLLME method for the analysis of brillant blue FCF was developed. For this purpose, DES solvent consisting of tetrabutyl ammonium bromide (TBAB and phenol (Ph) was synthesized in a very short time by heating method. It was utilized for the determination of brillant blue FCF in beverages, candies, water and chewing gum food samples.

Experimental

Instrumentation and Reagents

Brilliant Blue FCF was analyzed using UV-Vis spectrometry (Perkin-Elmer Lambda 25; Norwalk, CT, USA). pH values for optimization and analyte determination in foods were measured with a pH meter (Hanna HI 2211, USA). The ultrasound-assisted DB-DLLME method employed an ultrasonic bath (J.P. Selectra, Spain) throughout the study. To prepare the deep eutectic solvents (DES), mixtures were homogenized using a heating device ((Velp Scientifica, Italy). Distilled water utilized in the experiments was sourced from a Nuve Water Distiller ND-4.

The DB-DLLME method was also conducted using reagents of analytical grade purity. First of all, the analyte was purchased from Sigma-Aldrich (USA). The solvents TBAB and phenol, used for the formation of DES, were sourced from Carl Roth (Karlsruhe, Germany), and (Isolab Chemicals, Germany) brands, respectively. Additionally, sodium chloride (NaCl) was procured from Isolab Chemicals, Germany. Tetrahydrofuran (THF) from Sigma-Aldrich was also employed to examine the influence of the dispersing solvent on the method.

Formation of DES

DESs are obtained by combining several hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) components with distinct structures. In this study, the formation of a DES consisting of tetrabutylammonium bromide (TBAB) and phenol (Ph) for Brilliant Blue FCF microtraction was investigated. TBAB and Ph were mixed in a 1:1 molar ratio in a laboratory flask and stirred on a magnetic heating plate until the mixture became homogeneous and colorless. Meanwhile, the temperature of the heater was maintained at a constant range of 60-80°C [23]. Subsequently, the resultant solvent was cooled to room temperature for application in the separation and enrichment of Brilliant Blue FCF from real samples using the DS-DLLME method.

Des Based- Dispersive Liquid-liquid Microextraction (DB-DLLME) Method

The method was initially optimized using model solutions to achieve maximum extraction efficiency before the spectrophotometric analysis of Brilliant Blue FCF from food samples. The DB-DLLME method, with experimental parameters set at pH 3, 0.1 g NaCl, and 200 µL of DES, was applied to 10 mL volume samples containing 0.793 µg/mL of the analyte. The developed method involved ultrasonic mixing of these solutions for 5 min. Subsequently, the resulting turbid solutions were centrifuged at 4100 rpm for 3 min. to separate the organic phase from the aqueous phase. The separated phase containing Brilliant Blue FCF was then made up to 1 mL by adding approximately 0.8 mL ethanol to the extraction phase to improve the extraction process. The blue-colored solutions were analyzed using a UV-Vis spectrophotometer at 627 nm. Additionally, a schematic representation of the DB-DLLME microextraction method is provided in Fig.1.

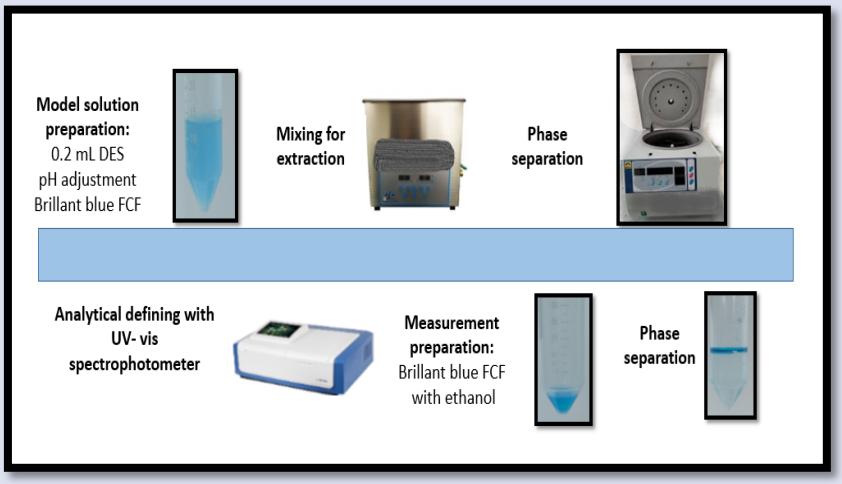

Figure 1. Schematic depiction of the DB-DLLME technique

Sample Preparation Procedures Prior to Analysis

Brilliant Blue FCF (E133) is widely used to impart a synthetic blue colour to a variety of food samples, making them readily available for analysis. Sugar confectionery, chewing gum, soft drinks were prepared for analysis using appropriate sample preparation procedures. To facilitate the dissolution of Brilliant Blue FCF, 2 grams of distilled water were added to each confectionery and chewing gum sample, which had been weighed individually. Following preparation, the samples were exposed to ultrasonic treatment for about 30 min. to aid in the extraction of the analyte. Subsequently, centrifugation was used to separate the phases and prepare them for analysis of Brilliant Blue FCF (E133). In addition, liquid samples were centrifuged prior to the application of the DB-DLLME method. Subsequently, 0.1-1 mL of the liquid phase was removed and subjected to the optimized method.

Results and Discussion

Effect of pH

pH plays a crucial role in the extraction efficiency of organic matter in the DB-DLLME method. The optimal pH, which is dependent on the structure of the analyte, facilitates a more rapid and quantitative transfer to the extraction phase. In this study, the developed method was tested on model solutions prepared at pH values of 1 and 8. The results, as depicted in Fig. 2, indicate that the interaction between brilliant blue FCF and the extraction phase is maximized at pH 3 and pH 4. However, extraction efficiency declines outside this pH range. At pH 3, the analyte's molecular form facilitates its transition from the aqueous phase to the deep eutectic solvent (DES) phase due to enhanced physical interactions. Consequently, a high extraction efficiency is achieved at this pH value. Given that the highest recovery was achieved at pH 3, this pH was selected as the optimal value. Subsequent optimization and actual sample analyses were conducted with the solvent adjusted to pH 3.

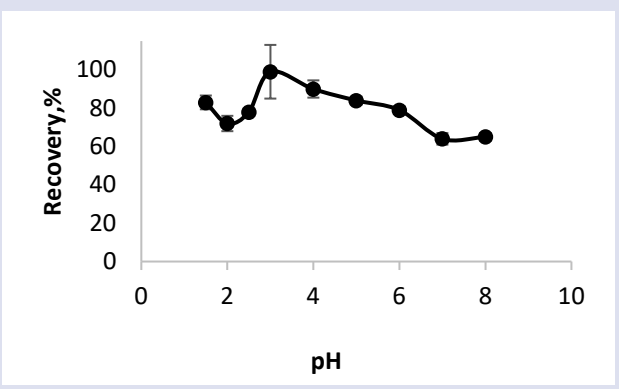

Figure 2. The optimization of pH (n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount:0.1g)

DES Type Selection

In the analysis of Brillant Blue FCF, trying different types of DES is a parameter investigated to obtain the highest extraction yield. Therefore, DLLME method was applied using different molar ratio combinations of DES formed from TBAB (HBA) and phenol (HBD). According to the results given in the Fig. 3, it is seen that the best extraction value is obtained from DES4 and DES5 among DES models such as DES1 (1:2), DES2 (1:3), DES3 (1:1), DES4 (2:1), DES5 (3:1) formed from TBAB: Ph.

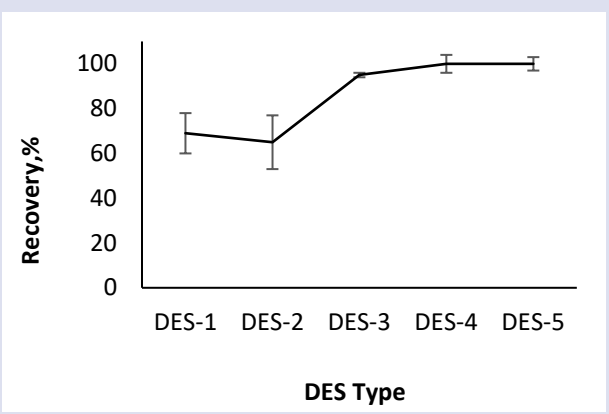

Figure 3. The impact of various DES compositions on the efficiency of Brilliant Blue FCF extraction (n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount:0.1g)

DES Volume Optimization

Solvent volumes ranging from 0.05 to 0.6 mL were systematically evaluated to determine the optimum DES volume required for the microextraction of Brilliant Blue FCF. Based on the analysed data, a DES volume of 0.2 mL was found to be sufficient to obtain quantitative extraction results, as shown in Fig. 4. The recovery values started to decrease after 0.2 mL DES volume. The primary reason for the observed decrease in extraction efficiency with increasing DES volume may be attributed to the diminished interaction between the analyte and the DES, which becomes excessively diluted at higher DES volumes. In addition, the viscosity of the DES may alter at higher volumes, complicating the analyte extraction process. These factors collectively influence the distribution coefficient of the analyte, leading to a subsequent decrease in recovery rates.

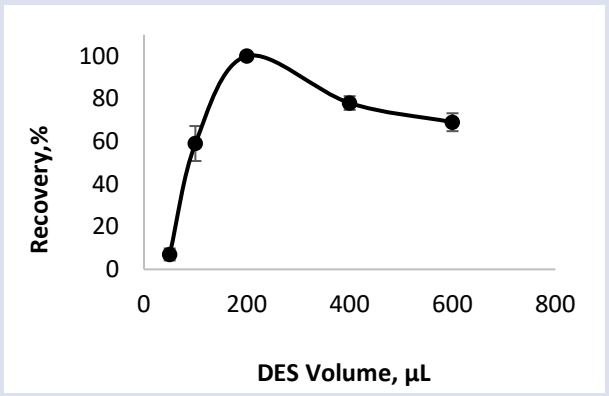

Figure 4. The impact of DES volume on the recovery of Brillant Blue FCF (n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount:0.1g)

THF Volume Effects on Analytical Performance

In studies involving DLLME, aprotic solvents such as ethyl acetate, acetonitrile, diethyl ether, and tetrahydrofuran (THF) are commonly utilized. In this investigation, THF was employed as the dispersive solvent to evaluate its efficacy in the extraction process. To ascertain the necessity of THF in the extraction procedure, varying volumes of THF, ranging from 0 to 600 µL, were systematically added to the samples. The findings demonstrated that the use of tetrahydrofuran (THF) is unnecessary for this microextraction method (Fig.5). Achieving 100% extraction efficiency with reduced chemical usage highlights the study's contribution to sustainable development objectives.

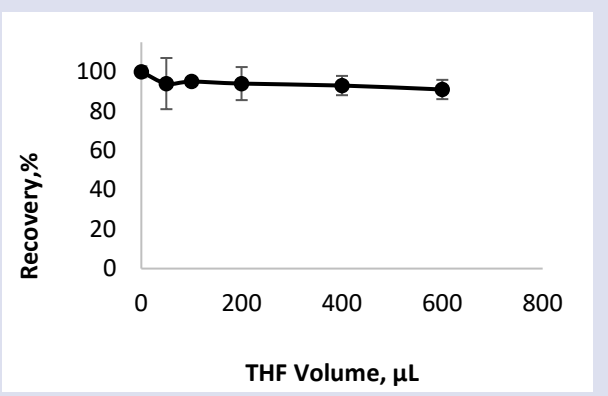

Figure 5. The impact of THF volume on the recovery of Brillant Blue FCF (n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount:0.1g)

Salt Effect

In the DB-DLLME method, the addition of salt to the samples is used as one of the phase separators. Since salt affects the ionic equilibrium of the solution, it generally increases the interaction between the analyte and the organic solvent. In this way it can play a role in improving the transition of the analyte from the aqueous to the organic phase. However, too little salt can cause incomplete extraction and too much salt can cause interference. Therefore, in this study 0-3 g of salt was added to the samples to evaluate the effect of salt.

According to the results presented in Fig.6, the highest recovery values were achieved with the use of 0.1 to 0.3 grams of salt, whereas extraction efficiency began to decline when the amount of salt exceeded 0.3 grams.

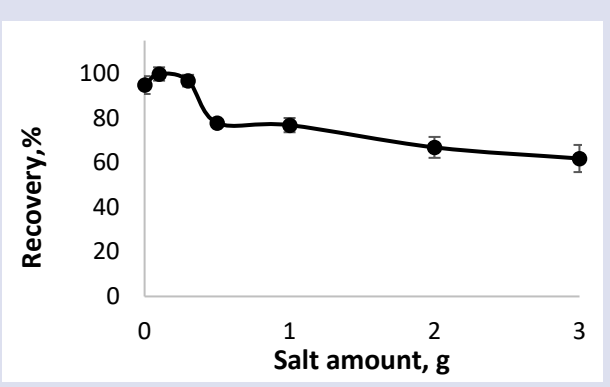

Figure 6. The impact of salt amount on the recovery of LGB (n: 3, eluent volume: 1 mL, DES volume: 0.2 mL)

Adjusting Extraction and Centrifugation Time for Optimal Performance

Determining the optimal extraction parameters for Brilliant Blue FCF is crucial for maximizing both time efficiency and extraction efficacy. In DLLME methods, either sonication or physical dispersion is typically employed. In this study, the effectiveness of the DLLME method was enhanced through sonication. To optimize the extraction process, samples were subjected to ultrasonic treatment for varying durations ranging from 1 to 10 minutes. Consistent distribution of the solute was observed across all time intervals, with high extraction efficiency achieved after 5 min. of sonication.

Additionally, model solutions undergoing the extraction process from the DES phase were subjected to rotational agitation at intervals of 1 to 10 minutes. The efficiency of the extraction process was evaluated, and the shortest duration yielding the most effective results was identified. The optimal process was determined to be a 3min. rotation period, during which recoveries exceeding 95% were consistently achieved (Fig.7).

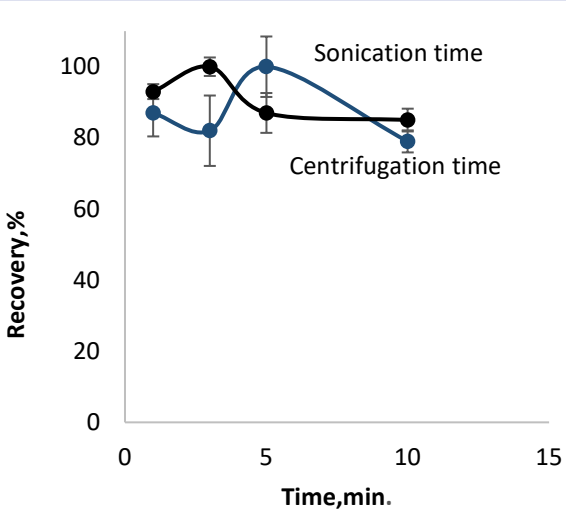

Figure 7. The effect of sonication and centrifugation time on the recovery of Brilliant Blue FCF (pH:3, n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount: 0.1g)

Sample Volume

In this section, the impact of sample volume on both the enrichment factor and the method's applicability was investigated. The microextraction of Brilliant Blue FCF was conducted using the Dispersive Liquid-Liquid Microextraction (DB-DLLME) method with sample volumes ranging from 5 to 25 mL. Analysis of the results, as illustrated in the Fig.8 revealed that the method maintained quantitative extraction efficiency up to a sample volume of 22.5 mL. However, extraction efficiency declined for volumes exceeding 22.5 mL. Consequently, given that the final extract volume was 1 mL and the maximum effective sample volume was 22.5 mL, the preconcentration factor was calculated to be 22.5.

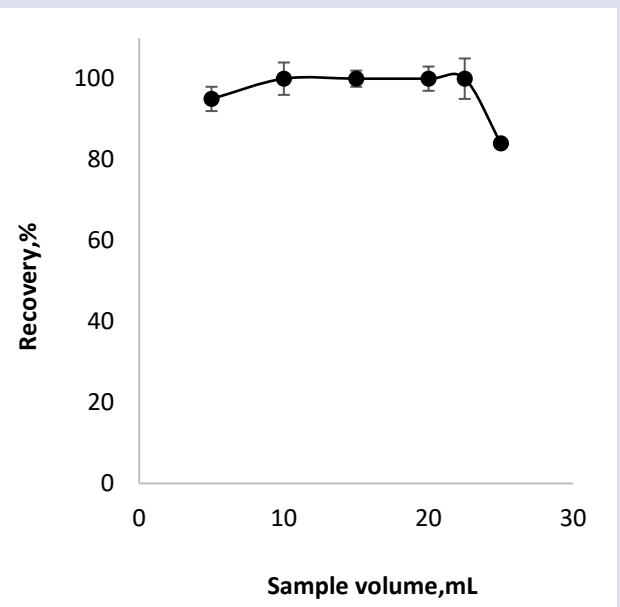

Figure 8. The effect of sample volume on the recovery of Brilliant Blue FCF (pH:3, n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount: 0.1g)

Matrix Effects

To evaluate the suitability of the DB-DLLME method for quantifying Brilliant Blue FCF in diverse matrixes, we investigated the potential interference from various food additives and elemental constituents. The method was tested with synthetic dyes such as rhodamine B, curcumin, chicago sky blue, β-carotene, sudan IV. Additionally, the maximum permissible concentrations of metals, including Ag^{2+}, Cd^{2+}, Mn^{+2}, Zn^{2+}, and K^{+} that do not adversely affect the method's performance, were identified. The allowable concentration levels for these metals are detailed in Table 1. The standard deviations and recovery rates at these concentrations were computed to evaluate the method's quantitative accuracy and reliability.

Table 1. Tolerance parameters for foreign ion contaminants (pH:3, n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount: 0.1g)

Foreign species	Concentration, µg L^{-1}	Recovery, %
Rhodamine B	239	98±4[a]
Curcumin	368	99±2
β carotene	2684	92±2
Riboflavin	1882	91±3
Sudan IV	380	98±4
Chicago sky blue	1986	100±4
K^{+}	120000	99±4
Ag^{2+}	500	97±2
Cd^{2+}	500	98±6
Mn^{+2}	1000	97±11
Zn^{+2}	1000	104±2

[a]Mean ± standard deviations

Real Samples Analysis

The optimized DB-DLLME method was employed for the spectrophotometric quantification of Brilliant Blue FCF in a variety of matrices, including beverages, confectioneries, chewing gum. Table 2 and Table 3 indicates that Brilliant Blue FCF was detectable in some food samples, whereas it was not found in others. Additionally, standard addition recovery experiments were conducted to verify the accuracy of the DB-DLLME method. These experiments showed that the analyte can be recovered with an efficiency in the range of 84-96%. Consequently, it can be concluded that the developed method is robust and suitable for the separation and enrichment of Brilliant Blue FCF in a wide range of food samples.

Table 2. Standard addition recovery studies on real samples (pH:3, n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount: 0.1g)

Samples	Added (µg·mL-1)	Found (µg·mL-1)	Recovery (%)
Drinking water	0.0	N.D [a]	-
	0.79	0.69±0.03	87.3
	1.59	1.40±0.13	88.1
Tap water	0.00	N.D [a]	-
	0.79	0.72±0.08	91.1
	1.59	1.52±0.10	95.6
Fruit juice1	0.00	0.28±0.01	-
	0.88	1.00±0.02	86.2
	1.76	1.77±0.02	86.8
Fruit juice2	0.00	0.34±0.02	-
	0.88	1.02±0.11	83.6
	1.76	1.79±0.12	85.2

[a]N.D.: Not Dedected

Table 3. Analysis of Real Samples (pH:3, n: 3, eluent volume: 1 mL, DES volume: 0.2 mL, salt amount: 0.1g)

Samples	Found(µg·g^{-1})
Candy	N.D [a]
Chewing gam1	0.16±0.03
Chewing gam2	0.06±0.00
Fruit juice1	0.28±0.01
Fruit juice1	0.34±0.02

[a]N.D.: Not Dedected

Analytical Performance

In order to evaluate the analytical performance of the DB-DLLME method, parameters such as relative standard deviation (RSD), correlation coefficient (R^2), limit of detection (LOD), limit of quantification (LOQ), preconcentration factor (PF) were studied.

Specifically, the LOD (calculated as 3sb/m) and LOQ (calculated as 10sb/m) were determined using the standard deviation (Sb) and slope (m) parameters, yielding values of 0.86 µg/L and 2.88 µg/L, respectively. The RSD, which indicates the repeatability of the method based on five parallel measurements, was found to range from 0.4 to 1.3%. The correlation coefficient (R^2) reflecting the degree of linearity was 0.9859. The calibration curve is shown by the following equation A = 0.6963C - 0.025 (A: Absorbance and C: Concentration). Additionally, the preconcentration factor was calculated to be 22.5.

Conclusions

In this study, a DES-based liquid phase microextraction (LPME) method was developed for the determination of Brilliant Blue FCF, a commonly used food additive in food samples. The DB-DLLME method was implemented by adding only 200 µL of a DES composed of TBAB/Ph to the samples, without the need for a dispersive solvent. The molar concentrations of the DES consisting of TBAB/Ph were tested at ratios of 1:2, 1:3, 1:1, 2:1, 3:1 and extraction efficiencies above 95% were obtained at 1:1, 2:1, 3:1. This approach demonstrates that the method is highly environmentally friendly and adheres to green chemistry principles. The method was optimized by investigating and adjusting crucial parameters such as solvent usage, extraction time, and separation agent, and was validated through recovery studies in various matrixes, as detailed in Table 1. The optimized DB-DLLME microextraction technique has been effectively employed for a diverse array of food samples. Real samples were prepared very simply by ultrasonic method. The results, as presented in Table 2,3 indicate high recovery rates in the range of 83.6-95.6%. Furthermore, the DB-DLLME method was compared with other methods reported in the literature, as listed in the Table 4, and was found to exhibit very low limits of detection (LOD) and quantification (LOQ). This DB-DLLME method offers significant advantages over other techniques due to its lower observable limit, enabling effective application even at trace concentrations of analytes. A rapid and straightforward spectrophotometric method, such as UV-Vis spectroscopy, was also employed for the precise analysis of various matrix media.

Table 4. Comparative assessment of the DB-DLLME method relative to existing techniques in the literature

Method	Analytical technique	Sample	LOD[a]	RSD[b] %	PF[c]	Recovery,%	Reference
Ultrasonic assisted ionic liquid dispersive liquid liquid microextraction (USA-IL-DLLME)	UV-vis	Energy, carbonated, fruity beverages	4.55 µg.L^{-1}	1.15	50	94.65-100.95	4
Green-ultrasound-assisted extraction technique	HPLC	Carbonated drink Fruit jelly Sugar confectionary, candy	0.42 µg·mL^{-1}	0.39-0.56		98.26- 102.5	7
Vortex assisted sequential-simultaneous liquid phase micro-extraction (VA-SS-LPME)	Uv-vis	Confectioneries, energy drinks, candies, jellies, pharmaceutical drugs and syrups, various teas, and cinnamon	19 µg·L^{-1}	3.2	50	96-102	24
Amine-based supramolecular solvent DLLME	*HPLC-PDA*	Spices, cotton candy, fruit-flavored candy, dried fruits, and chocolate dragee	0.07 mg.kg^{-1}	4\1-5\3	-	71-102	25
Deep eutectic solvent-based dispersive liquid-liquid microextraction (DB-DLLME)	Uv-vis	Beverage, chewing gum, candy, water samples	0.86 µg L^{-1}	0.4-1.3	22.5	84-96	This study

LOD[a]: Limit of dedection, RSD[b]: Relative standart deviation, PF[c]: Preconcentration factor

Conflicts of interest

There are no conflicts of interest in this work.

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