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Development And Characterisation of Deep Eutectic Mixture Containing Fexofinadine to Enhance Dissolution

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ABSTRACT

The outstanding qualities of deep eutectic mixture—high solvent capacity, high biodegradation, low volatile organic compound character, and comparatively low toxicity—come from liquid mixes of solid components at ambient temperature. The main aim of the paper is to develop deep eutectic mixture containing fexofenadine to enhance its dissolution. We concentrated on health-related applications in this assessment. Although it is still in its infancy, the creation of oral liquid formulations of poorly soluble active medicinal substances is one of the most promising uses of DES. In this context, we have examined the capabilities and constraints of DES. DES has also been employed as a synthesis medium. The use of DES to produce bioactive natural compounds through synthesis or extraction was updated in this work. Lastly, the effectiveness of DES in other intriguing applications for advancing health has also been investigated. These include genomics research, nano-carriers for the encapsulation of anticancer medications, and sample stabilization for medical uses.

Keywords: *DEM; NADES; deep eutectic mixture; applications; natural compounds.*

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1. Introduction

It is difficult to design methods for analyzing complicated matrices. Specifically, because of the high complexity and/or low concentration of the analytes, the majority of biological matrices necessitate a sample preparation step before instrumental analysis. Complex biological matrices are typically used in clinical, toxicological, and forensic evaluations. such as urine, oral fluids, plasma, and blood.[1]

A common biological matrix made primarily of water, urine is utilized extensively in toxicological analysis. Given that urine contains about 50% of the chemicals eliminated by human metabolism, this matrix is especially relevant. Another extremely intricate biological matrix that plays a significant part in toxicological and forensic analysis is blood. This matrix takes part in the removal and transportation of various materials, even poisonous ones. Blood can either be used in its entirety or undergo sample preparation in analytical procedures, which often entails centrifugation and protein precipitation.[2,3]

Other matrices, such as oral fluid, which is made up of a combination of saliva and other elements like mucous cells found in the mouth cavity, have also been investigated in chemical analysis. This matrix is typically used to determine whether chemicals have been consumed recently in their original form. Information gathered using this matrix may occasionally take the place of those from blood that show the potential for matrix replacement.[4,6]

Given the aforementioned factors, biological matrix analysis demands careful consideration. It is important to note that an analytical methodology's effectiveness typically depends on preparation of the sample with successful target analyte extraction. This vital stage in chemical analysis is necessary to ensure that the sample is compatible with the analytical equipment as well as to eliminate any potential interfering substances. As a result, the goal of sample preparation procedures is to separate and concentrate the analytes at levels appropriate for a successful chemical analysis. In this instance, microextraction techniques might be emphasized as environmentally benign and sustainable sample preparation methods.[7,8]

In addition to offering safer substitutes for conventional sample preparation methods, microextraction techniques have been proposed to preserve acceptable analytical performances. Liquid-phase microextraction (LPME), sometimes referred to as liquid-liquid microextraction (LLME) or solvent microextraction (SME), is a group of methods that use small amounts of solvents (usually a few microliters), which is advantageous for the environment and the analyst. These methods have benefits like satisfactory extraction. efficiency, sufficient sample purification before instrumental analysis, and high preconcentration factors.[9-10]

The use of DES in analytical extractions has been gaining significant attention in recent years, particularly due to the structural versatility and large applicability. These solvents exhibit advantageous physico-chemical properties, and they generally consist of mixtures with lower

melting points compared to those of individual components. This emerging class of solvents is increasingly being examined for the development of novel analytical strategies consisting of environmentally friendly alternatives to traditional methodologies based on toxic organic solvents.[11-13]

With an emphasis on microextraction methods, this study sought to present a current overview of the application of DES for the investigation of biological matrices, including urine, blood, plasma, and oral fluid. Analytical A table of applications for these sustainable solvents is presented, along with highlights of the reviewed techniques' key aspects. A brief summary is provided on the basics, experimental considerations, and upcoming developments in sample preparation using DES. Using the descriptors "deep eutectic solvents," "DES," "biological matrices," and "microextraction," the literature was searched using the Pubmed, Scopus, and Web of Science databases. The discussion was focused on studies released within the previous five years (2017–2021). As far as we are aware, this is the first study of DES applications particularly.[14,15]

2. Experimental Work

2.1 UV absorption maxima of Fexofenadine

UV-visible spectrophotometer is generally used for structural information of various drugs to obtain specific information on the chromophoric part of the molecules in solution when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption. The UV spectrum is generally recorded as a plot of absorbance versus wavelength. Double beam UV-visible spectrophotometer (Shimadzu, UV-1800, Japan) was used to know the λ_{max} of drug. 800µg/ml solution of Fexofenadine was scanned in the range of 200-400 nm.[16-18]

2.2 Solubility Studies

The spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called solubility. For quantitative solubility study, 10mg of drug was taken in thoroughly cleaned culture tubes containing 3 ml of different solvents and put into Culture tubes and closed tightly. These Culture tubes were shaking on water bath shaker at 25°C for 24 h at room temperature. After 24 h each sample was centrifuged 15,000 rpm and supernatant was withdrawal. After that supernatant was filtered and filtrates was suitably diluted and determined spectrophotometrically.[19,22]

2.3 FTIR of Fexofenadine and Excipients

The FT-IR (Fourier Transform Infrared) spectra of a substance or medication can reveal the groups that are present. For structure investigation, FT-IR spectroscopy was employed. For the purpose

of identifying any potential medication interactions with excipients, an FT-IR spectrum of a mixture of Fexofenadine and other ingredients was recorded. The FT-IR chamber received 5-10 mg of Fexofenadine. The region between 4000 and 400 cm^{-1} of the infrared spectrum was observed.[23-25]

3. RESULTS

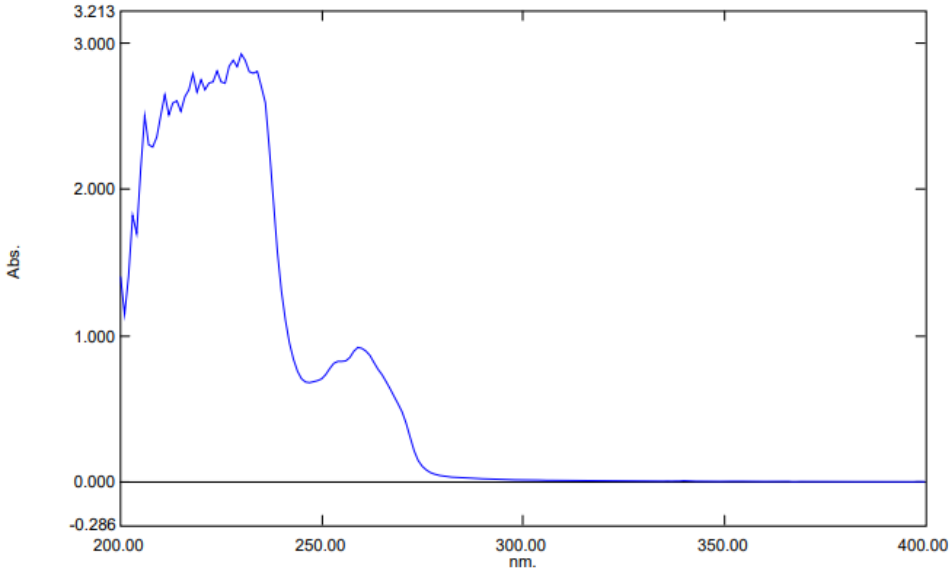
The aim of preformulation studies is to investigate the physical and chemical properties of a drug substance. The selected drug Fexofenadine was subjected for investigation of physical characterization parameters such as:

- UV-visible spectra
- Solubility
- FT-IR spectra

3.1 UV Spectroscopy

3.1.1 Determination of absorption maxima in Methanol

A double beam UV-visible spectrophotometer was used for quantitative analysis of the drug. 1000 µg/ml solution of Fexofenadine in methanol was scanned in the range of 200-400 nm. The result of UV spectrum of Fexofenadine is shown in Figure 1.



No.	P/V	Wavelength	Abs.	Description
1	↑	372.00	0.008	
2	↑	259.00	0.921	
3	↓	368.00	0.006	
4	↓	247.00	0.681	

Figure 1: UV Spectrum of Fexofenadine in Methanol

Table 1: Absorption maxima (λ_{max}) of Fexofenadine in Methanol

Name of drug	Absorption maxima (λ_{max})	
	Observed	Reference
Fexofenadine	259	259

3.1.2 Discussion: The maximum wavelength of Fexofenadine was observed at 259 nm similar to literature Table 1

3.2 Preparation of standard curve of Fexofenadine in Methanol

Table 2: Calibration curve of Fexofenadine in Methanol (λ_{max}= 259 nm)

Sr. No.	Conc. µg/ml	Absorbance
1	100	0.125±0.004
2	200	0.215±0.001
3	300	0.344±0.003
4	400	0.455±0.002
5	500	0.546±0.002
6	600	0.683±0.003
7	700	0.793±0.003
8	800	0.924±0.003

Value is expressed as mean ± SD; n = 3

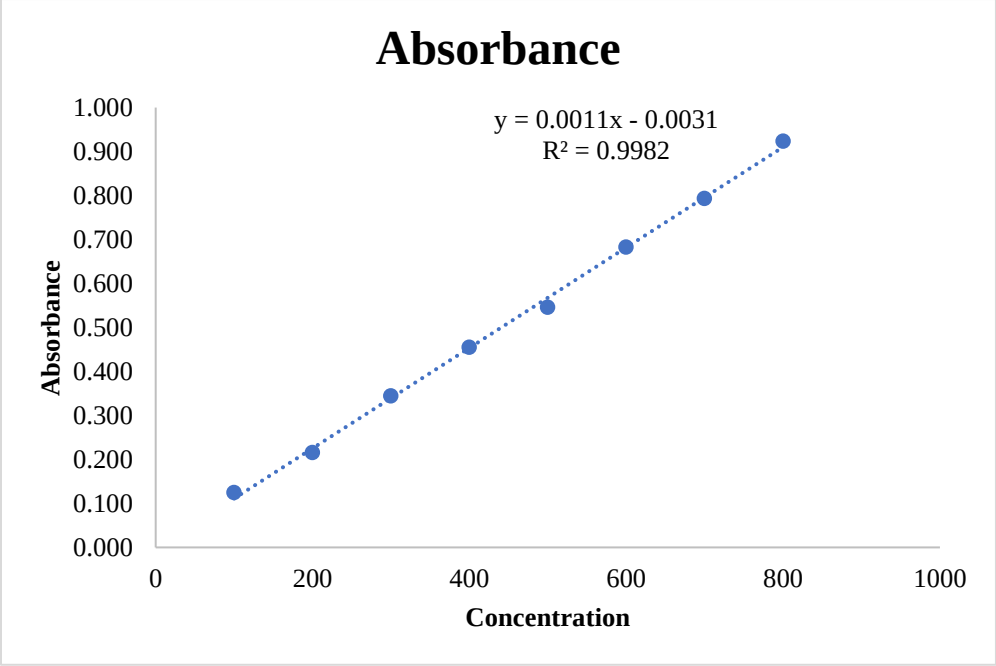


Figure 2: Standard calibration curve of Fexofenadine in Methanol

Table 3: Result of regression analysis of UV method

Statistical parameters	Results
λ_{max}	259 nm
Regression equation (y =mx+ c)	y = 0.0011x - 0.0031
Slope (m)	0.0011
Intercept (C)	0.0031
Correlation coefficient (R^2)	0.9982

3.2.1 Solubility studies

Solubility of drug in various solvents, were carried out in order to screen for the components to be used for formulation development. Analysis of the drug was carried out on UV Spectrophotometer at 259 nm.

Table 4: Solubility studies of Fexofenadine for different solvents

Sr. No.	Solvent	Mean±SD
1	Methanol	85.130±0.189
2	Ethanol	72.161±0.430
3	Phosphate buffer pH 6.8	14.161±0.139
4	0.1N HCl	10.767±0.605
5	Acetate	46.191±0.091

Value is expressed as mean ± SD; n = 3

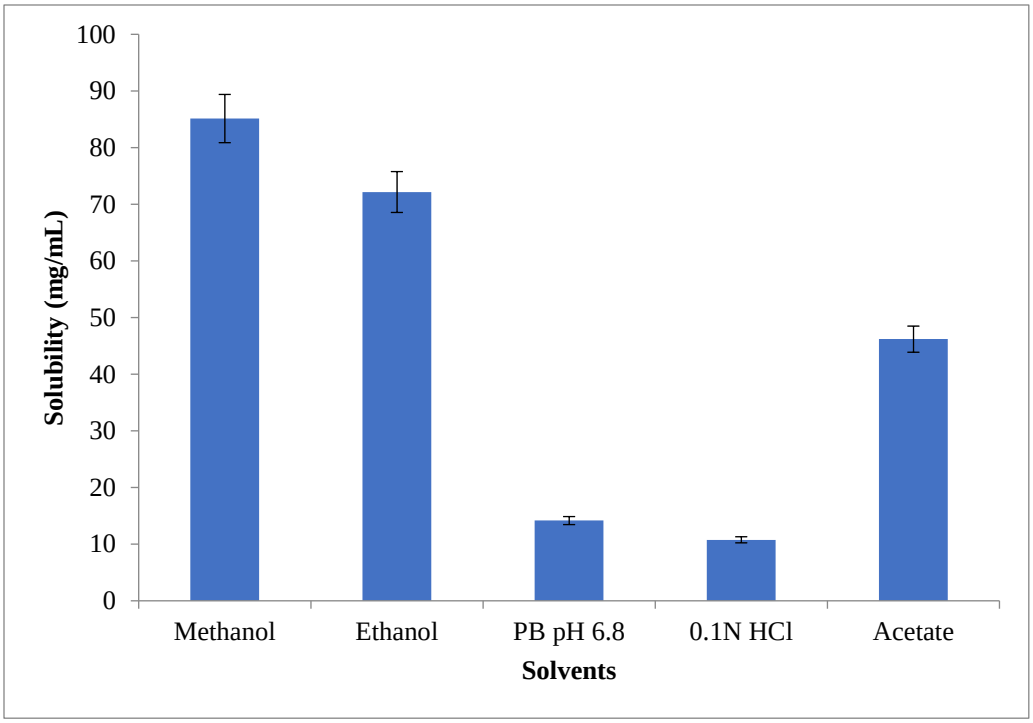


Figure 3: Solubility study of drug in different solvents

3.3 FTIR analysis of pure drug and excipient

3.3.1 FTIR of Fexofenadine

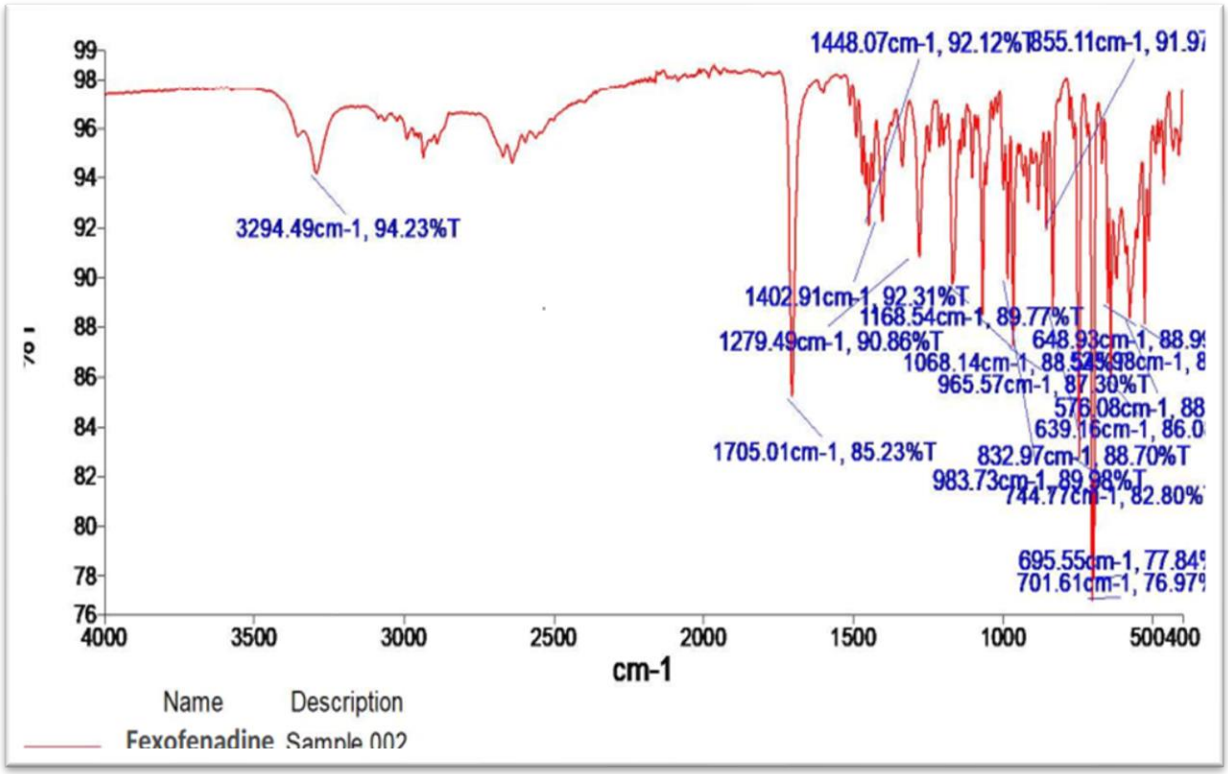


Figure 4: FTIR spectrum of Fexofenadine

Table 5: FTIR interpretation of Fexofenadine

Sr. No.	Characteristics Peak	Reference (cm^{-1})	Observed (cm^{-1})
1.	O-H- Stretching	3291.03	3294.49
2.	C=C stretching of aromatic ring	1448	1448.07
3.	CO stretching of tertiary alcohol	1167.57	1168.54
4.	CO stretching of secondary alcohol	1067.94	1068.14

3.3.2 FTIR of Choline Chloride

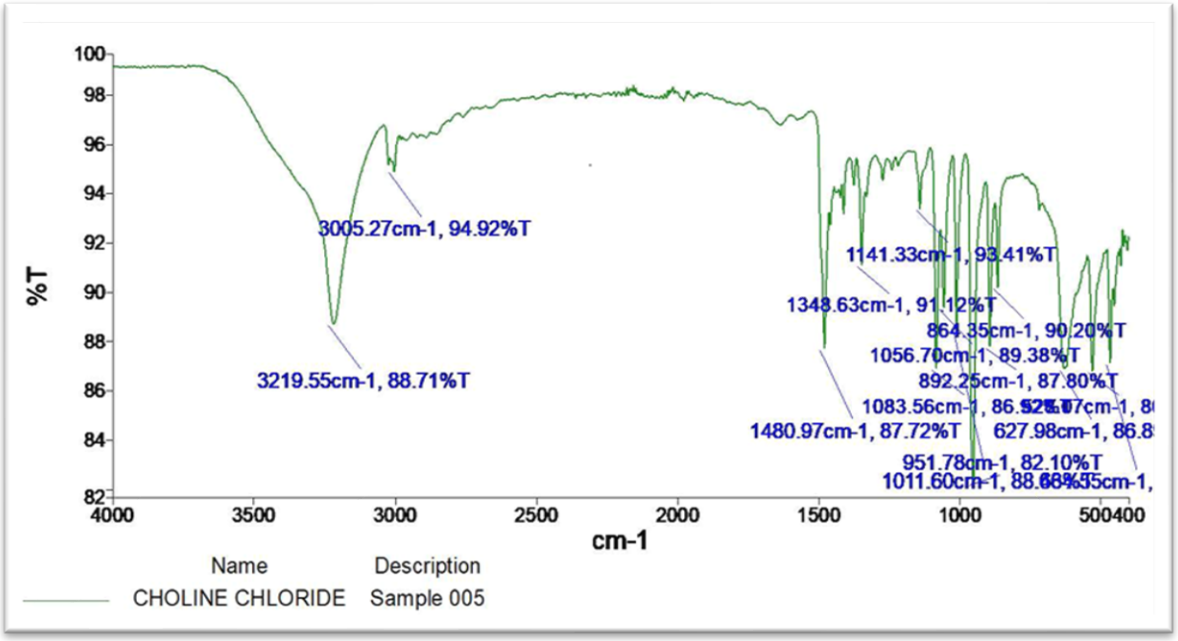


Figure 5: FTIR spectrum of Choline Chloride

Table 6: Interpretation of FTIR spectrum of Choline Chloride

Functional group	Reported peak (cm^{-1})	Observed peak (cm^{-1})
C–H vibration	3025.82	3005.27
C-N stretching	1086	1083.56
O–H vibration	1441.65	1480.97
C=O vibration	1348.26	1348.63

3.3.3 FTIR of Thiourea

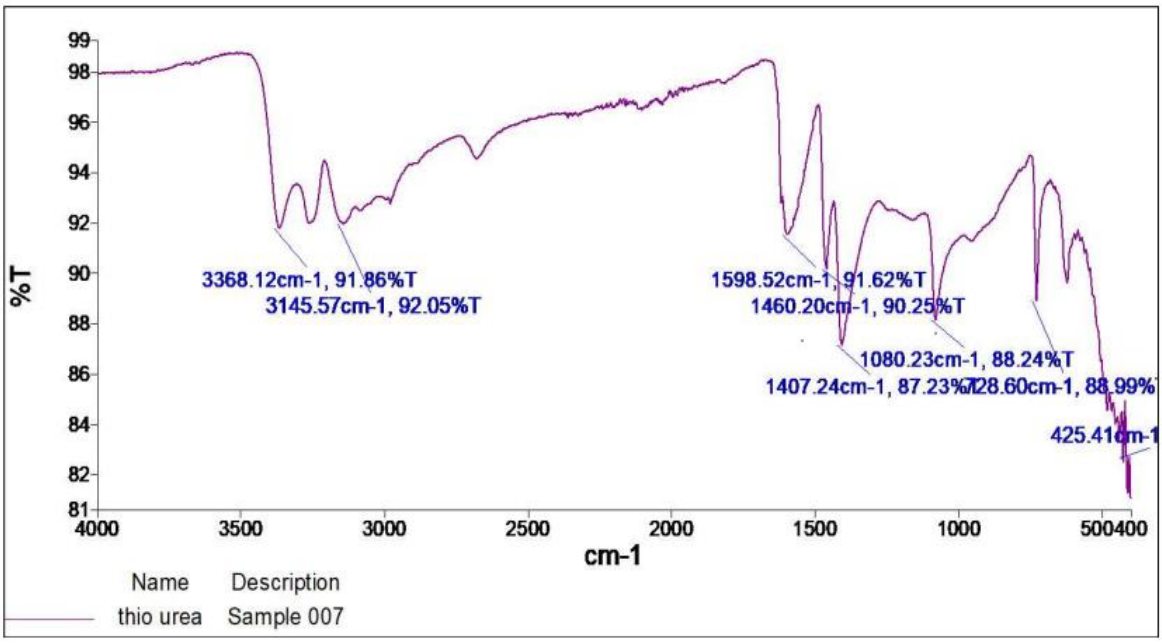


Figure 6: FTIR spectrum of Thio-Urea

Table 7: Interpretation of FTIR spectrum of Thio-***Urea***

Functional group	Reported peak (cm^{-1})	Observed peak (cm^{-1})
N-H stretching	3448	3368.12
C-N Stretching	1460	1460.20
Hydrogen bonding	1628	1598.52
NH2 bending	1055	1080.23

3.4 Evaluation of Deep Eutectic Solvent Mixture of Fexofenadine

3.4.1 Appearance and pH of the Solution

The solutions prepared were subjected to pH estimated and was recorded as shown in table7.3.

Table 8: Appearance and pH data of DESM of Fexofenadine

Sr. No	Formulation Code	Appearance	pH
1	F1	White Turbid Solution	3.17±0.032
2	F2	White Turbid Solution	3.3±0.023
3	F3	White Turbid Solution	3.16±0.030
4	F4	White Turbid Solution	4.34±0.012
5	F5	White Turbid Solution	5.08±0.021
6	F6	White Turbid Solution	5.23±0.012

7	F7	Transparent Solution	4.10±0.010
8	F8	White Turbid Solution	4.15±0.031
9	F9	White Turbid Solution	5.23±0.015
10	F10	White Turbid Solution	4.43±0.025
11	F11	White Turbid Solution	5.08±0.021
12	F12	White Turbid Solution	5.35±0.025
13	F13	White Turbid Solution	3.15±0.030
14	F14	White Turbid Solution	3.14±0.032

Table 9: Appearance and pH data of DESM of Fexofenadine with urea

Sr. No	Formulation Code	Appearance	pH
1	F7(A1)	White Turbid Solution	4.57±0.021
2	F7(A2)	White Turbid Solution	4.62±0.006
3	F7(A3)	White Turbid Solution	4.32±0.025
4	F7(A4)	White Turbid Solution	4.41±0.020
5	F7(A5)	Transparent Solution	4.63±0.015
6	F7(A6)	White Turbid Solution	4.43±0.010
7	F7(A7)	Transparent Solution	4.34±0.020

3.4.2 Drug Content

Table 10: Drug Content of Fexofenadine DESM with Thio-Urea

Sr. No	Formulation Code	% Drug content
1	F7(A1)	91.783±0.315
2	F7(A2)	93.399±0.315
3	F7(A3)	84.258±0.303
4	F7(A4)	78.854±0.087
5	F7(A5)	69.611±0.231
6	F7(A6)	63.551±0.231
7	F7(A7)	54.460±0.231
8	F7(A8)	34.106±0.303

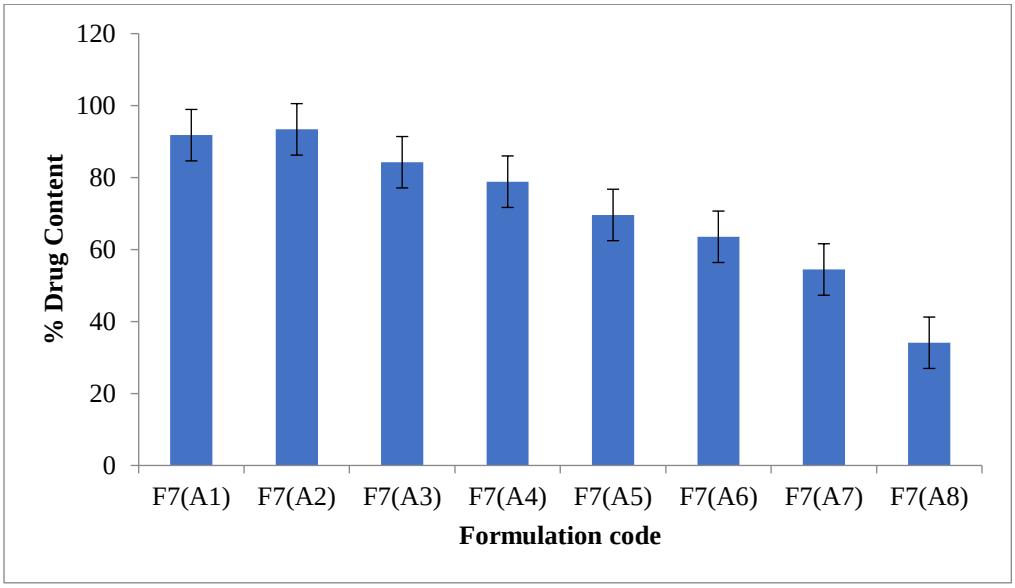


Figure 7: Drug Content of Fexofenadine DESM with Urea

3.5 In-vitro Drug release study

The in-vitro drug release of pure drug & Formulation F7 (A2) was given in a table 6.16.

Table 11: In-vitro drug release study of Fexofenadine loaded DESM

Sr. no.	Time (mins)	% Drug release of Pure drug	% drug release of formulation F7 (A2)
1	5	12.793±0.231	20.167±0.401
2	10	19.157±0.234	46.833±0.303
3	15	25.369±0.532	65.066±0.700
4	30	30.217±0.315	78.652±0.401
5	60	30.217±0.231	89.207±0.532
6	90	34.662±0.303	91.833±0.303
7	120	39.106±0.324	98.096±0.463

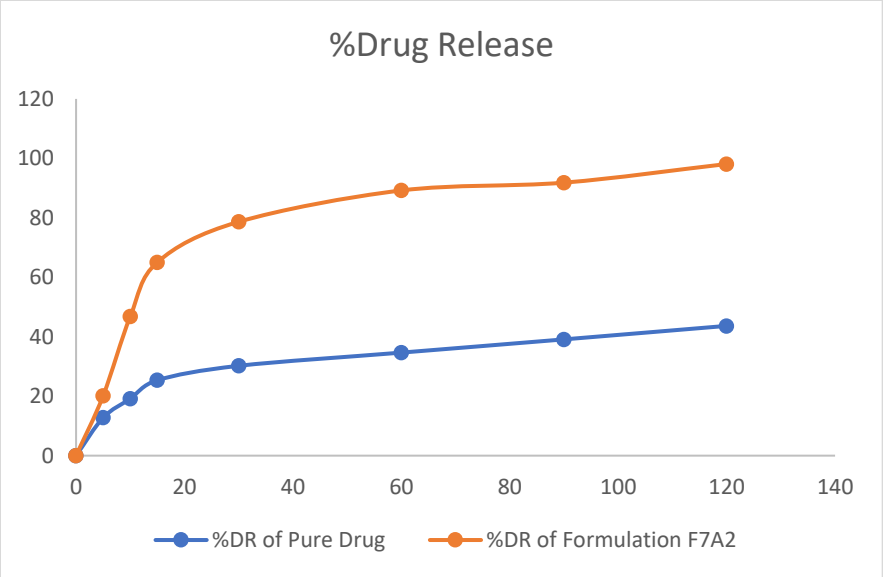


Figure 8: In-Vitro Drug release of Fexofenadine loaded DESM

4. Conclusion

The study investigated the preformulation and formulation development of Fexofenadine, a poorly water-soluble drug, using Deep Eutectic Solvent Mixtures (DESM) to enhance its solubility and bioavailability. Comprehensive preformulation studies were carried out to characterize the drug and establish its compatibility with excipients, ensuring the foundation for successful formulation. Organoleptic evaluation confirmed that Fexofenadine is a white, odorless, and bitter compound, aligning with literature references. The melting point, observed at 190–192°C, matched the reference range, indicating drug purity. UV spectroscopy revealed a λmax at 259 nm with a highly linear calibration curve ($R^2 = 0.9982$), ensuring accurate quantification. Solubility studies showed that the drug exhibited higher solubility in organic solvents like methanol and ethanol compared to aqueous media, consistent with its lipophilic nature, which was further confirmed by a log P value of 4.51. FTIR analysis demonstrated no interaction between the drug and excipients, indicating compatibility.

5. Future Perspective

This study highlights the potential of Deep Eutectic Solvent Mixtures (DESM) in pharmaceutical formulation science, particularly for enhancing solubility and bioavailability of poorly water-soluble drugs like Fexofenadine. Future research should explore DESM's compatibility with complex drugs and molecular mechanisms. The study also suggests investigating DESM's scalability for industrial manufacturing, incorporating advanced analytical techniques, and

validating efficacy and safety in humans. DESM's eco-friendly nature aligns with global sustainability goals.

6. Conflict of interest

The authors have no conflict of interest.

7. Acknowledgement

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