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Development and optimization of itraconazole-loaded topical gel using DESM technique

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ABSTRACT: Deep eutectic solvent mixtures (DESM) are often less hazardous to human health, simpler to make, and cheaper than ionic liquids (ILs). Because of these benefits, there has been a recent uptick in the number of uses for DESM, such as using it as a solvent in a variety of different separation procedures. Itraconazole (ICZ) was classified as a BCS-II medication. DESM technique was used to enhance the solubility of the drug by reducing the crystallinity region of the drug molecule. In different molar ratios Drugs, carboxylic acid, and choline chloride were used. From the carboxylic acid urea showed the best solubility profile. So it was chosen for fabricating the topical gel formulations. The prepared gel exhibits a pH nearly equal to the skin pH. Increasing the carbopol amount increases the viscosity and decreases the spreadability. From the FTIR analysis, it was found that ICZ peaks were preserved in the formulations, and no extra peak suggested the absence of interaction between the drug and excipients. In the release study, it was found that the release of the drug was sustained by increases in the carbopol. Release kinetics showed the drug was released from the gel by both fickian and non-fickian mechanisms. From the docking study, it has been established that ICZ has a strong binding affinity towards candida pepsin-2 (-9.3Kcal/mol). From the above finding, it was established that the Development and optimization of itraconazole-loaded topical gel using DESM Technique was successfully prepared. In gist, it can be concluded that ICZ-based topical gel can be used against the fungal infection.

KEYWORDS: DESM technique; itraconazole; fungal infection; carboxylic acids; sustained drug release.

1. INTRODUCTION

Many different types of topical fungal disorders may affect human beings, including dermatophytosis, onychomycosis, and superficial candida infections [1, 2]. Dermal infections caused by fungi impact 20–25% of the world's inhabitants and are rising yearly[3]. Candida alone causes 1 billion cases a year. The majority of fungal infections infiltrate the stratum corneum (SC), continue to permeate deeper layers of the skin, and eventually develop significant cutaneous human candidiasis if treatment is not provided. In modern times topical medications have become the preferred choice for treating fungal infections. The advantages of topical administration avoids gastrointestinal issues due to water solubility, pH, drug-food interactions, and pre-systemic metabolism [3]. ICZ is an antifungal drug that belongs to the triazole category with a wide range of activities. Because ICZ is well tolerated by patients, it is often used for treating mycological infections. This nature makes ICZ more popular concerning other antifungal drugs. Individuals who are immunocompromised or non-immunocompromised, as well as individuals who are unable to take amphotericin B therapy, are the ideal candidates for treatment with ICZ[4]. However, because of its hydrophobic qualities and the fact that people's oral bioavailability varies greatly from one another, its usage has been restricted. Percutaneous preparations' therapeutic impact relies on the drug's activity and other vehicle structural parameters[5]. According to a recent publication, the most frequent method for enhancing the solubility and dissolution rate of ICZ is to transform the drug into an amorphous state by generating a variety of solid dispersions that are based on polymer [6]. Recent pharmaceutical technology

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advancements include designing novel forms that boost the therapeutic efficacy of already existing active pharmaceuticals. These days, an innovative method known as DESM is considered to be at the forefront of technological development. DESM is a kind of eutectic mixture that is distinguished from other eutectic mixes by the fact that the melting temperature of the combination at the eutectic point is much lower than the melting temperature of the pure components [7]. In the same way, as ILs are considered to be designer solvents and have a lower vapor strain, DESM are also considered to be in the same category. On the other hand, DESMs are often less hazardous to human health, simpler to make, and cheaper than ILs. The abovementioned characteristic makes DESM more user-friendly rather than the IL's technique. For instance, it is now being used as a solvent in different sectors like separation processes [8], as a medium for chemical [9], electrochemical [10], and biological interactions [11,12], in polymer chemistry [13,14], and for enhancing the solubility of active medicinal components[15]. Up to this point, the design of DESM has been carried out almost entirely via the process of trial and error. In the majority of works that have been published, predetermined ingredients are combined using several different fixed molar ratios, such as 1:1 or 1:2, and combinations that can retain their liquid state when brought to room temperature are chosen for further testing.

In this study, ICZ, choline chloride (CC), and different types of carboxylic acid (oxalic acid, lactic acid, benzoic acid, resorcinol, phenol, menthol, gallic acid, urea, and citric acid) are used in the molar ratios 1:1:1 to 1:1:10. Urea showed the best results among all the carboxylic acids. Then, varying the urea and CC ratio in a continuous format optimized DESM mixture was obtained. Carbopol 934P was used as a gelling agent to prepare the topical gel. Aqueous NaOH solution 1M was used to maintain the pH of the topical formulations.

2. RESULTS

2.1. Visual appearance

All the fabricated gels were shiny and found to be slightly turbid. No lumps were present indicating the homogeneous texture of the prepared formulations. FCU-1 was slightly viscous, whereas FUC-4 was sticky. FUC-2 and FUC-3 were found to be uniform.

2.2. Drug Content

The drug content found in FCU-3 was the highest (88.85%). The drug content was found in increasing order in FCU-1, FCU-2, and FCU-4 (85.19, 86.13, and 87.82%) respectively.

2.3. pH of the gel

The pH of the gel is present in Table 1. It was found in the range of 6.53 to 7.46. It was assumed to give no irritation to the epidermal tissues because the pH of the skin ranged between 5.9 to 6.8.

2.4. Viscosity of the Gel Sample

The viscosity of the prepared gel is represented in Table 1. In FCU-1, the viscosity was found to be 8379 cps. In FCU-2, FCU-3, and FCU-4 it was found to be 10833, 13535, and 15373 respectively.

2.5. Spreadability of the gel

The spreadability profile is represented in Table 1. It has been found that FCU-1 has the highest spreadability (7.46 g×cm/sec), whereas FCU-4 (6.53 g×cm/sec) has the lowest. FCU-2 and FCU-3 spreadability was found to be 7.34 g×cm/sec and 7.27 g×cm/sec respectively.

2.6. FTIR Results

FTIR results are demonstrated in Figure 1. Figure 1 (A) displays the characteristic peak of ICZ. ICZ shows distinctive peaks at 1750, 1697.71, 1509.26, 1451.32, 1379.34 and 1101.67, cm^{-1}. A peak was also found near 2822.79 cm^{-1} in the pure drug. Figure 1 (B), at regions 3224.77, 1480.46, and 952.03 cm^{-1} CC shows the intense peak. In Figure 1(D), FCU-3 shows a broad peak in the region of 3338.76 cm^{-1} and other peak were found at 2981.56, 2110.92,1635.38, 1509.26, 1473.63, 1380.05.34, 1153.67 and 1015.33 cm^{-1}.

Table 1. Optimized formulation table

Sr.No.	Ingredients (%)	Formulation Code				Appearance of Gel	Drug Content	pH	Viscosity	Spreadability (g×cm/sec)
		FCU-1	FCU-2	FCU-3	FCU-4	Less Viscous Gel Formed	85.19±0.16	7.19±0.010	8379±0.58	7.46±0.006
1	DESM (ml)	5	5	5	5	Uniform Gel Formed	86.13±0.14	7.25±0.006	10833±0.58	7.34±0.010
2	Carbopol 934p (w/v)	0.5	1	1.5	2	Uniform Gel Formed	88.85±0.08	7.32±0.006	13535±1.00	7.27±0.010
3	NaOH solution (ml)	Q. s	Q. s	Q. s	Q. s	Sticky Gel Formed	87.82±0.14	7.16±0.010	15737±1.53	6.53±0.010

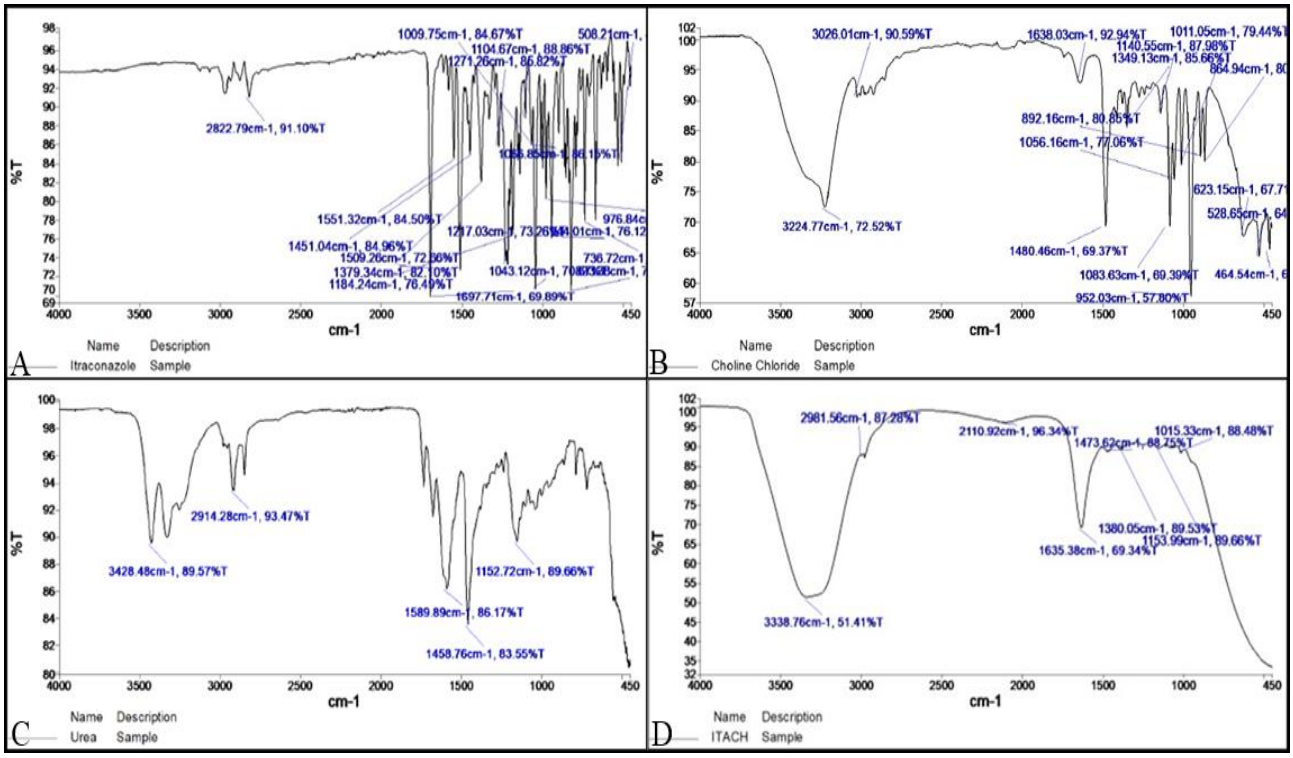

Figure 1. FTIR spectra of (A) ICZ, (B) CC, (C) Urea and (D) FCU-4

2.7. *In-vitro* drug release study and kinetics

From the release study, it has been found that FCU-1 releases the drug in a sustained manner, but other gel formulations show release in a continuous, sustained manner (Figure 2). Within 12 hours. FCU-1 (75%), FCU-2 (71.54%), FCU-3 (45.85%), and FCU-4 (33.17%) of release were obtained. In release kinetics, the KP model diffusion constant (n) shows 0.38, 0.43, 0.58, and 0.72 for FCU-1, FCU-2, FCU-3, and FCU-4 respectively. In the PS model diffusion constant (m) shows values for FCU-1 (0.46), FCU-2 (0.50), FCU-3 (0.44), and FCU-4 (0.53). In the Higuchi model, increases in carbopol and decreases in the Higuchi constant were found.

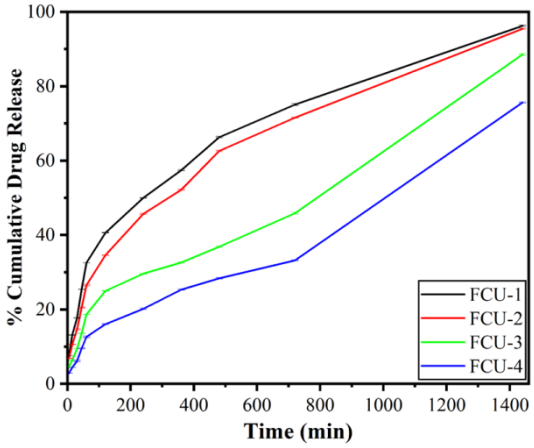

Figure 2. Drug release profile of the prepared gel formulations

Table 2. Release kinetics of the prepared gel

Release Model	Parameter	FCU-1	FCU-2	FCU-3	FCU-4
Higuchi	KH	2.849	2.694	2.011	1.584
KP Model	Kp	5.853	4.073	1.136	0.373
	n	0.388	0.436	0.588	0.720
PS Model	Kd	4.481	3.197	1.736	0.737
	Kr	-0.042	-0.018	0.061	0.015
	m	0.464	0.501	0.444	0.534

2.8. Docking Study

From the computational analysis, the docking score was found to be -9.3 Kcal/mol. Figure 3 (A) represents the 3D- structure of docking, whereas Figure 3 (B) represents the 2D- structure of docking [16].

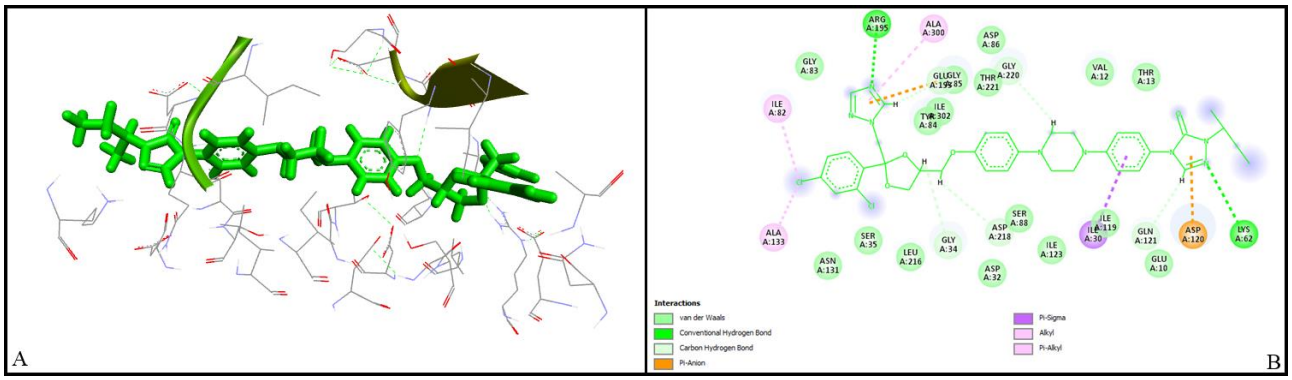

Figure 3. Docking Study of ICZ and Candidapepsin-2 (A) 3D-structure, (B) 2D-structure

3. DISCUSSION

3.1.Visual appearance

The prepared formulation was inspected visually for color, odor, and homogeneity. No particles were found by rubbing it with two fingers, revealing a smooth texture demonstrating the homogeneity in nature. The absence of large particles and lumps indicates the fabricated gel was uniformly mixed.

3.2. pH of the gel

The of the skin was found to be 5.9-6.8 [17]. All the formulations' pH ranged between 6.53 to 7.46. As the pH of the skin and fabricated formulation pH was nearly the same it may be assumed that it does not cause cell shrinking. So, it can be assumed that the prepared formulation was free from irritation.

3.3. Viscosity of the prepared gel

Carbopol was known as a viscosity enhancer. Viscosity was increased with increasing in the carbopol concentration. All topical gel exhibited pseudoelastic behavior with the shear thickening property as viscosity was found to increase with an increase in shear rate (Table 1).

3.4. Spreadability of the gel

The spreadability of the gel was found to be decreased. This observation can be correlated to the viscosity profile. this could be possible due to the shear thickening properties of the prepared formulations.

3.5. FTIR Discussion

The peak near 2900 cm^{-1} was due to the stretching vibration of the -NH_2 group [18]. A sharp peak found in the region of 1697.71 cm^{-1} was due to the C=O of the drug [19]. The peak found in the region of 1271 cm^{-1} was due to C-N stretching [20]. In formulation Figure 1(D), a broad peak was found due to the -OH bond stretching [21]. At region 2961 cm^{-1}, a peak was found due to the presence of urea, which represents the formation of DESM. In the gel formulation, the presence of a characteristic peak stated that there was no interaction between the drug and the polymer.

3.6. In-vitro drug release study and kinetics

From release kinetics, it was found that the Higuchi constant decreased with an increase in the carbopol concentration (Table 2). This may be explained due to the controlled drug release of the ICZ from carbopol. In the KP model, the release mechanism was dependent on the 'n' value. Fickian transport ($0.45 \leq n$), anomalous (non-Fickian) transport ($0.45 \leq n < 0.89$), and/or super case-II transport ($n > 0.89$). FCU-1 and FCU-2 show fickian-driving drug release, whereas FCU-3 and FCU-4 show anomalous or nonfickian-driving drug release. In the PS model, if Kd> Kr, then the process is fickian diffusion, and in reverse, it is erosion-based. If Kd is equal to Kr, then the process follows both diffusion and erosion control. In our release profile, all the formulations show Kd> Kr, which shows fickian diffusion-based drug release.

3.7. Docking Study

It has been shown that the docking profile shows a binding profile of -9.3 kcal/mol. Which suggests that it has a good binding affinity. Triazole atoms connected with Asp 120 with pi-anion bonding. Lys 62, and Arg 195 were connected with the azole functional group by conventional hydrogen bond. Ill 30 was connected with the center benzene ring with the help of the Pi-Sigma bond, whereas Ala 133, Ile 82, and Ala 300 were connected with chlorine atoms with the Pi-Alkaly bond. Val 12, Thr 13, Asp 32, Asn 131, Ser 35, Leu 216, Ser 88, Glu 10, and Gly 83 were among the other amino acids having hydrophobic residues that were typically in touch with the remainder of the ICZ molecule. [16,22,23].

4. CONCLUSION

From the above finding, it was established that the development and optimization of itraconazole-loaded topical gel using the DESM technique were successfully prepared. In the FTIR study, no new peak was found or diminish of any peak was observed suggesting that no interaction between the excipient and ICZ molecule. From viscosity analysis, it was observed that Viscosity was increased with an increase in the carbopol concentration. The pH of the gel formulation was non-irritant to the human skin. The spreadability profile was decreased with increases in the carbopol concentration resulting in the shear thickening behavior of the formulations. A drug release study revealed that the drug was driven through the fickian and non-fickian diffusion mechanisms. From the release pattern, it was found that the drug was driven through both fickian and anomalous diffusion mechanisms. Different mathematical models support the finding. Binding affinity was found to be -9.3 Kcal from the docking study. In gist, it can be concluded that ICZ-based topical gel can be used against the fungal infection.

5. MATERIALS AND METHODS

5.1. Materials

Different carboxylic acids were procured from local suppliers. Carbopol 934P and sodium hydroxide were purchased from Sisco Research Laboratories Pvt. Ltd. Mumbai, India. CC was obtained from Spectrum

Chemical, United States. ICZ was purchased from TCI Chemicals Pvt. Ltd. (CAS no: 84625-61-6). Double-distilled water was used throughout the study.

5.2. Preparation of the DESM mixture

Drug: CC: carboxylic acid in molar ratios of 1:1:1 to 1:1:10 were prepared and optimized through the drug content. It was discovered that urea had the greatest concentration. With varying the urea and CC in a continuous mode, the CC: Urea ratio (2:8) shows high solubility and this concentration was fixed for further use.

5.3. Preparation of topical gel

Carbopol 934p was used in different concentrations (0.5%, 1%, 1.5%, and 2%) to prepare the gel formulation. Optimized DESM mixture (ICZ: CC: Urea; 1:2:8) 5 mL was taken and added to the different ratios of carbopol 934p gel formulation. Then the mixture was allowed to homogenized for 24 hours through the magnetic stirrer. After the mixing, the gel product was kept in an air-tied container for further use.

5.4. Visual appearance

The prepared topical gel was inspected visually for different physical properties like smoothness, color, and texture.

5.5. Drug Content

A prepared gel containing 10 mg of the drug was dissolved in methanol. After dissolving the gel, it was filtered through Whatman filter paper 41. After that the 5 ml of solution was taken and the volume of makeup was increased to 25ml and scanned at 262 nm with the help of a UV-visible photo spectrometer (JASCO V-630 spectrophotometer, Software: Spectra Manager).

5.6. pH of the gel

The electrode of the pH meter was dipped into the gel formulation for 30 seconds, without disturbance. Then pH was recorded and the procedure was repeated in triplicate.

5.7. Viscosity of the prepared gel

The gel's viscosity was measured using a Brookfield viscometer (DV-II+ Pro). Gels were spun at 24 rpm on spindle L4 at ambient temperature. İn gist, Spindle L4 was dipped into the sample holder containing 20 gm of prepared gel, and dial readings were taken at each speed, with an angular range from 0.1 to 1 rpm.

5.8. Spreadability of the gel

The following method was used to ascertain the gel's smearability: On a glass plate with a 1 cm diameter circle drawn on it, 0.5 g of gel was deposited, and then another glass plate was set on top of that. The top glass plate had 500 g of weight left on it for 5 minutes. It was observed that the gels' spreading caused a noticeable rise in their diameter [23].

5.9. FTIR Study

The FTIR study was performed in ATR mode (Alpha-E; Bruker). 0.1g of gel sample was placed on the ATR reflector and scanned within the wavenumber range 4000–400 cm^{-1}, each with 36 scans [24]. The resolution of the instrument was $4cm^{-1}$.

5.10. Drug release study and release kinetics

The Franz diffusion cell was used to perform the drug release analysis, which was conducted across a dialysis membrane. The membrane was positioned in the diffusion cell between the donor and the acceptor regions, and the receptor compartment was filled with 7.4 pH phosphate buffer. 1g of gel sample was placed in the donor compartment with a fixed RPM of 100 while maintaining the temperature of 37±0.5°C. At different intervals, the sample was withdrawn and replaced with the blank buffer. Higuchi, Korsmeyer-Peppas (KP), and Peppas-Sahlin (PS) models were used to establish the drug's release mechanism in vitro release data [25,26].

Higuchi presented the kinetics of drug release as a linear connection between the square root of the time plot and the cumulative percentage of drug release. Diffusion constant (n) defines the release pattern in the KP model, whereas in the PS model (m) determines the release mechanism.

$$\text{Higuchi Model: } C = K\sqrt{t} \quad (1)$$
$$\text{KP Model: } \frac{M_t}{M} = K \,.\, t^n \quad (2)$$
$$\text{PS Model: } P = K_d t^m + K_r t^{2m} \quad (3)$$

5.11. Docking Study

Candidapepsin-2 (PDB ID: 1eag) was retrieved from the RCSB Protein Data Bank, with uniport accession ID: P28871. ICZ was docked with the receptor at the X axis: 41.47, Y axis: 24.85, and Z axis: 13.16. Docking was performed with the help of AutoDock software and docking was visualized by Discover Studio 2021.

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