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Self-emulsifying micelles as a drug nanocarrier system for itraconazole oral bioavailability enhancement; *in vitro* and *in vivo* assessment

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ABSTRACT

Itraconazole (ITZ) is a renowned antifungal medication, however its therapeutic efficacy is limited by low solubility and oral bioavailability. The current research work attempted to augment the oral bioavailability of ITZ by incorporating into self-emulsifying micelles (SEMCs). To fabricate the SEMCs, various preparation techniques including physical mixture, melt-emulsification, solvent evaporation and kneading, were opted by using different weight ratio of drug and solubilizers i.e. Gelucire-50/13 or Gelucire-44/14 and characterized both in vitro and *in vivo*. The prepared SEMCs were found to be in the size range from 63.4 ± 5.2 to 284.2 ± 19.5 nm with surface charges ranging from −16 ± 1.2 to −27 ± 2.0 mV. The drug solubility was improved to a reasonable extent with all investigated formulations, however, SEMCs in group 6 prepared by kneading method (KMG6) using Gelucire-44/14: drug (10:1 presented 87.6 folds' increase (964.93 ± 2 μg/mL) compared to solubility of crystalline ITZ (11 ± 2 μg/mL) through kneading method. In addition, KMG6 SEMCs shows the fast drug release compared to other SEMCs. Further, KMG6 SEMCs also exhibited 5.12-fold higher relative intestinal serosal fluid absorption compared to crystalline ITZ. The pharmacokinetic parameters such C_{max}, AUC and T_{max} of KMG6 SEMCs significantly improved compared to crystalline ITZ. In conclusion, the manipulation of ITZ solubility, dissolution rate and absorption using SEMCs is a promising strategy for bioavailability enhancement.

1. Introduction

The bioavailability of poorly soluble drugs may be hampered by many factors i.e. absorption solubility, or dissolution rate. It is noteworthy that solubility is the rate limiting factor for the oral bioavailability, so, the oral bioavailability can be improved with the help of solubility enhancing strategies (Khan et al., 2022). In addition, the bioavailability of drugs depends on drug absorption from oral solid dosage forms. Many strategies were previously opted to enhance the oral bioavailability by addressing the dissolution and absorption of an active pharmaceutical ingredients (APIs) (Shekhawat and Pokharkar, 2017).

ITZ as an API has been extensively used for fungal infections treatment. ITZ has good tissue distribution properties and strong affinity for fungal cytochrome *P*-450 that makes it broad spectrum candidate for systemic fungal infections (Lestner and Hope, 2013). Besides, ITZ evades serious invasive fungal infections through prophylaxis (Allegra et al., 2017). It is categorized in Biopharmaceutical Classification System in class-II drugs owing to its poor solubility (Matsui et al., 2016). The prevailing ITZ formulations have shown large variability in results from dosage form to interpersonal pharmacokinetics (Abuhelwa et al., 2016). In fact, ITZ has showed 50 % oral bioavailability (Heykants et al., 1989, De Beule, 1996). Along with the poor aqueous solubility, P-glycoprotein

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(P-gp) and high metabolism rate might be the other possible reasons of low bioavailability of ITZ. Therefore, dissolution and absorption enhancement is necessary to improve the bioavailability of ITZ and good therapeutic results (Deshpande et al., 2018).

Previously, various approaches have been tried to address oral bioavailability issue of ITZ. Among them, solid dispersion (Thiry et al., 2017), spray dried dispersion (Adhikari and Polli, 2020), liquisolid compacts (Thakkar et al., 2020), liposomes (Li et al., 2017), polymeric film (Karagianni and Peltonen, 2020), porous spheres (Pawar et al., 2017), nanoparticles (Bilgili et al., 2018), nanoemulsion (Botros et al., 2020), self-micro-emulsifying drug delivery system (Quan et al., 2017), and nanocomposities (Bhakay et al., 2018), are few approaches that were applied to improve the oral bioavailability. Moreover, the main reason of SEMCs selection for oral bioavailability enhancement of ITZ is that SEMCs as a binate system have shown promising results in improving bioavailability of different poorly soluble drugs (Zhang et al., 2017). SEMCs can increase the solubility by decreasing the molecular size of drug particles (Italiya et al., 2019). Further SEMCs can convert the crystalline drug to amorphous form (Indulkar et al., 2019). SEMCs preparation is very simple, easy and economical method to increase solubilization and bioavailability of poorly soluble drug molecules at industrial scale (Hwang et al., 2020). Generally, the solubilization of lipophilic drugs with lipid excipients increases dissolution rate, absorption and bioavailability. Thus biopharmaceutical properties along with physiochemical features of drug might be improved with lipophilic polymers (Patel et al., 2018).

Mixture of glycerides and polyethylene glycol (Gelucire-44/14 and Gelucire-50/13) with HLB values of 13 and 14 is promising for micelles preparation, high drug loading, and stability of SEMCs (Panigrahi et al., 2018, Teixeira et al., 2018, Etezadi et al., 2020). In addition, these amphiphilic polymers have self-emulsifying properties that can help in the solubilization and absorption of ITZ (Ali and Staufenbiel, 2020, Nardin and Köllner, 2019). Besides, these polymers can promote water solubility of hydrophobic drugs (Tran et al., 2019, Alshehri et al., 2020). Thus they are well recognized for solubilizing poorly soluble drugs and act as polymer in SEMCs (Eedara and Bandari, 2017).

The current research work was planned to improve therapeutic efficiency of ITZ by increasing its oral bioavailability by preparing SEMCs using Gelucire-44/14 and Gelucire-50/13. In SEMCs preparation, solubilizers were used in various weight ratios following different preparation methods to evaluate relevant parameters that could be involved in improving the solubility and bioavailability. The performance of solubilizers was assessed on the basis of their solubility and bioavailability enhancing efficiency of ITZ. The novelty of this work is that self-emulsifying polymers were used first time for the bioavailability enhancement of ITZ through micellar system and can be an excellent clinical slant.

2. Materials and methods

Itraconazole was generously donated by Vision Pharmaceuticals Islamabad, Pakistan. Gelucire-50/13, Gelucire-44/14 and Transcutol-P® were provided by Gattefossé, France. All analytical grade chemicals were used for analysis.

2.1. Preparation of SEMCs

The formulations description of the physical mixtures of ITZ and Gelucires were shown in Table 1. Moreover, SEMCs of ITZ with Gelucires were prepared using different w/w ratios through melting method as presented in Table 1. Briefly, the solubilizers were melted at 60 °C and simultaneously drug was added. Afterwards, the blend was homogenized well (Fritz et al., 2018). Likewise, SEMCs were prepared with little modification in the kneading method as formerly described by Tambe Amruta et al (Tambe and Pandita, 2018). The solubilizers and ITZ were blended in different w/w % ratios, as given in Table 1. The mixtures were triturated in a glass pestle and mortar for 10 min with slow addition of Transcutol-P® (2.5 mL). The obtained mass was added to water (Verma et al., 2017). Moreover, SEMCs were prepared by solvent evaporation method as demonstrated in Table-1. Concisely, solubilizers were thawed in ethanol (5 mL) under magnetic stirring. Then, the ITZ was added and the resultant mixtures were added to water (10 mL) and subjected to magnetic stirrer for 60 min. Subsequently, the solutions were subjected to rotatory evaporator to remove organic solvent under reduced pressure at room temperature. The consequential SEMCs were bath-sonicated with 2.0 mL water (Bothiraja et al., 2020, Zhang et al., 2020).

The code represents PMG; physical mixture of ITZ and Gelucires, MEG; SEMCs with melt-emulsification method, KMG; SEMCs with kneading method, SEG; SEMCs with solvent evaporation method.

2.2. Solubility

The saturation solubility of crystalline ITZ with particle size of 50 μm and developed $SEMC_S$ were determined in aqueous media, respectively. Briefly, either 20 mg of pure ITZ or SEMCs formulation equivalent weight to 20 mg of ITZ were taken in glass test tubes supplied with 10 mL aqueous methylene chloride solution and aqueous media final volume. Subsequently, the test tubes were placed on a shaker at 37 °C for 24 h. Further, the tubes were bath-sonicated, centrifuged at 5000 rpm for 20 min, samples were filtered using a syringe filters of 0.45 μm, then diluted with simulated gastric fluid and finally analyzed at wavelength of 256 nm on a UV spectrophotometer Shimadzu-UV-2600, (Shimadzu Corporation, Kyoto, Japan) (Jung et al., 1999).

2.3. In vitro drug release

The dissolution studies of pure ITZ, Sporanox® capsules and SEMCs were performed in 900 mL gastric fluid (pH 1.2) consisting of 7 mL of c-HCl and NaCl (2 g/l) at 100 rpm stirring speed and 37 ± 0.5 °C temperature, using USP-dissolution method-2. The accurately weighed SEMCs equivalent to 100 mg of ITZ were filled in size "0″ gelatin two capsules and placed into the dissolution vessels. Accurately, 3 mL of samples were collected at pre-determined time intervals (10, 20, 30, 40, 50 and 60 min) and replenished with the same volume of fresh simulated gastric fluid. The samples were filtered by 0.45 μm syringe filters and diluted with simulated gastric fluid, then subsequently analyzed by a UV spectrophotometer Shimadzu-UV-2600 (Shimadzu Corporation, Kyoto, Japan) at 256 nm wavelength. Sampling volume was replenished by adding equal amount of fresh simulated gastric fluid (Tao et al., 2009).

Table 1
Detailed description of prepared SEMCs formulations (weight % ratio).

Code	ITZ	Gelucire 50/13	Code	ITZ	Gelucire 50/13	Code	ITZ	Gelucire 50/13	Code	ITZ	Gelucire 50/13
PMG1	1	1	MEG1	1	1	KMG1	1	1	SEG1	1	1
PMG2	1	5	MEG2	1	5	KMG2	1	5	SEG2	1	5
PMG3	1	10	MEG3	1	10	KMG3	1	10	SEG3	1	10
		Gelucire 44/14			**Gelucire 44/14**			**Gelucire 44/14**			**Gelucire 44/14**
PMG4	1	1	MEG4	1	1	KMG4	1	1	SEG4	1	1
PMG5	1	5	MEG5	1	5	KMG5	1	5	SEG5	1	5
PMG6	1	10	MEG6	1	10	KMG6	1	10	SEG6	1	10

Drug release mechanisms were investigated using kinetic models such as the Korsmeyer Peppas model, Zero Order model, First Order model, and Higuchi model.

2.4. Micelles size, polydispersity index (PDI) and zeta potential

The size and PDI of SEMCs were examined by dynamic laser light scattering (DLS) using Zetasizer Nano-ZS (Malvern Panalytical GmbH, Kassel, Germany) fortified with 10 mW HeNe laser with a scattering light detection of 173° and a wavelength of 633 nm at 25 °C. The instrument automatically adjusted the measurements and laser attenuation positions. Disposable capillary cell (DTS 1060, Malvern instrument) was used for the measurements. Moreover, the dispersions were diluted properly with purified water for micelle size analysis. Each measurement was performed in triplicate consisting of 15 runs based on the sample. The zeta potential (ζ) of SEMCs was tested by computing electrophoretic mobility at a scattering angle of 17° and a temperature of 25 °C with laser doppler velocimetry. The data for three independent samples are expressed as mean + SD.

2.5. Entrapment efficacy and drug loading

The entrapment efficiency of micelles was calculated using both direct and indirect method (Miyata et al., 2011, Kim et al., 2010). The micelles solution was subjected to centrifuge machine at 20000 rpm for 15 min at 4 °C. The supernatant was filtered and analyzed. The separate out mass of micelles was lyophilized and loaded drug was extracted by dissolving in DMSO. By this way, calculate the free drug and loaded drug in micelles. The analysis of supernatant was performed at Agilent HPLC system (1290, infinity II). The column C-18 (4.6 × 150 mm, 5 µm), mobile phase (acetonitrile and tetrabutyl ammonium hydrogen sulphate 0.01 N 55:45, v/v), flow rate of 1 mL / minute, and UV detector at 260 nm were used to determine the ITZ encapsulated in micelles (Janssens et al., 2008). The EE (%) and DL (%) were calculated by following equations

$$\mathbf{EE}(\%) = \frac{\mathbf{TotalamountofITZ - amountofunbounddrug}}{\mathbf{TotalamountofITZincorporated}}\mathbf{x}100 \quad (1)$$

$$\mathbf{DL}(\%) = \frac{\mathbf{amountofITZencapsulatedinmicelles}}{\mathbf{TotalamountofITZandsolubilizer}}\mathbf{x}100 \quad (2)$$

2.6. Colloidal stability

The colloidal stability of the as-prepared KMG6 SEMCs in different dissolution media (distilled water, PBS, DMEM, 5 % glucose, 0.9 % NaCl) at 4 °C was determined by measuring the hydrodynamic particle size (DLS) at specified intervals of time (0, 6, 12, 24, 48, 96 and 120 h).

2.7. FTIR analysis

FTIR spectra were recorded in the range of 500 and 4000 cm^{-1} wavenumbers using a Fourier transform infra-red spectrophotometer Cary-360 FTIR (Agilent Technologies Inc., Santa Clara, CA, USA). The background scans were taken to trace any impurity in samples and the spectrum was recorded in transmittance mode.

2.8. Differential scanning calorimetry (DSC)

In order to study drug polymorphism, differential scanning calorimetry (DSC) analysis was performed to identify the stable modification through differential scanning calorimeter DSC-8000 (Perkin Elmer, USA). Samples (ITZ and KMG6) were put in crucibles and excited from room temperature to 200 °C keeping a heating rate of 10 °C /min under nitrogen purge (20 mL/min) (Hamishehkar et al., 2014). Difference in heat flow was observed to note whether heat was absorbed or released. The polymorphic transitions were noted from the thermograms of samples.

2.9. Powder X-ray studies (PXRD)

The solid-state characteristics of ITZ in SEMCs were evaluated by PXRD analysis. The X-ray diffraction of ITZ and KMG6 SEMCs was measured using an X-ray diffractometer D8-Advance (Bruker Corporation, Billerica, MA, USA). The tests were accomplished at room temperature with a scanning rate of 0.02 degrees/min between 5° and 70°. The voltage and the current were set at 35 kV and 35 mA respectively.

2.10. Ex vivo absorption using reverted rat gut sacs

Male Sprague-Dawley rats (200 ± 10 g body weight) were used for the *ex vivo* absorption study. The rats were sacrificed and small intestine was rapidly removed and washed several times with normal saline (0.9 %, w/v) at room temperature. Afterward, the intestine was put into warm buffer medium (37 °C) (pH 7.4) and cutted into small pieces. The gut was reverted with glass rod. The large duodenum sac was cut into 2 cm length size sacs. Subsequently, one side of small sacs was tied with a silk suture then filled with buffer medium (pH 7.4). The small sacs were incubated in a 50 mL beaker comprising 20 mL of buffer medium (pH 7.4) in a gentle shaking water bath at 37 °C. Next, 100 µg/mL ITZ, and KMG6 SEMCs were added into beaker and incubated for one hour. The serosal solution was obtained by cutting sac and collected in a clear tube. The sac tissues were homogenized after adding 2 mL acetonitrile and then centrifuged at 13,000 rpm for 10 min. The supernatants (20 µL) were collected and analyzed for ITZ using Agilent HPLC system-1290, infinity II (Agilent Technologies Inc., Santa Clara, CA, USA).

2.11. Oral bioavailability

All the animal experiments were conducted according to the guidelines provided by Government College University (GCU) Faisalabad (S/No.19668/09/19). The University of Veterinary and Animal Sciences, Lahore (Pakistan) provided male Sprague-Dawley rats (200 ± 10 g body weight). Rats were divided in two group; each group have six rats (n = 6). Rats were kept at 25 ± 2 °C on a 12-hour dark-light cycle with free access to water and food. The pentobarbital 50 mg/kg was given intraperitoneally for anesthesia. Each rat was given ITZ equivalent to 1 mg/kg of ITZ, hydroxy ITZ (H-ITZ), KMG6 SEMCs and hydroxy KMG6 (H-KMG6) SEMCs by oral route. Blood samples were collected in heparin tubes directly from jugular vein at predetermined time intervals (0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h). A 200 µL blood sample was taken at each time point.

2.11.1. Sample preparation

The plasma was separated from blood specimens by centrifugation at 4 °C for 10 min at 15000 rpm. Carefully, pipetted out the supernatant and kept at cold temperature (-20 °C for supplementary analysis. Bifonazole was used as an internal standard. Further, the protein in plasma samples was precipitated by mixing (100 µL) with acetonitrile (200 µL). The solution was centrifuged at 10,000 rpm for 10 min to obtain supernatant. The samples were injected in HPLC port to calculate the drug concentration in plasma at particular time.

2.11.2. HPLC method

Plasma ITZ concentration was determined by using modified HPLC method of Wei Meng Lim's (Lim et al., 2014). The analysis was performed on Agilent HPLC system (1290, infinity II). The column C-18 (5 µm, 4.6 × 150 mm,), a UV detector, and pump (1290 infinity) were equipped with HPLC. The mobile phase was composed of tetrabutyl ammonium hydrogen sulphate and acetonitrile 0.01 N 45: 55, v/v. The base line was corrected by running the mobile phase at 1 mL / minute flow rate for analysis. The ITZ was detected at wavelength of 260 nm.

The pharmacokinetic parameters were calculated using non-compartmental method by PK solver (version 11) (Zhang et al., 2010, Paudel et al., 2018). The percent bioavailability of SEMCs (KGM6) was calculated with reference to ITZ suspension using following formula.

$$\textit{Bioavailability}(\%) = \frac{AUC_{SEMCs}}{Dose_{SEMCs}} x \frac{Dose_{ITZ}}{AUC_{ITZ}} x 100 \quad (3)$$

2.12. Statistical analysis

All the experiments were performed at least thrice and presented as the mean ± standard deviation. The one-way ANOVA was applied on in-vitro and in-vivo drug release data followed by a post hoc Tukey test using SPSS software (version 21) keeping significance level $P \leq 0.05$.

3. Results and discussion

3.1. Solubility

ITZ has very low aqueous solubility due to its highly hydrophobic nature, as a results, it provides low oral bioavailability (Kojo et al., 2017). Thus, to achieve high drug plasma concentration, it is necessary to follow such techniques that can improve its oral bioavailability (Zhang et al., 2017). Furthermore, Gelucire-50/13 and Gelucire-44/14 were used in the preparation of SEMCs. The high hydrophilic-lipophilic balance (HLB) values and low melting point of Gelucires make them highly attractive candidates for improving the dissolution rate and solubility of poor soluble drug (Shaker, 2018). In this regard, the saturated solubility of ITZ was evaluated in both Gelucire-50/13 and Gelucire-44/14. Both the solubilizers were found effective in improving solubility of ITZ, and therefore were further proceed to develop SEMCs (Panda et al., 2016, Lee et al., 2018). The solubility profile of ITZ pure drug and developed SEMCs are shown in Fig. 1. The solubility of physical mixture of drug and solubilizer was found between 36 and 332 μg/mL. For example, the solubility of PMG3 and PMG6 was 268 and 332 μg/mL respectively. In addition, solubility of ITZ was enhanced more proficiently with melt-emulsification method compared to physical mixture. The melt-emulsification method enhanced solubility from 94 to 896 μg /mL. The solubility of MEG3 and MEG6 was 727 and 896 μg/mL respectively. Also, the solubility of ITZ was enhanced by solvent evaporation method more than pure drug, physical mixture and melt-emulsification method but less than kneading method. In this case, KMG3 exhibited 882 μg/mL solubility and KMG6 displayed 964 μg/mL aqueous solubility of ITZ. The physical blend of ITZ and Gelucires did not improve the solubility to reasonable extend. The SEMCs of ITZ and Gelucire-44/14 having 1: 10 ratio exhibited 70-fold increase in solubility with solvent evaporation method, 84-fold increase with melt-emulsification method and 87-fold increase with kneading method compared to pure ITZ (Fig. 1). The solubility of ITZ was also increased with Gelucire-50/13 but less than Gelucire-44/14. Further, the concentration of Gelucires has critical role in solubility enhancement. As the concentration of solubilizers was increased in the formulations, the solubility of ITZ was also increased in linear fashion. This improvement in ITZ solubility is attributed to good wettability properties of gelucires. The Gelucire-44/14 displayed superior results compared to Gelucire-50/13 owing to better solubilization and emulsifying properties (Chamieh et al., 2018). The order of solubility enhancement of ITZ was found as KMG > MEG > SEG > PMG > ITZ. In particular, the highest solubility was achieved though kneading method thus selected for further studies.

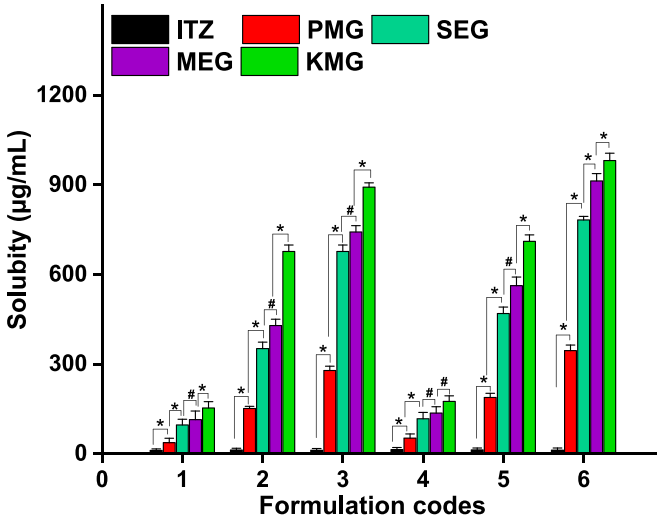

Fig. 1. Solubility studies of ITZ and developed SEMCs (PMGs, SEGs, MEGs and KMGs) in aqueous media.

3.2. In vitro drug release

The dissolution profiles of crystalline ITZ, Sporanox® capsules, physical mixture, SEMCs by melt emulsification method (MEG), SEMCs by kneading method (KMG), and SEMCs by solvent evaporation method (SEG) are shown in Fig. 2A, 2B, 2C, and 2D, respectively. Crystalline ITZ was dissolved only 48.20 % in 60 min indicating the abridged dissolution rate and poor solubility. ITZ physical mixtures with Gelucire-50/13 (PMG1, PMG2, and PMG3) have shown release 56.3 %, 67 % and 100 % in 60 min, respectively. The physical mixture of ITZ with Gelucire-44/14 (PMG5, PMG4, and PMG6) presented release profile from 83.2 to 100 %. The dissolution data clearly postulated that the physical mixture of pure ITZ with Gelucire-50/13 could not escalate the dissolution rate significantly. While the SEMCs with melt emulsification method improved 70 to 100 % release profile of ITZ depending upon different concentration. In addition, the SEMCs with kneading method provided drug release quick release compared to other methods. The drug release from KMG6 SEMCs was 100 % within 30 min. All formulations exhibited first order drug release kinetics as r^2 values are near to 1. ($r^2 = 0.998$). Besides, the SEMCs with evaporation method showed dissolution rate between 76 and 100 %. Thus, micelles preparation methods had impact on release profile of ITZ.

The difference in the release profile of SEMCs may be due to degree of drug solubilization tempted by the solubilizers. The obtained results clearly showed that Gelucire-44/14 improved the dissolution of ITZ significantly higher compared to Gelucire-50/13 ($P < 0.05$). Increased Gelucire-44/14 concentration clearly resulted in improving dissolution rate. The KMG6 SEMCs dissolution rate was almost 5 times higher than pure ITZ and Sporanox® capsules ($P < 0.05$). This dissolution increase may be related to the superior solubilization and emulsifying properties of Gelucire-44/14. The presence of Gelucire-44/14 diminishes the interfacial tension and increases the wettability between ITZ and dissolution medium thus increases the dissolution rate. The thing to notice was that higher concentration of Gelucire-50/13 reduced the release profile of ITZ. So, it is clear that Gelucire-50/13 has more drug retarding properties compared to Gelucire-44/14. Moreover, it is reported that the chemical structure of Gelucires has impact on dissolution rate (Panigrahi et al., 2018). The carbon chain length of Gelucire-50/13 is between C16-C18 and comprised of palmitostearic fatty acids structure while the carbon chain length of Gelucire-44/14 is between C12-C14 and comprised of lauric and myristic acids (Panigrahi et al., 2018). The overall effect of solubilizers, on drug dissolution rate was reasonably encouraging. The prompt dissolution of drug in gastric media triggered by ITZ-Gelucire-SEMCs is an indication of improved bioavailability (Li et al., 2017). Also, ITZ's logP value is high (around 6.2), suggesting that dissolved ITZ could easily penetrate biological membranes (Andrade et al., 2019).

Due to superior solubility and dissolution or release profile of SEMCs preparing by kneading method (KMG6), thus selected for SEM, XRD, DSC and *in vivo* studies.

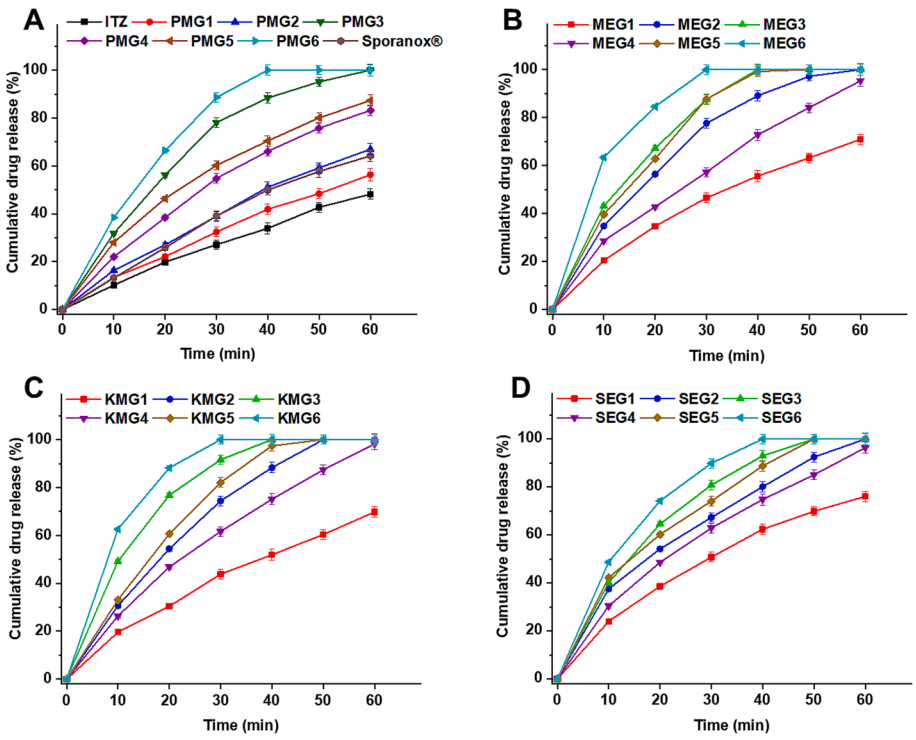

Fig. 2. *In vitro* drug release profile (A) Pure ITZ, Sporanox® and physical mixtures, (B) SEMCs of melt emulsification method, (C) SEMCs prepared by kneading method, (D) SEMCs prepared by solvent evaporation method.

3.3. Micelles size, PDI and zeta potential

The particle size is an important parameter for intracellular payload delivery because small-sized micelles with large surface area are beneficial to enhance the absorption rate in intestine. The average size of KMG6 micelles was found to be 220 ± 38.2 nm with PDI of 0.27. Further the average charge of SEMCs was found –23 ± 4.2 mV measured by zeta sizer (Table 2). The zeta potential, which depends on the surface charge, is important for the stability of nanoparticles in suspension form and is also the major factor in the initial adsorption of nanoparticles.

In addition, all the micelles exhibited slightly negative surface charge at pH 7.4, indicating a good steric protection (Table 2). The nearly net surface charge of the micelles was able to prevent the self-aggregation providing good colloidal stability. Surface charge plays a crucial role in the colloidal stability of SEMCs. The stability of SEMCs is determined by the balance between attractive and repulsive forces acting on the particles. Surface charge arises from the presence of ions or charged functional groups on the surface of colloidal particles (Rasmussen et al., 2020). These charges can be negative or positive, depending on the nature of the particle and the surrounding medium. The surface charge creates an electrical double layer around each particle, consisting of a layer of ions of opposite charge attracted to the surface and a diffuse layer of ions of the same charge as the particle. This double layer generates repulsive electrical forces between particles of the same charge. The repulsion between like-charged particles is essential for colloidal stability, as it prevents the particles from coming together and flocculating (aggregating and settling).

Table 2
Hydrodynamic size and Zeta potential of SEMCs.

Code	Size	Zeta Potential	Code	Size	Zeta Potential
PMG1	163.4 ± 5.2	−16 ± 1.2	SEG1	136.5 ± 11.5	−18.2 ± 2.2
PMG2	269.7 ± 6.8	−16.5 ± 1.5	SEG2	142.7 ± 10.3	−16.9 ± 3.0
PMG3	272.2 ± 5.6	−16.7 ± 2.0	SEG3	147.2 ± 12.6	−21.7 ± 3
PMG4	266.4 ± 6.1	−17.1 ± 1.6	SEG4	168.4 ± 17.5	–22 ± 3.5
PMG5	269.8 ± 5.5	−17.5 ± 2.2	SEG5	171.8 ± 20.5	−19.5 ± 3.7
PMG6	273.5 ± 6.2	−17.7 ± 2.5	SEG6	185.5 ± 19.2	−20.9 ± 4.2
Code	**Size**	**Zeta Potential**	**Code**	**Size**	**Zeta Potential**
MEG1	63.4 ± 2.5	−16 ± 2.6	KMG-1	206.5 ± 19.5	−19 ± 2.7
MEG2	82.7 ± 5.3	−16.9 ± 2.0	KMG-2	242.7 ± 22.2	−19.4 ± 2.1
MEG3	97.2 ± 6.6	−17.7 ± 2.3	KMG-3	247.2 ± 35.4	−26.7 ± 1.5
MEG4	108.4 ± 8.5	−18 ± 2.9	KMG-4	284.4 ± 39.8	−24 ± 3.2
MEG5	111.8 ± 9.5	−18.5 ± 2.7	KMG-5	271.8 ± 34.6	−27 ± 2.0
MEG6	125.5 ± 8.2	−18.9 ± 3.3	KMG6	220 ± 38.2	–23.0 ± 4.2

3.4. Entrapment efficiency and drug loading

The entrapment efficiency of KGM1-6 SMCs was found between 67.34 ± 2.18 % to 82.7 ± 3.11 %. Similarly, drug loading of KGM1-6 SEMCs was found between 8.18 ± 0.13 % to 9.01 ± 0.04 %. As the concentration of Gelucires was increased the EE% and DL% was also increased proportionally. Gelucire is a pharmaceutical excipient that can be used to improve drug solubility and enhance drug delivery system. The higher concentrations of gelucire allows for higher concentrations of active pharmaceutical ingredients (API) in formulation, leading to improved drug efficacy and controlled release. The obtained results showed reasonable drug loading and entrapment efficiency of Gelucires.

3.5. Colloidal stability study

The *in vivo* fate of nanoformulations greatly depends on the colloidal stability in a physiological medium, their distribution throughout the whole volume and their capacity to stay alienated from each other with time (Iqbal et al., 2022). The colloidal stability of the KMG SEMCs in various physiological mediums such as distilled water, 1X PBS, DMEM, 0.9 % NaCl and 8.0 % glucose was evaluated. The obtained data revealed that no obvious change was observed with average hydrodynamic particle size of KGM6 after dispersion in different media over a period of 120 h at 4 °C (Fig. 3), indicating the enhanced colloidal stability of SEMCs favoring *in vivo* applications in clinic.

3.6. FTIR analysis

Fourier transform infrared spectroscopy (FTIR) was used to detect any sort of change in IR spectra. The IR spectra scans of all ingredients and SEMCs were obtained (Fig. 4). The ITZ exhibited major attributed peaks at 950, 1100, 1350, 1500, 3050 and 3135 cm^{-1}. Gelucire-44/14 displayed peaks around 1100, 1300, 3070 and 3120 cm^{-1} respectively. No new peak was appeared in the spectra of KMG6 SEMCs formulations. The characteristics peak of ITZ was remained intact in KMG SEMCs indicating materials were compatible with each other. Similarly, no characteristic peaks were disappeared in IR spectra of SEMCs depicting no significant chemical reaction occurred among the components of micelles. In addition, the presence of attributed peaks of ITZ in KMG6 SEMCs IR spectrum indicating the successful loading of ITZ into KMG6 SEMCs.

3.7. DSC study

The thermal changes in developed SEMCs were observed using differential scanning calorimetry. Results of ITZ–excipient compatibility study performed by DSC are shown in Fig. 5.

DSC thermogram for pure ITZ shows sharp endotherms at 166 °C that corresponds to the melting point of ITZ. In DSC thermogram of KMG6 SEMCs, ITZ endotherm disappeared, indicating that the drug transformed from the crystalline to partially amorphous state. Amorphous state of drug leads to high-energy state resulting in enhanced solubility. The disappearance of melting peaks in SEMCs could be reasonably associated with the complete solubilization of ITZ in the Gelucire-44/14.

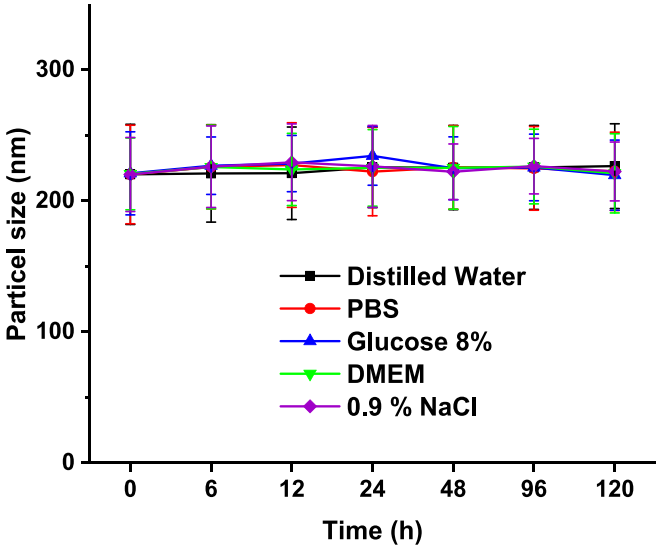

Fig. 3. Colloidal stability of KMG SEMCs in distilled water, 1X PBS, DMEM, 0.9 % NaCl and 8.0 % glucose. Data are expressed as mean ± SD.

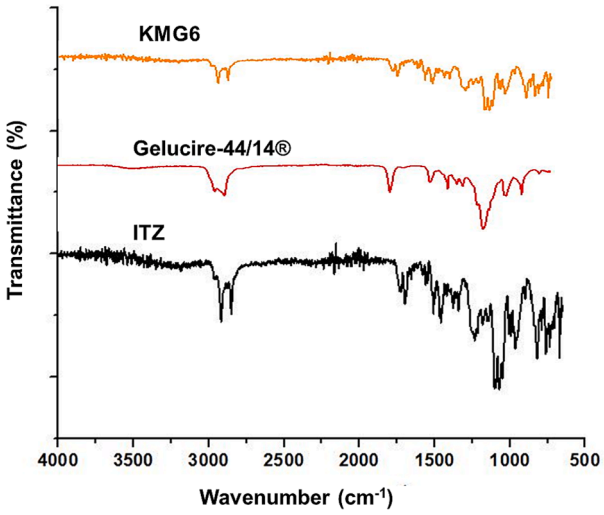

Fig. 4. FTIR spectra of ITZ, Gelucire-44/14® and KMG6 SEMCs.

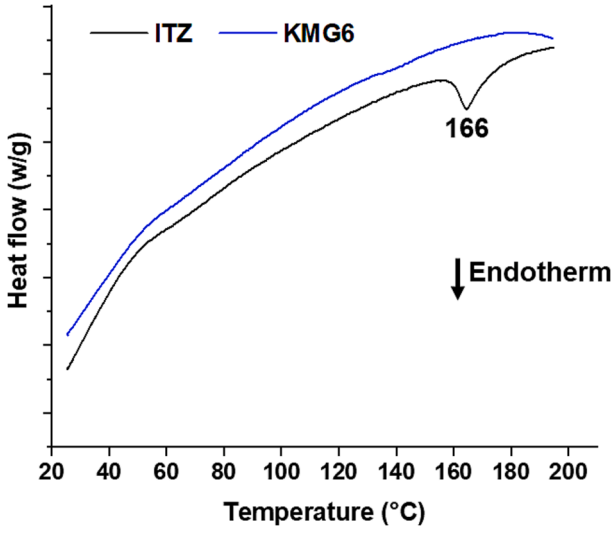

Fig. 5. Differential scanning calorimetry thermograms of ITZ and KMG6.

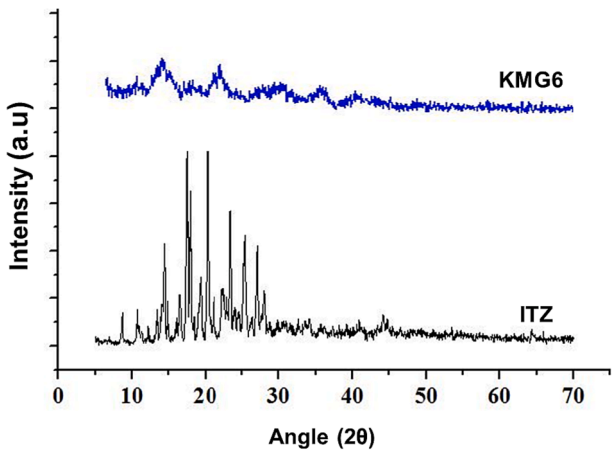

Fig. 6. Powder X-ray diffraction of ITZ, and KMG6.

3.8. PXRD analysis

The PXRD pattern of ITZ displayed high-pitched sharp edge diffraction peaks at 14.4°, 17.7°, 20.4°, 23.5°, 25.3°, 27.3° at 2 theta endorsing the crystalline structure of the drug (Fig. 6). While the formulated SEMCs of Gelucire-44/14 and ITZ did not exhibit any sharp peak assuring the conversion of crystalline drug into amorphous structure (Jung et al., 1999). The large percentage of peaks has been disappeared in KMG6 SEMCs diffractogram. Further, the DSC results were confirmed by diffractograms of the KMG6 SEMCs which exemplify the absence of sharp distinctive peaks of itraconazole.

3.9. Ex vivo absorption

The amount of ITZ absorbed into the serosal fluid through sac tissue was observed. The reverted sac containing ITZ, and KMG6 samples were incubated for 1 h. The absorption of ITZ from the formulation was vastly increased in the duodenum. The amount of ITZ content absorbed from KMG6 was higher than pure drug solution ($P < 0.05$). The ITZ concentration from KMG6 in the intestinal serosal fluid was 5.12-fold higher than ITZ (Fig. 7). It was observed after formulating ITZ with Gelucire 44/14, amount of ITZ in the intestine was significantly increased, which subsequently the improved bioavailability and therapeutic efficacy of ITZ. After ingestion, the main area for ITZ absorption could be from small intestine. Through the incorporation of ITZ via SEMCs, the absorption of ITZ expressively increased. Thus, improving the absorption rate of ITZ in the intestine may increase the bioavailability of ITZ.

3.10. Bioavailability and pharmacokinetics

The pharmacokinetic parameters of pure ITZ and KMG6 SEMCs after single oral dose in rats blood plasma were shown in Table 3. The C_{max} of crystalline ITZ and KMG6 was found 0.039 μg/mL and 0.544 μg/mL respectively ($P < 0.05$). The area under curve (AUC) of crystalline ITZ was observed to be 0.356 μg/mL/h and 0.6731 μg/mL/h for KMG6 ($P < 0.05$). A significant increase in AUC supported an enhancement in ITZ absorption through SEMCs. The ITZ was metabolized into its active metabolite; hydroxyitraconazole, in GIT and liver thus AUC of hydroxyitraconazole was also determined and a significant enhancement in AUC of hydroxyitraconazole was found. The T_{max} of KMG6 was found to be (4 h) that was almost half as compared to crystalline ITZ (8 h) ($P < 0.05$). Moreover, the bioavailability of KMG6 was about 14 times superior to that of pure ITZ (Fig. 8).

C_{max}, T_{max}, AUC of ITZ and HITZ are shown in Table 2. A significant statistical difference ($P < 0.05$) within pharmacokinetic variables of pure ITZ and ITZ micelles is found.

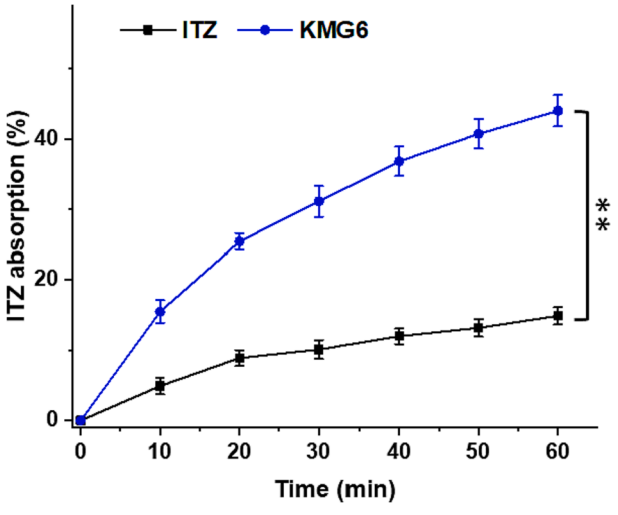

Fig. 7. *Ex vivo* absorption of KGM6 and ITZ. Data are expressed as a mean ± SD. ** $P < 0.001$ value indicating statistical difference.

Table 3
Pharmacokinetic parameters for the crystalline ITZ and SEMCs formulation.

Pharmacokinetic Parameters of ITZ		
Pharmacokinetic Parameters	**Crystalline ITZ**	**KMG6**
C_{max} (ng/mL) ITZ	39.1 ± 3.18	544.2 ± 5.61
C_{max} (ng/mL) HITZ	102.6 ± 4.22	1294.8 ± 3.01
T_{max} (h) ITZ	7 ± 1	4 ± 1
T_{max} (h) HITZ	7 ± 1	3 ± 1
AUC_{0-24} (ng/mL/h) ITZ	356 ± 21.31	6731 ± 23.09
AUC_{0-24} (ng/mL/h) HITZ	688 ± 26.51	9284 ± 21.06

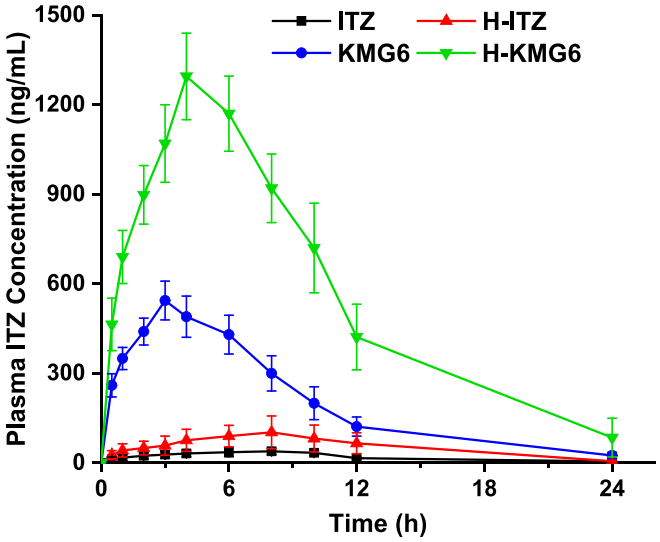

Fig. 8. Plasma concentration time curve following administration of single oral dose of ITZ, hydroxyitraconazole (H-ITZ), KMG6 and hydroxy-KMG6 (H-KMG6) SEMCs via oral route (average ± SD, n = 6).

The *in-vivo* results showed a significant enhancement in ITZ's oral bioavailability through the developed micelles ($P < 0.05$). The pharmacokinetic profile of KMG6 displayed a 14-fold increase in C_{max} and about 18-fold increase in AUC. The increase in bioavailability might be induced by the enhanced drug absorption in the gastrointestinal tract (Stewart et al., 2017). The increase in absorption may be due to an improvement in the surface area and dissolution rate by SEMCs in the GIT (Nicolas et al., 2017). The presence of Gelucire-44/14 in SEMCs is the main reason of absorption enhancement because drug was released in sustain manner and thus provided sufficient residence time to micelles for absorption (Jadhav et al., 2018). The underlying absorption mechanism of ITZ is due to the intensive self-emulsification properties of Gelucire-44/14 (Shin et al., 2019). Gelucire-44/14 reduces the micelle size of drug and hence increases the absorption and bioavailability (Ochiuz et al., 2016). All in all, the oral bioavailability was increased due to improved dissolution and high absorption of ITZ through Gelucire SEMCs.

4. Conclusion

The research study determined that this strategy could be useful to augment the oral bioavailability of ITZ and treat fungal infections. The Gelucire-44/44 micelles formulated through kneading technique enhanced the solubility and dissolution rate of ITZ compared to other methods. The Gelucire-44/14 micelles successfully improved the ITZ bioavailability. Moreover, KMG6 SEMCs showed better results compared to all other formulations prepared through melt-emulsification and solvent evaporation method. The findings of in-

vitro dissolution tests, DSC and PXRD supported the stable and amorphous MCs. In-vivo experiments presented an improved oral bioavailability of KMG6 SEMCs. The Gelucire-44/14 and ITZ showed the distinguished results of solubility and dissolution enhancement when combine in ratio of 10: 1. Therefore, Gelucire-44/14 micelles provides a suitable vehicle to increase the solubility, dissolution rate and oral bioavailability of ITZ.

5. Ethics approval and consent to participate

This study was approved by the Human Ethics Committee and the Research Ethics Committee of Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government of Faisalabad University College (GCUF), Pakistan for animal studies (S/No.19668/09/19). And the study is reported in accordance with ARRIVE guidelines.

CRediT authorship contribution statement

Nayyer Islam: Investigation, Methodology, Validation, Data curation, Formal analysis. **Naveed Ullah Khan:** Investigation, Methodology, Validation, Data curation, Formal analysis. **Anam Razzaq:** Investigation, Methodology, Validation, Data curation, Formal analysis. **Zaheer Ullah Khan:** Software, Visualization, Data curation, Formal analysis. **Farid Menaa:** Software, Visualization, Data curation, Formal analysis. **Mohammad Y. Alfaifi:** Software, Visualization, Data curation, Formal analysis. **Serag Eldin I. Elbehairi:** Software, Visualization, Data curation, Formal analysis. **Haroon Iqbal:** Conceptualization. **Jiang Ni:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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