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Original Article

DEVELOPMENT AND EVALUATION OF ITRACONAZOLE SOLID DISPERSION GEL CUTANEOUS DELIVERY

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ABSTRACT

Objective: The objective of this research is to enhance the permeation of low bioavailable drugs with suitable dosage forms by utilizing various permeation enhancers.

Methods: Solid dispersions (SDs) were prepared by kneading, whereas physical mixtures (PM) were prepared by simple mixing with polymers PEG 6000 and PEG 20000 and evaluated for various physicochemical parameters. Optimized SDs were converted to gels using a variety of polymers and were evaluated for *in vitro* and *ex vivo* permeation studies.

Results: It was found that the percentage of drugs in SDs and PMs was within the limit. The dissolution of SDs and PMs was found to be the highest with PEG-6000 (99.78% within 240 min) compared to PEG 20000. The maximum drug release (92.9% within 8 h) was achieved with oleic acid in both *in vitro* and *ex vivo* permeation studies, as evidenced by the *in vitro* and *ex vivo* permeation studies. The developed formulations showed no incompatibility between drugs and excipients, as demonstrated by drug and excipient interaction studies.

Conclusion: The results that were observed confirmed that the itraconazole PEG-6000 gel developed has promising effects on desirable skin permeation.

Keywords: Permeation, Dissolution, Kneading, Physical mixture, Solid dispersion

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INTRODUCTION

Itraconazole (ITZ) is a triazole antifungal agent and cytochrome P450 3A4 isoenzyme inhibitor and it is indicated in the treatment of various fungal infections such as histoplasmosis, blastomycosis, aspergillosis, oesophageal candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis and onychomycosis respectively. It acts by inhibiting the synthesis of fungal cell membrane. On oral administration, ITZ has poor bioavailability (55%) due to its low aqueous solubility and poor dissolution rate [1, 2]. In the current market, three types of commercial products are available, which include oral Sporanox® capsules filled with sugar beads coated with the HPMC solid dispersion of ITZ, which are protected by a layer of PEG, and Sporianox® intravenous injection and oral solutions containing a solubilizing agent hydroxypropyl beta cyclodextrin (HP-β-CD). HP-β-CD, may give rise to toxicity issues when the amount of intake exceeds certain threshold level [3, 4]. Drug solubility is the key factor to develop a transdermal product to enhance the drug permeation through the skin. ITZ solubility limits its permeation; hence in the current research, we are proposing to developing dispersions by selecting suitable carriers. However, these dispersions may not have enough permeation as such so that theses can be converted into gels for easy permeation [5].

Many pharmaceutical techniques are available to improve the solubility of poorly soluble drugs either by altering drug particle size or reducing the drug crystallinity and improves wetting nature i.e., Micronization [6], Sonocrystallization [7], Complexation [8], salt formation [9], solubilizing agents [10, 11], solid dispersion [12, 13] etc. Based on the available literature to improve the solubility of ITZ, we have proposed to improve solubility by solid dispersion technique by PEGylation and converted into a suitable dosage form for dermal delivery to treat dermatitis. The main features of SDs are that they have capable to improve the solubility of poorly water drugs by reducing their particle size and resulting increase in surface area respectively [13]. To develop the solid dispersions, we have selected polyethylene glycol (PEG) as the carrier. It is a stable, hydrophilic substance, non-irritant to the skin and it acts as a permeation enhancer. In this study, an attempt was made to enhance the solubility and dissolution profile of ITZ by taking two grades of PEG (PEG 600 as low grade and PEG 20000 as a higher grade) in varying drug-polymer ratios and loading the optimized solid dispersion into a suitable gel base for dermal application to treat superficial fungal infections and eliminates the side effects associated with oral administration of ITZ [10-14].

Skin is the largest organ of the human body and controls the influx and efflux of substance through the stratum corneum, which is the first layer of the skin. The route of dermal drug delivery is an alternative route to the oral route of administration, especially for antifungal therapy. The dermal delivery offers more cutaneous drug absorption, avoiding drug transportation (Flux) across the deep skin layers. The dermal route of administration provides more drug retention on the skin and provide an effective cutaneous fungal therapy [15].

The objectives of the present investigation are to prepare solid dispersions of water-insoluble ITZ using polyethylene glycol (PEG) of low molecular weight (PEG 6000) and high molecular weight (PEG 20000) by varying drug-carrier ratios using kneading method in order to understand the effect of carrier concentration on the solubility and dissolution of ITZ. The optimized solid dispersions loading into gel bases using carbopol 940 and HPMC K4M. While optimizing the SD's loaded gels, we have selected five different chemical permeation enhancers, such as propylene glycol, dimethylsulfoxide (DMSO), tween 80, oleic acid and sodium deoxycholate, to know the impact of permeation of drug from gel base [15, 16].

MATERIALS AND METHODS

Materials

ITZ purchased from Sigma Aldrich Pvt Ltd India, Polyethylene glycol 6000 and 20000 were kindly gifted by Merck Pvt Ltd India, Carbopol 940 and HPMC K4M were kindly gifted by Colorcon Pvt Ltd India, Dimethyl sulfoxide, Tween 80, Oleic acid, Sodium Deoxycholate were purchased from Merck Pvt Ltd India.

Methods

Preparation of solid dispersions by kneading method

The solid dispersions were prepared by the kneading method. ITZ and PEG were taken at different ratios of 1:0.5, 1:1, 1:1.5, 1:2 and

1:2.5 using PEG 6000 (SD1 to SD5) and PEG 20,000 (SD6 to SD10). Initially, PEG was taken in a mortar and pestle and 30 ml of methanol was added to it and mixed uniformly. After adding drug, the mixture was kneaded for 30 min until a paste is formed. The obtained paste was placed in a CaCO3 dessicator for 24 h. The final solid mass is scraped off, crushed and pulverized. The mixture was processed through sieve no. 60 ASTM and stored in a dessicator, yielding a solid dispersion of 5 gm [17-19].

Preparation of physical mixtures

The physical mixtures of drug with PEG 6000 (PM1 to PM5) and PEG 20000 (PM6 to PM10) were prepared separately at different ratios of 1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5 by triturating the powder mix in motor and pestle for 3-5 min. The mixture was passed through sieve no. ≠60 ASTM and stored in $CaCO_3$ dessicator. A physical mix equivalent to 5g has been prepared [13, 14]. The compositions are illustrated in table 1.

Table 1: Formulation composition of SD's and PM's and their codes

S. No.	Formulations	Code
1	Drug: PEG 6000 (1:0.5)	SD1 and PM1
2	Drug: PEG 6000 (1:1)	SD2 and PM2
3	Drug: PEG 6000 (1:1.5)	SD3 and PM3
4	Drug: PEG 6000 (1:2)	SD4 and PM4
5	Drug: PEG 6000 (1:2.5)	SD5 and PM5
6	Drug: PEG 20000 (1:0.5)	SD6 and PM6
7	Drug: PEG 20000 (1:1)	SD7 and PM7
8	Drug: PEG 20000 (1:1.5)	SD8 and PM8
9	Drug: PEG 20000 (1:2)	SD9 and PM9
10	Drug: PEG 20000 (1:2.5)	SD10 and PM10

Evaluation of prepared solid dispersions

Estimation of drug content

Solid dispersion powder equivalent to 50 mg of ITZ was extracted with 10 ml of methanol and volume was made up to 50 ml with pH 6.8 phosphate buffer. Furthermore, it was diluted with pH 6.8 phosphate buffer and the absorbance was evaluated at 262 nm [20].

***In vitro* dissolution studies**

These studies were performed to know the % drug release of the formulations and to compare the rate of dissolution of solid dispersions with that of pure drug and physical mixtures. The test was conducted using a USP type II (paddle) apparatus. The SD's powder that was equivalent to 100 mg of drug was dispersed into the dissolution vessel that contained 900 ml of pH 6.8 phosphate buffer. The dissolution media were maintained at 37 °C±0.5 °C and paddled at 100 rpm. A sample of 5 ml withdrawn periodically by means of a syringe fitted with 0.45 µm prefilter (PVDF) and immediately replaced with 5 ml of fresh dissolution medium, which was maintained at the same temperature. The filtered samples were examined using a UV-visible spectrophotometer at 262 nm. The dissolution studies were performed for both SD's and PM's. The dissolution data was analyzed by drug release kinetics such as zero order, first order and drug release mechanism by higuchi diffusion and Korsmeyer-Peppas. The gels were loaded with the optimized solid dispersion using carbopol 940 and HPMC K4M as gel bases [21].

Preparation of solid dispersion-loaded gel bases

The selected polymers were taken and soaked in a pH 6.8 phosphate buffer for up to 24 h. 0.1N sodium hydroxide solution was added to the polymer base to neutralize the pH. Solid dispersion equivalent to 0.4% of drug was added and stirred well. Continuous stirring was used to add the necessary amounts of glycerin and methylparaben until a homogenous gel was obtained and stored in a suitable container [22]. The composition of gel bases loaded with solid dispersion is depicted in table 2.

Table 2: Formulation of solid dispersion-loaded gel bases

Ingredients	Carbopol gel (G1)	HPMC K4M gel (G2)
Drug amount in SD4 powder	40 mg	40 mg
Carbopol 940	400 mg	-
HPMC K4M	-	400 mg
Glycerin	0.4 ml	0.4 ml
Methylparaben	0.1 g	0.1 g
0.1 N Sodium Hydroxide	0.1 ml	0.1 ml
pH 6.8 phosphate buffer	9 ml	9 ml

Table 3: SD gel formulations with various permeation enhancers

Formulation codes	F1	F2	F3	F4	F5
Ingredients	Permeation enhancers				
	Propylene glycol	DMSO	Tween 80	Oleic acid	Sodium deoxycholate
Drug (mg)	40	40	40	40	40
Carbopol 940 (mg)	400	400	400	400	400
Propylene glycol (ml)	0.5	-	-	-	-
DMSO (ml)	-	0.5	-	-	-
Tween 80 (ml)	-	-	0.5	-	-
Oleic acid (ml)	-	-	-	0.5	-
Sodium deoxycholate(g)	-	-	-	-	0.5
Glycerin (ml)	0.4	0.4	0.4	0.4	0.4
Methyl paraben (g)	0.1	0.1	0.1	0.1	0.1
0.1N NaOH (ml)	0.1	0.1	0.1	0.1	0.1
pH 6.8 phosphate buffer (ml)	9	9	9	9	9

Formulation of gels with various permeation enhancers

Based on our laboratory trials, using 4% carbopol 940 as a gel base, the effect of various permeation enhancers such as propylene glycol, DMSO, tween 80, oleic acid and sodium deoxycholate on the permeation of drug from gel was studied. To complete its swelling, the carbopol 940 was immersed in a pH 6.8 phosphate buffer for 24 h. 0.1N sodium hydroxide was added to carbopol gel to neutralize it. Solid dispersion equivalent to 0.4% of the drug was added and stirred well. The required amounts of glycerin, methylparaben and permeation enhancers have been added, as indicated in table 3.

Evaluation of prepared gels

Physical appearance and homogeneity

The prepared ITZ gels were visually inspected for clarity, color, homogeneity, particulate and fiber presence after the gels were placed in the container [23].

Percentage yield

The weight of the container before and after filling it with gel was noted. In order to achieve a practical yield, the weight of the empty container was reduced from the weight of the container with gel [24]. The following equation was used to determine the percentage yield.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \text{X100}$$

Drug content

The test gel formulation was weighed, transferred to a 10 ml volumetric flask that contained 5 ml of methanol, and shaken for 15 min. The pH 6.8 phosphate buffer was used to make the volume up to 10 ml and then filtered. The solution was diluted again with pH 6.8 phosphate buffer, and the absorbance was determined to be 262 nm. The amount of drug in each formulation was calculated. The solution absorbance was measured using a UV spectrophotometer at 262 nm [20].

pH measurement

1 g of gel was dissolved in 10 ml of distilled water and stored for one hr. Then, the pH was determined by using a digital Elico pH meter. The pH measurements for each formulation were done in triplicate and the average values were calculated [23, 24].

Spreadability

A weighed quantity (500 mg) of prepared gel was placed within circle of 1 cm diameter pre-marked on a glass plate (10×5 cm), over which another glass plate (10×5 cm and 5.8±1g) was placed. The upper glass plate allowed a weight of 25 g to rest for 5 min. After 1 minute, the diameter of the spread gel circle was measured [23, 24].

Viscosity determination

A rotational Brookfield viscometer with a cone and plate structure with a spindle CP-52 was utilized to determine the viscosity of the prepared gel formulation at 25 2 °C.

***In vitro* drug release studies**

In vitro studies on drug release were carried out using a vertical Franz diffusion cell with a capacity of 25 ml in the receptor compartment. The diffusion cell has a synthetic cellophane membrane (grade 60) that was mounted between the donor and receptor compartments. The formulated gels were weighed up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with pH 6.8 phosphate buffer. The entire assembly was placed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred with magnetic beads at 600 rpm. The temperature was maintained at 37±2 °C. The aliquots of 1 ml were withdrawn at time interval of 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 were analyzed for drug content spectrophotometrically at 262 nm against blank. An equal volume of phosphate buffer was reconstituted in the receiving phase each time a sample was taken [23, 24].

***Ex vivo* study for the optimized gel formulation**

Preparation of rat skin

For the *ex vivo* studies, the skin of the rat was removed from the abdominal area of the albino rat. The hair on the abdominal area was thoroughly removed using depilatory cream and spatula. Cotton dipped in isopropyl alcohol (IPA) was used to clean the adhering subcutaneous fat and it was immediately kept in a phosphate buffer solution. After this step, the layer remained wrinkle-free, and then the skin was washed with distilled water.

***Ex vivo* permeation studies**

Ex vivo permeation experiments were conducted using Franz diffusion cells to excise rat skin for the optimized gel formulations. The skin was trimmed to the appropriate size and mounted on the diffusion cell such that the stratum corneum of the skin facing the donor cell and dermis facing the receiver cell. The pH 6.8 phosphate buffer was placed in the receptor compartment. The unit was placed on a magnetic stirrer and stirred magnetically using a 600 rpm magnetic cord placed in the receiving cell. Drug permeation studies were carried out for 5 h at 37±2 °C temperature. The aliquots of 1 ml withdrawn from the receptor compartment at predetermined time intervals of 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min and were replaced by the same volume of buffer. The samples were analyzed using spectrophotometry at 262 nm against blank. Flux (µg/cm²/h) was calculated from the following formula [23, 24].

$$\text{Flux} = \frac{\text{Amount permeated}}{\text{Surface area}} \text{X time}$$

Drug–excipient interaction studies by fourier transform infrared spectroscopy (FTIR)

Drug-excipient interaction plays an important role in the release of drugs from the formulation, among other things. There is always a possibility of drug polymer interaction in the formulation because of their intimate touch. FTIR spectroscopy is used in the present investigation to study the interaction between drugs and polymers. Infrared spectral analysis of pure samples of ITZ, polyethylene glycol 6000, carbopol, HPMC K4M, optimized solid dispersion formulation SD4 (1:2), Physical mixture of optimized formulation, carbopol gel and HPMC K4M gel were done using Fourier transform infrared spectrophotometer (Shimadzu model 8300). The IR spectra were conducted against the KBr background [20].

Table 4: Physicochemical properties of PM and SD

S. No.	Formulation code	Drug content (%)	Physical mixer code	Drug content (%)
1	SD1	98.00±0.003	PM1	99.87±0.006
2	SD2	97.56±0.004	PM2	98.68±0.002
3	SD3	96.56±0.011	PM3	98.88±0.004
4	SD4	98.25±0.005	PM4	97.01±0.008
5	SD5	97.43±0.009	PM5	96.76±0.006
6	SD6	96.89±0.019	PM6	98.99±0.002
7	SD7	97.25±0.009	PM7	99.37±0.006
8	SD8	95.29±0.008	PM8	94.58±0.004
9	SD9	95.82±0.006	PM9	97.55±0.002
10	SD10	94.38±0.002	PM10	98.28±0.011

Each value represents mean±SD (n=3)

RESULTS

In the current study, ITZ-solid dispersions were prepared by kneading using Polyethylene glycol 6000 and 20000. The gel was used to incorporate the optimized SD's for dermal delivery. The percentage of drugs was in the range of 94.38-98.25% for SDs and MPs, respectively. The maximum percentage of drug substance was found to be 98.25 0.005% in the S4 formulation. All the SD's were found to be within the range as per the USP limit, i.e. 90 to 110%, respectively. The percentage of drug content results are tabulated in table 4.

The percentage of drug release of the formulations was determined through *in vitro* dissolution studies of physical mixtures and solid dispersions. To compare the rate of dissolution of solid dispersions with that of pure drugs and physical mixtures, the samples were spectrophotometrically analyzed at 262 nm. The *in vitro* release profiles of various batches of solid dispersions and physical mixtures were demonstrated in (fig. 1a and b). Among all the prepared solid dispersions, SD4 shown greater drug release (99.78±0.06%) within 240 min due to higher solubility of the drug in the respective carrier. As compared with PEG 20,000 carrier, PEG 6,000 carrier had great impact on drug solubility as it was proven through drug release from its physical mixture.

In order to establish the order and mechanism of drug release, the experimental data was fitted to popular models viz., zero-order, first order, Higuchi and peppas equation. The 'r' values of SD4 and PM formulation are for zero-order (SD-0.911 and PM-0.881), first-order (SD-0.844 and PM-0.944), Higuchi diffusion (SD-0.976 and PM-0.921), Korsemeyer-Peppas (n value for SD-1.33 and PM-1.00) equations. SD4 has been incorporated to gels using carbopol 940 (G1) and HPMC K4M (G2). The permeation of gel was evaluated by examining the effects of various permeation enhancers such as propylene glycol (F1), DMSO (F2), tween 80 (F3), oleic acid (F4) and sodium deoxycholate (F5), respectively. The gels that were prepared were tested for their percentage yield, drug content, pH, homogeneity, spreadability, viscosity, and *in vitro* diffusion.

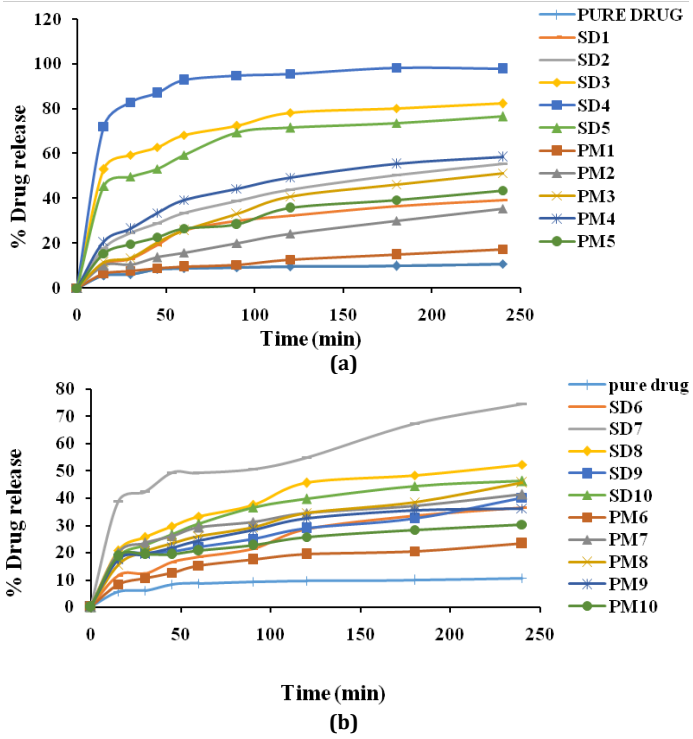

Fig. 1(a-b): Dissolution patterns for test formulations

All prepared solid dispersion gels were visually inspected for clarity, colour and consistency. The formulations that were observed are white viscous creamy preparations, except for the gel that contains oleic acid as the permeation enhancer, which is yellow in color. The gel formulations that were developed have a good homogeneous texture without any gritty particles or lumps. The solid dispersion incorporated gels produced a percentage yield of 94.59 98.88%. In the F2 formulation, the maximum yield was found to be 98%. The estimated drug content of the formulated gels was found to be within the official limits with a range of 95-98% gel. The determination of drug content also showed that the drug was distributed uniformly across the gel. The pH values for all developed formulations were in the range of 6-7, which is considered acceptable to avoid the potential for skin irritation during application. Spreading is very important because it shows the behavior of the gel emerging from the tube. According to table 5, the spreadability values show that all gels spread with a small amount of shear, except for HPMC gel. The viscosity of the gel formulations was determined using a rotational Brookfield viscometer with a cone and plate structure with spindle CP-52 at 25 2 °C.

Table 5: Physicochemical properties of test gels

Formulation code	Homogeneity	% yield	Drug content (%)*	pH	Spreadability (cm)*	Viscosity (cps)
Carbopol G1	Excellent	94.59	96±0.9	7.0±0.1	6.4±1.2	72928
HPMC K4M G2	Good	98.17	97±0.8	6.2±0.1	5.1±0.9	73817
F1	Excellent	96.99	97±0.4	6.6±0.2	6.8±1.1	70534
F2	Good	98.87	98±0.1	7.1±0.4	7.3±1.2	75111
F3	Good	98.41	97±0.6	6.5±0.4	7.5±1.2	71863
F4	Good	96.86	95±0.4	6.8±0.1	6.6±1.3	75954
F5	Good	97.24	96±0.2	7.0±0.1	6.8±1.4	71543

*Each value represents mean±SD (n=3)

The gels prepared with cellophane membrane (grade 60) were subjected to *in vitro* diffusion studies for 8 h. The maximum drug release of 83.89% and 71.5% for 8 h was displayed by carbopol 940 and HPMC K4M gels that were prepared without any permeation enhancer. The diffusion profiles of pure and loaded solid dispersion carbopol and HPMC K4M gels were presented in (fig. 2).

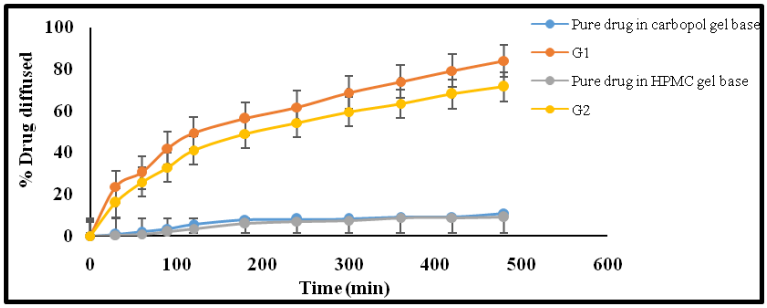

Fig. 2: Diffusion profiles of optimized ITZ solid dispersion incorporated gel bases. Data is expressed as mean±SD, n=3

To study the impact of different permeation amplifiers on drug release, propylene glycol (F1), DMSO (F2), tween 80 (F3), oleic acid (F4), and sodium deoxycholate (F5) were used to formulate the carbopol gels at a 5% concentration. The *in vitro* release profile of the drug from different formulations is depicted in (fig. 3). The diffusion profiles of these permeation enhancers were compared to formulations without penetration enhancers, indicating that these formulations produced better diffusion of the drug compared to formulations without penetration enhancers.

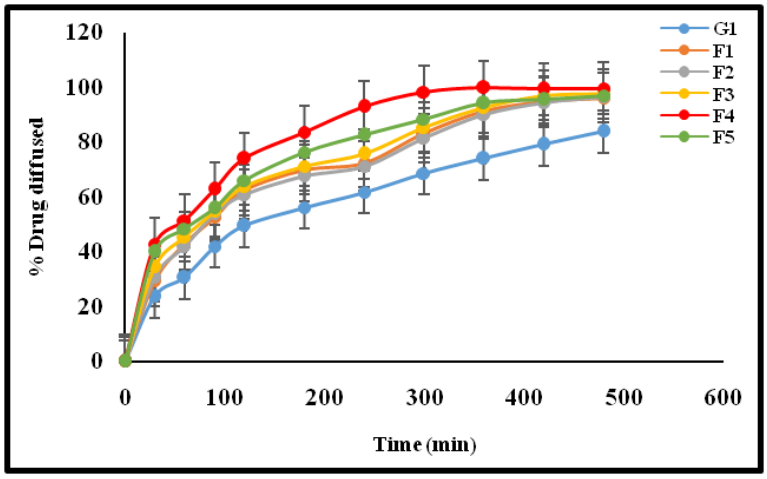

Fig. 3: Diffusion profiles of carbopol gels containing various permeation enhancers. Data are expressed as mean±SD, n=3

Based on the evaluated physicochemical parameters and *in vitro* diffusion study, the gel containing 5% oleic acid as a permeation enhancer was the most optimized among all the formulations. To determine the drug's permeation through the skin, an *ex vivo* study was conducted on the excised rat abdominal skin. Based on the *ex vivo* permeation studies, the quantity of medication was found to be comparatively less common from the skin than from the cellophane membrane. The rat abdominal skin was penetrated by the drug for 8 h and it was found to contain 92.9%. The drug release profiles of F4 *in vitro* and *ex vivo* were exhibited in (fig. 4).

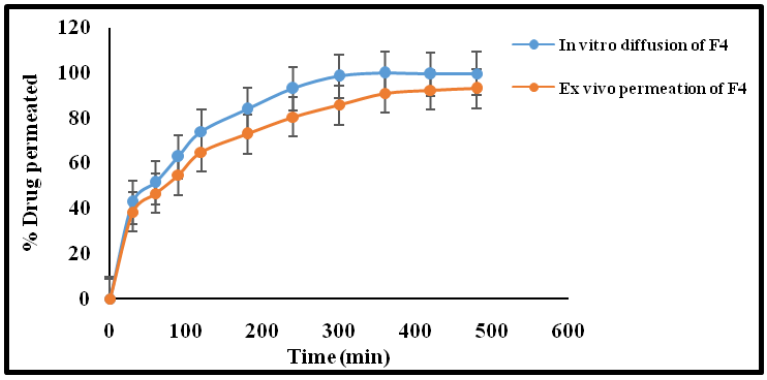

Fig. 4: Comparison of *in vitro* and *ex vivo* drug release of F4, data are expressed as mean±SD, n=3

The permeation of the drug for transdermal administration was described as the flux of the gel formulation. Moreover, flux can be utilized to predict the *ex vivo* and *in vivo* behavior of gel from other test formulations. Apart from all the test formulations, F4 flux was found to be high (82.85 µg/cm^2/h). Current research predicts that incorporating oleic acid as a permeation enhancer in gel formulation increases the diffusion of drug molecules in the deeper layers of the skin. The maximum flux was observed near the other permeation enhancers, including tween 80 (F3) and sodium deoxycholate (F5). The drug flux values from various test formulations were shown in table 6.

FTIR analysis

The FTIR spectra of the pure drug ITZ, SD4, PM4 and Carbopol gel were demonstrated in (fig. 5). The test formulations exhibit a FT-IR spectrum that is similar to that of pure ITZ. The pure ITZ peak is 3,461 cm^{-1}, belonging to the N=CH-N group. The spectrum of the test formulations had these peaks.

Table 6: Flux of drug from different gel formulations

Formulation code	Flux (µg/cm^2/h)
Carbopol G1	69.59±0.2
HPMC K4M G2	59.12±0.1
F1	79.87±0.2
F2	76.51±0.6
F3	81.04±0.1
F4	82.85±0.4
F5	80.44±0.2
F4 (*ex vivo)*	77.04±0.1

Each value represents mean±SD (n=3)

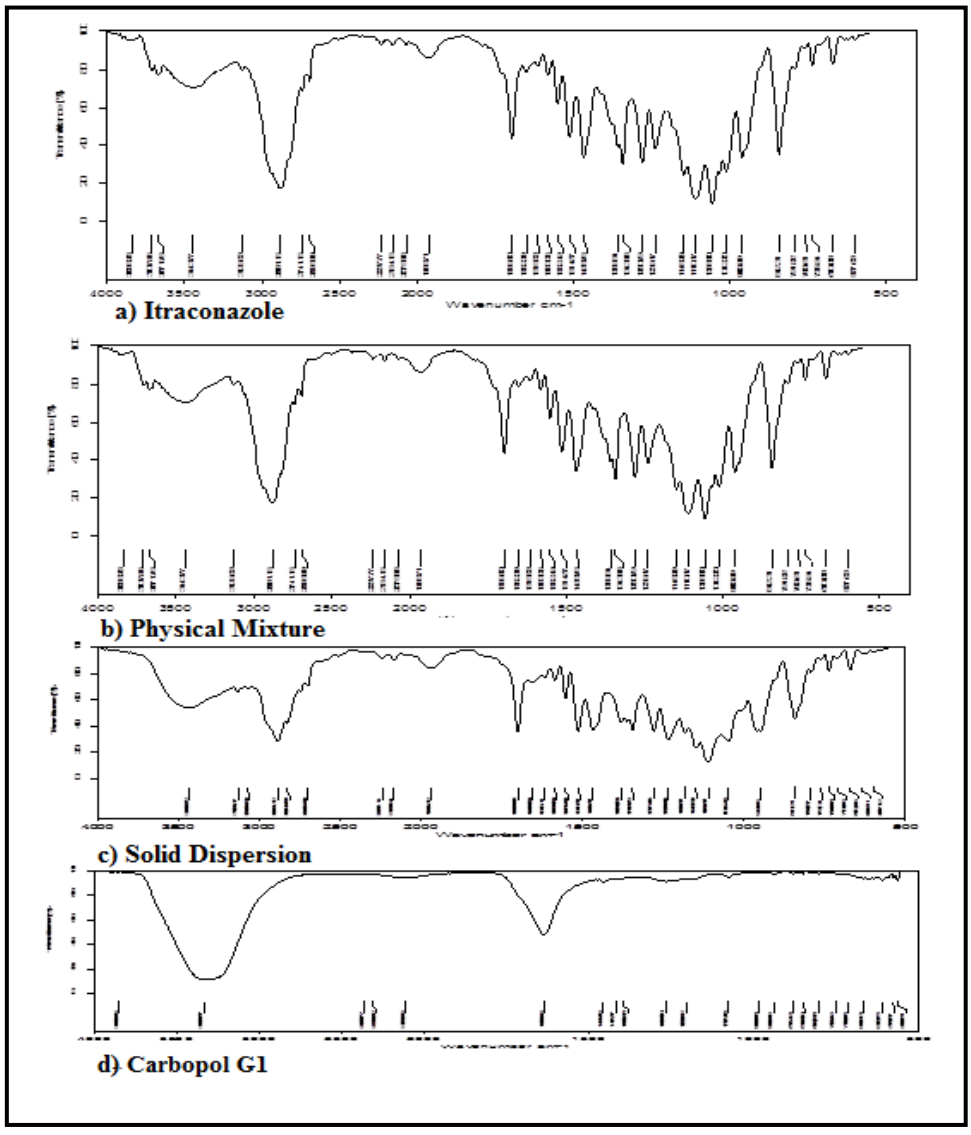

Fig. 5: FTIR spectra of ITZ, SD4, PM4 and carbopol G1

DISCUSSION

The current research aims to develop gel based on ITZ-loaded SDs to improve the solubility and permeability of ITZ. The SDs were made by kneading and the optimized SD formulation was added to gels using carbopol and HPMC polymers. The gels were made by mixing and the optimized SD formulation was added to them with carbopol and HPMC polymers. The initial estimation of ITZ concentrations was made by using UV spectroscopy at 262 nm, which followed Beer's law and was in the range of 4-12 g/ml. The degree of linear relationship correlation coefficient (r) was calculated and it was found to be 0.997, indicating a positive correlation between the concentration of ITZ and the corresponding absorbance values. ITZ-SD's were made with kneading, while ITZ-PM's were made with just

bending with PEG 6,000 and PEG 20,000 ratios. All of the formulations' percentage drug content was found to be within the USP limit, or 90 to 110%, respectively. Apart from all nine SDs, SD4 (drug: PEG 6000 1:2 ratio) batch had shown the highest drug content i.e., 98.25±0.005% respectively, whereas the physical mixture PM1 (drug: PEG 20,000 1:0.5 ratio) batch had shown highest drug content i.e., 99.87±0.006% respectively.

According to the *in vitro* drug release studies, SDs and PMs made from PEG 6000 had the highest percentage of drug release compared to PEG 20,000. The high molecular weight of PEG 20, 000 failed to improve the solubility as enhanced by PEG 6000. The high molecular weight of PEG 20000 results in a highly viscous solution around the drug particles, which can hinder dissolution to a certain level. The above statement is well correlated with previous works, Biswal *et al.* (2008) reported on the enhancement of the gliclazide dissolution rate by using solid dispersions with PEG 6000 and concluded that it has a high dissolution rate due to high solubilization effect [12]. In another study, Noushin Bolourchian *et al.* (2013) investigated the impact of PEG molecular weight on drug dissolution by comparing the dissolution profile of prepared SDs with three different molecular weights (6000, 12000 and 20000), respectively. Among these, PEG-12000 showed the highest dissolution of all of them, which may be due to the high viscosity of the solution around the particles, which reduces the drug dissolution and for PEG-6000, due to lower hydrophilicity, the drug dissolution may be delayed. Hence, they concluded that for maximum drug dissolution, molecular weight plays a key role and should be optimal [11]. Based on the dissolution profile, the SD4 dispersion was optimized for further studies. Based on the 'r' value of release kinetics, optimized formulation (SD4) followed the zero-order drug release and non-fiction mechanism of drug transport.

The 4% w/w of both carbopol 940 (G1) and HPMC K4M (G2) was chosen from the prepared concentrations. The homogeneity of the prepared formulations has been excellent for G1 and F1 formulations, respectively. The F3 formulation had more spreadability because tween 80 is a non-ionic surfactant and a more water-soluble permeation enhancer. F1 exhibited a low viscosity, while the remaining six gel formulations have similar viscosity values. This result is totally dependent on the nature of the gelling agent or permeation enhancer. The *in vitro* diffusion studies revealed that maximum drug permeation was found with G1 and G2 (without adding any permeation enhancer) within 8 h. Carbopol 940 (G1) had more viscoelastic properties than HPMC K4M (G2), and hence, it was easily diffused into the skin layers without adding any permeation enhancer. The SD formulations with gel bases show maximum drug permeation as compared with pure drugs with gel bases.

The *in vitro* drug release from gels containing penetration enhancers can be ranked in ascending order as follows: DMSO (F2)<propylene glycol (F1)<Tween 80 (F3)<sodium deoxycholate (F5)<oleic acid (F4). Among these formulations, oleic acid followed by sodium deoxycholate produced a significant increase in diffusion profile compared with the control gel, while dimethyl sulfoxide and propylene glycol only increased the diffusion slightly. At the end of 8 h, all the gel formulations showed a maximum drug release of 96%, whereas oleic acid gel (F4) attained 96% within a remarkable time of 5 h. The order of percentage drug release was: oleic acid>sodium deoxycholate>tween 80>propylene glycol>DMSO. The result indicates that oleic acid has the strongest penetration enhancement activity among the five penetration enhancers studied. Oleic acid has two types of permeation enhancement mechanisms: (a) lipid fluidization and (b) lipid phase separation. In the case of *ex vivo* studies, maximum drug permeation was observed with F4, and the flux across the rat skin was also higher.

CONCLUSION

In the present investigation, the enhancement of ITZ solubility is highly dependent on the type of PEG and their concentration ratios. Different ratios of SDs were prepared by the kneading method. The percentage of drug content in ITZ-SDs and PMs was found to be within the limit. The dissolution of ITZ-SDs and PMs was found to be higher in PEG-6000 compared to PEG-20000. Furthermore, the optimized SDs were converted into gels using carbopol 940 and HPMC K4M (G2). The prepared gel was evaluated along with different permeation enhancers. The gel formulation showed desirable physicochemical properties. The *in vitro* and *ex vivo* permeation studies conclude that the order of percentage drug release was oleic acid>sodium deoxycholate>tween 80>propylene glycol>DMSO, respectively. The drug-excipient interaction studies proved that no incompatibility was found among the drugs and excipients in the developed solid dispersion and their gel formulations. The results recommended that the developed ITZ-PEG-6000 gel has great potential for enhanced skin permeation of the drug.

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AUTHORS OF CONTRIBUTIONS

All authors have equally contributed

CONFLICT OF INTERESTS

All the authors in the manuscript declares that there is no conflict of interest for the current work.

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