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Research Article

Design And Characterisation Of Beta Cyclodextrin Tolnaftate Inclusion Complex For Topical Delivery

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ABSTRACT

This research aimed to improve the transdermal permeation of Tolnaftate, a poorly water-soluble drug that uses Cyclodextrin based novel drug delivery system in order to improve the solubility, penetration of drug. Phase solubility profile showed that the solubility of Tolnaftate was suggestively increased in the presence of β-Cyclodextrin (β-CD). Tolnaftate/β-CD inclusion complex was prepared by three different methods such as kneading, co-precipitation, freeze- drying method. This complex was confirmed using U.V visible spectroscopy, Differential scanning colorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR). This complex was used to prepare topical gel and compared with gel contains Tolnaftate only. The prepared gel was evaluated by measuring the physical appearance, pH, viscosity, washability, spreadability, drug content & in vitro, ex vivo studies on pig skin using Franz diffusion cell. The cumulative amount of drug that permeated after 480mins, flux, and coefficient of permeability was evaluated. Studies of stability were done over two months. According to the results, freeze dried products showed better complexation. The release profile revealed that the percentage cumulative drug release after 480 minutes was greater for suspension relative to gel formulation. Good linearity was observed for final gel formulation which fits well Higuchi's model (R2 > 0.99). The solution containing inclusion complex provided a significantly higher amount of cumulative permeation, steady state flux and permeability coefficient into the skin compared to pure drug, plain gel & gel containing tolnaftate/ β-CD inclusion complex. Stability studies showed that there was no major change in the characteristics indicated when compared to the original formulation

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The Results showed that inclusion complexation with β-Cyclodextrin improved the solubility of Tolnaftate, also enhance the permeability & extend tolnaftate's pharmacological effect.

INTRODUCTION

Tinea pedis is the widespread form of superficial dermatophytic infection in the developing world, affecting 10 per cent of the population at any given time[1]. The second half of the 20th century saw an increase in tinea pedis worldwide, as well as the clonal spread of the major causing agent T. rubrum. This is because of the development and also utilization of sports and fitness provision. Tinea pedis frequently spread through autoinoculation, results in other different conditions like tinea manuum, tinea inguinal, and tinea unguium. Unsuitable therapy can result in various bacterial infections also different allergic conditions [2]. Fungal infections are one of the most common diseases that affect the skin. Antifungal drugs both topical and oral types are used in treatment. The topical route is usually favoured due to the possibility of side effects of oral treatments. To develop a suitable dosage form, many variables must be considered: the flux of the drug through the skin, the retention of the dosage form on the skin surface, the reserve capability of the dosage form and the patients' approval of formulation[3]. Traditional products such as creams, ointments and gels can quickly become obsolete due to advancements in the formulation industry. Every formulation have their drawbacks thus, mild temporary stinging is observed in aerosols and creams, gels take a long time to penetrate so, require long time treatment for healing and it reduces patient consent[4]. So, to improve the penetration, solubility, and bio-availability and to minimize the side effect it could be formulated as liposome, ethosome, trasfersome and inclusion complex can be made with cyclodextrin. In the pharmaceutical industry, Cyclodextrins (CD) have mostly been used as complexing agents. The ability of CD to form inclusion complexes with a variety of organic/inorganic guest molecules of appropriate size and polarity results in a shift in the physicochemical properties of the guest. Inclusion complex with CD provides multiple benefits over conventional systems by reducing the problems associated with them, such as oxidative deterioration or enhancement of solubility of water-immiscible materials in aqueous liquids, damage by ultraviolet light, stability of volatile materials, and conversion of liquid substances into powders and removal of unpleasant odour or taste of materials[5]. Inclusion complexes are molecular compounds with the adduct configuration, in which one molecule (host molecule) surrounds the other. Inclusion complexation is achieved by the interaction between guest and CD, this causes partial or complete penetration of the guest molecule into the cavity of CD[6].

Gels are semisolid formulations made up of smaller inorganic or large organic particles interpenetrated by liquid meant to be spread on the skin surface. Most topical gels are made with organic polymers, such as carbomers, which offer the drug an esthetically appealing, translucent and sparkling appearance and are quickly washed with water off the skin. For the topical delivery of antifungal drug tolnaftate, in this present study gel of tolnaftate, β-cyclodextrin inclusion complex was prepared. Tolnaftate is an antifungal drug that is used topically to treat or prevent superficial dermatophyte infection, various forms of tinea and pityriasis Versicolor [7]. It works by preventing fungus growth and they are available in the form of cream, paste, spray, aerosol and gel. Tolnaftate is a selective, reversible, non-competitive thiocarbamate derivative that inhibits squalene epoxidase, which is an enzyme that leads to the biosynthesis of ergosterol[8]. Though it relieves discomfort from tinea pedis, tinea cruris, and tinea corporis, it also effectively avoids fungal symptoms including itching and burns[9]. Hence

in this study, an attempt has made to prepare a topical gel of tolnaftate β-cyclodextrin inclusion complex.

MATERIAL,EQUIPMENTS AND METHODS

Materials

Sr. No.	Material	Source
1	Tolnaftate	Yarrow chem products, Mumbai
2	β-Cyclodextrin	Hi Media Laboratories Pvt. Ltd
3	Methanol	Lobachemie, Mumbai
4	Disodium hydrogen phosphate	Lobachemie, Mumbai
5	Potassium dihydrogen Orthophosphate	Lobachemie, Mumbai
6	Carbopol 934	Lobachemie, Mumbai
7	Triethanolamine	Lobachemie, Mumbai

Equipments

Sr. No	Equipment	Model/Company
1	UV/Visible Spectrophotometer	Jasco-V-630
2	Electronic balance	DS-852G Essae-Teraoka
3	FTIR spectrophotometer	Alpha Bruker
4	Mechanical stirrer	REMI- 1MLH. Mumbai
5	pH-meter	Eutech instruments, Mumbai
6	Refrigerator	Whirlpool
7	Magnetic stirrer	1MLH, Remi equipment's
8	Lyophilized	EBT 10 N Esquire Biotech, Chennai, India
9	Brookfield viscometer	DV- 11+pro

Formulation studies

Identification of drugs Description/ appearan

It was observed visually to check whether it conforms to the specification given in IP.

Melting point

The melting point of tolnaftate was determined by using the Thiele tube method. The result was verified as per IP.

Fourier Transform Infrared Spectroscopy (FTIR) Studies

Fourier Transform Infrared Spectroscopy was performed using Shimadzu FTIR 8300 Spectrophotometer and the spectrum was recorded from 4000 to 400 cm-1.

UV spectroscopy

10mg of tolnaftate was dissolved in 50ml of methanol in a 100ml volumetric flask and made up the volume to 100ml with distilled water to get the concentration of 100µg/ml which was the stock solution. Then 10ml of the stock solution was withdrawn and transferred to 100ml and volume was made up to 100ml using methanol-water in a 1:1 ratio to obtain the second stock solution of concentration 10µg/ml.

Phase solubility studies

The influence of cyclodextrin on the solubility of tolnaftate was carried out according to the technique established by Higuchi and Connor. In 100ml volumetric bottles, an excess of tolnaftate (25mg) was added to 25ml of an aqueous solution containing different concentrations (2-16Mm) of β-CD. In a controlled shaking water pan, the obtained suspension was shaken for 7 days at 37 ± 0.5º C. aliquots were taken after 7 days of shaking

and filtered via a 0.45µm membrane filter. The quality of tolnaftate was measured using spectrophotometry at 257nm containing the same proportion of β-CD and each process was performed in triplicate. The solubility of tolnaftate in Mm was plotted against the concentrations of the CDs used to create phase solubility diagrams & coefficient of determination ($r2$) was find out [43].

Fig.no.1 Controlled shaking water bath

Formulation and characterization of tolnaftate- β-CD solid inclusion complex

Preparation of tolnaftate β-CD solid inclusion complex

The tolnaftate-β-CD solid inclusion complex was prepared by using different techniques, Physical mixtures were also prepared for the comparative studies, which are explained below in detail.

Kneading method

To the tolnaftate-β-CD physical mixture of 1:1 molar ratio, a small volume of water-ethanol (10/10 v/v) were added. Those mixtures were properly kneaded with pestle unless homogenous slurry obtained. Proceed with kneading till the solvent was completely removed. To get rid of traces of solvents and also for further use in gel formulation those kneaded products were kept desiccator [44]

Co-precipitation method

The inclusion complex of tolnaftate and β-CD was developed at a 1:1 molar ratio. Weighed quantity of tolnaftate was dissolved in 5ml acetone and added dropwise to an aqueous solution of β-CD (considered quantity of β-CD in 120ml of distilled water). That mixture was constantly stirred for about 6hours. The solvent was removed by using a water bath. The obtained product was kept in a desiccator to remove the traces of solvent. Stored in an airtight container for further use [45]

Freeze drying

Inclusion complex of tolnaftate and β- CD was prepared at a 1:1 molar ratio. The weighted quantity of tolnaftate was dissolved in 30 ml of methanol.CD was dissolved in 60ml of distilled water. The contents of the two beakers are then mixed. The obtained solution is kept in sonication for about 25minutes and solvent methanol was removed by using a water bath. The resultant solution was then frozen by placing it in the freezer for at least 24 hours to confirm that the solution is completely frozen. After that frozen solution was kept in a vacuum chamber where freeze-drying takes place [46] To verify the formation of complexes and show their potential configurations, characterization was carried out.

UV visible spectroscopy

The absorption spectra of Tolnaftate, β-CDs and Tolnaftate/β-CDs inclusion complex sample solution were measured using a UV-Visible spectrophotometer (Jasco-V-630) in the size range of 200-400nm (6)

Differential scanning calorimetry (DSC)

To validate the creation of inclusion complexes Differential scanning calorimetry thermograms were obtained for Tolnaftate, β-CD, physical mixture, and solid inclusion complex (prepared from kneading method, co-precipitation, and freeze-drying) using a DSC 60 instrument (Shimadzu®). The tests were performed in aluminum capsules holding about 2mg of the sample at temperatures ranging from 30 to 300º C, under a dynamic nitrogen environment (100ml/min), with the heating set at 10º C/min. Indium(purity>99 per cent) was used to calibrate the DSC- 60 earlier [47].

Fourier transform infrared spectroscopy (FTIR)

Bruker FT-IR spectrometer (alpha brukerInc Germany) was used to capture FT-IR spectra of CDs, free TNF, their physical mixtures, and their complexes (prepared from 3 different methods) over a scanning range of 4000-400 cm^{-1}. Each sample was cut onto 1mg fragments and immersed in 100mg of KBr [48].

Preparation of topical gel containing inclusion complex of tolnaftateβ- CD

1% Carbopol gel was formulated and to that freeze-dried inclusion complex of tolnaftate and β-CD were added. This was accomplished by dissolving 0.5gm of Carbopol 934 gel in 50 ml of distilled water and magnetically stirring it for 2 hours [49]. After that, the freeze-dried inclusion complex was weighed accordingly equivalent to 0.5 g of drug and then dissolved (10%w/w) in the smallest quantity of methanol or an aqueous solution consisting of the smallest amount of methanol (lidocaine article). The topical gel was prepared, by adding the suspension consisting of inclusion complex which has 0.5g of drug to 1% Carbopol gel at ratio 1:1(w/v) and stirred continuously by adding a small amount of triethanolamine to achieve the gel-like consistency [50].

Characterization of topical gel incorporated with solid inclusion complex Physical appearance

Visual inspection was used to determine the physical appearance of the formulation [51].

Measurement of pH

The pH of the gel was measured by dissolving the 1g of prepared gel in 20mL of purified water until a stable solution was obtained and then the pH value was measured using a digital pH meter [52].

Measurement of viscosity

Viscosity is the resistance of a solution to flow. As the viscosity value rises gel becomes thicker and resists flow, while the gel becomes thinner as the viscosity decreases. The Brookfield viscometer (DV-11 +pro D220) measured viscosity by selecting the spindle number T-94 and varying the rpm fitted with an F96 “t bar spindle” with speeds of 5, 10, 20, 50, 100 rpm [53].

Washability

The washability of the prepared gel was checked by rubbing a small amount on the hand and then wiping it off with water by not using soap [54].

Spreadability

The word spreadability refers to how much the gel extends on the skin surface after it has been applied. The gel’s spreadability was determined using a modified wooden block and glass slide apparatus. A specified amount of gel was mounted on a fixed glass slide, and a movable pan with a glass slide was added to it and positioned above the fixed glass slide for 5 minutes i.e., is sandwiching the gel between two glass slides. Spreadability was measured using the formula

$$S = M \times L / T$$

Where S = is the spreadability,

M = is the weight in the pan (attached to the upper slide),

L = is the length transferred by the glass slide and

T = reflects the time required to remove the slide entirely from each other [55] On this ground slide, an excess of gel (approximately 1gm) was weighed. The gel was then sandwiched between this slide and another glass slide with a predetermined ground slide length and fitted with the hook. To remove air and have a transparent gel film between slides, a 100gm weight was put on each slide for 5 minutes. The leftover gel in the corners was scraped away. Following that, a 30gm pull was applied to the top plate. The time (in seconds) taken by the top slide to cover 5cm using the string attached to the handle. A shorter time is guaranteed by better spreadability [56].

Fig.no.2 Instrument for testing Spreadability

RESULTS AND DISCUSSION

The related findings were collected based on the methods and are presented in the "Results" chapter below.

Pre formulation Studies

Under pre-formulation studies, identification of drugs, FTIR studies and U.V were performed.

Table 3 Identification of drug (Tolnaftate)

Studies	Method	Result
Description/Appearance	Visually observed	White crystalline powder
Taste	_	Tasteless
Oduor	_	Odorless
Melting point	Thele's tube method	112º C

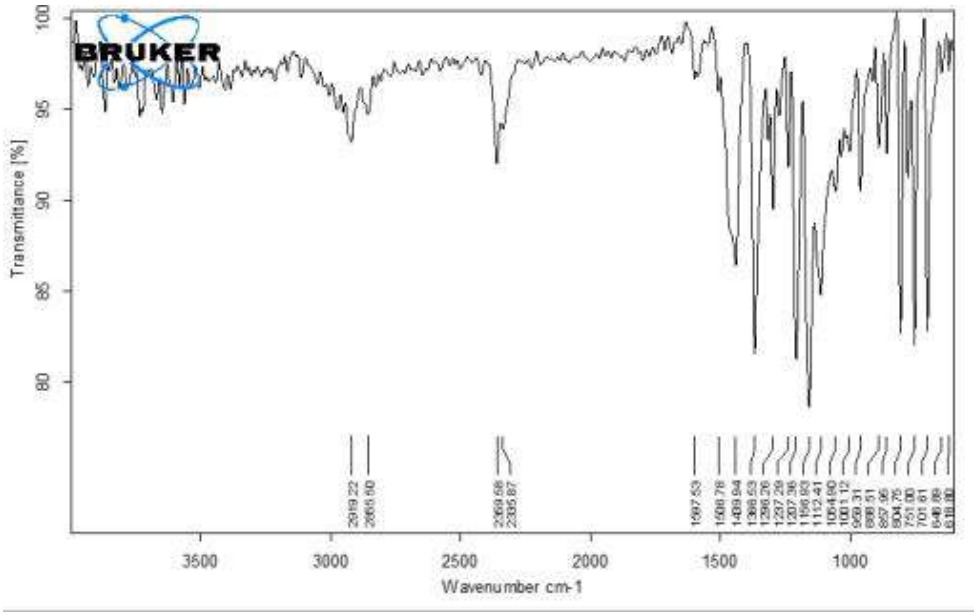


Fig 3 FTIR of tolnaftate

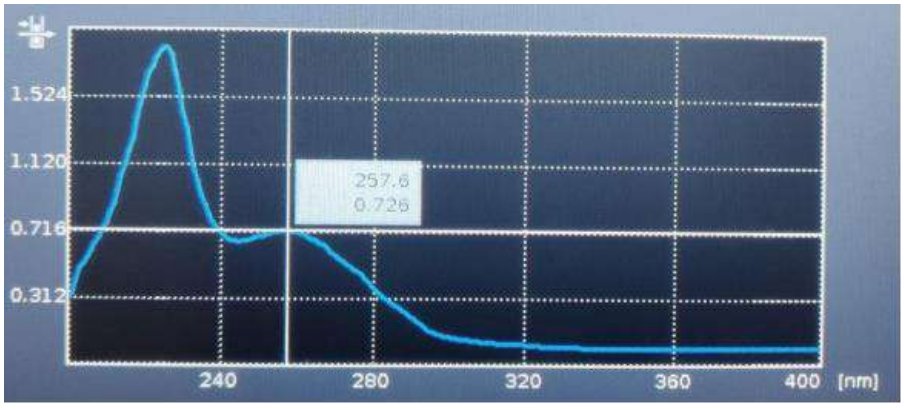


Fig 4 U. V Spectra of tolnaftate at 257nm

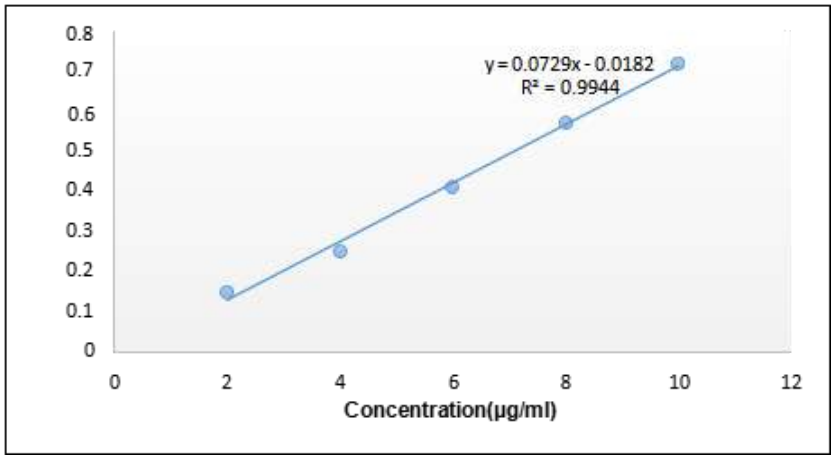
Analytical Methods

Calibration data of tolnaftate in methanol-water in 1:1 ratio

Absorbance values of different concentrations of tolnaftate in water and methanol mixture at 257 nm are given in Table 3.2.

Table 4 Calibration curve of the tolnaftate in methanol-water mixture at 257 nm

Sr No.	Concentration (µg/ml)	Absorbance ± SD
1	2	0.149 ± 0.0326
2	4	0.249 ± 0.0081
3	6	0.4106 ± 0.0184
4	8	0.5693 ± 0.0181
5	10	0.7176 ± 0.0073



Average of three determinants; SD = Standard Deviation

Fig. 5 Calibration curve of tolnaftate using a water-methanol mixture

Phase solubility studies

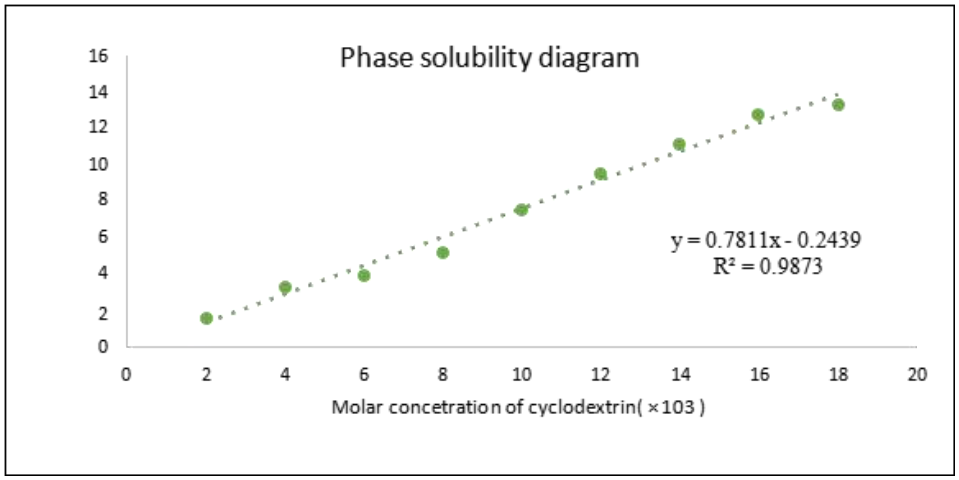


Fig 6 shows the phase solubility diagrams of tolnaftate with β- Cyclodextrin in distilled water at 37±0.5⁰ C.

Preparation and characterization of solid inclusion complex Formulation of solid inclusion complex

Solid inclusion complex containing tolnaftate was prepared according to the procedure mentioned in section 3.4.

a) Kneading method

b) Freeze-drying method

c) Co-precipitation method

Fig 7 Preparation of inclusion complex using different methods

Characterization of solid inclusion complex

U. V Visible Spectroscopy

The confirmation of the inclusion complex between tolnaftate and β- cyclodextrin is conducted using U.V Spectrophotometer (Jasco, V-630, Japan). The absorbanc Table 3.3 Absorbance obtained by U.V Visible Spectroscopy Fourier

Tolnaftate	257nm
β- cyclodextrin	Did not show any spectrum
Kneading method (1:1)	255nm
Co-precipitation method (1:1)	255.5nm
Freeze-drying method (1:1)	254nm

Transform Infrared Spectroscopy (FTIR) Studies obtained is mentioned in table 3.3 below The intermolecular interaction between the tolnaftate and β- Cyclodextrin in the inclusion complex is determined by FTIR spectra. FTIR spectra are shown in Fig 3.4.

Table 5 Major FTIR peaks of pure Tolnaftate and other different formulation

Co-precipitation method (1:1)	1643.41,1372.17,1296.77,1239.09,1151.21,1076.47,1023.08 ,997.06,855.44,805.96,753.76
Freeze-drying method (1:1)	1025.23,1421.10,1457.19,1542.18,1648.15,1697.84,1794.49 ,2382.00,2784.33,3114.05,3609.43,3801.07, 3958.02
Sample	**Major peaks (wave numbers cm^{-1})**
Pure drug	2925.62,1625.89,1606.80,1444.12,1367.81,1297.07,1238.42

	,1209.80,1156.01,1079.08,1027.27,888.65,804.88,751.76,702.35
β- Cyclodextrin	3316.55,1456.99,1370.38,1212.97,1156.02,1026.21,753.87
Kneading method (1:1)	1599.59,1370.03,1296.23,1211.66,1153.75,1024.70,890.40, 859.04,776.811,702.58

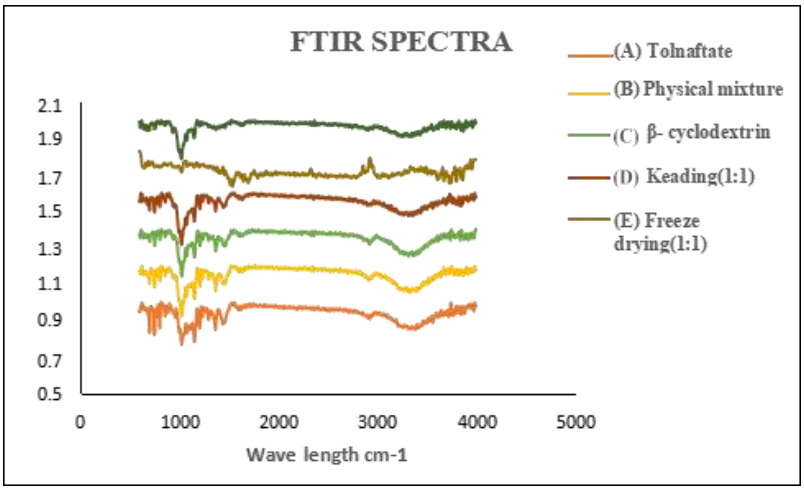


Fig 8 Comparative FTIR spectra of different formulation

Differential scanning calorimetry

The DSC findings for tolnaftate, β-Cyclodextrin, physical mixture, and inclusion complexes of three distinct procedures are shown in Fig 9

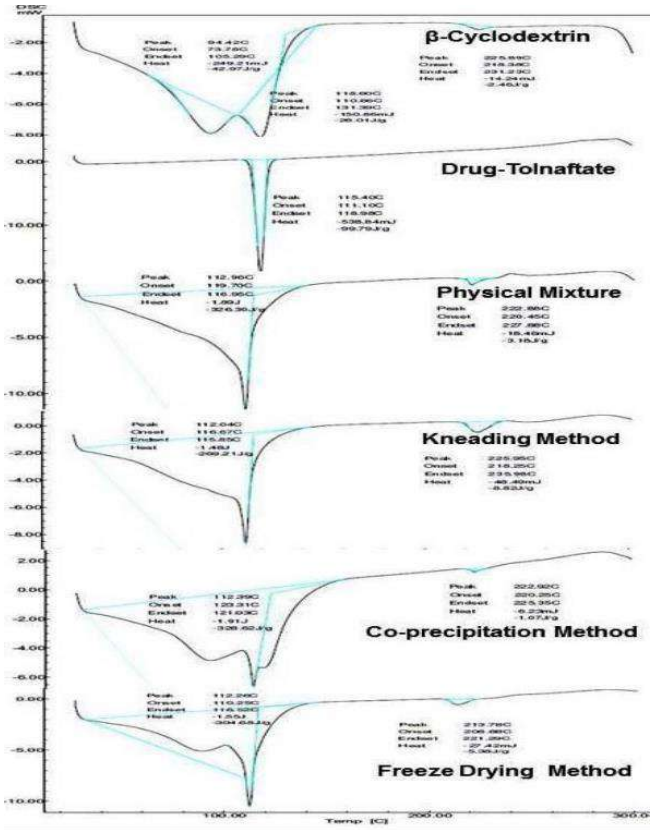


Fig 9 Thermograms of tolnaftate, β- Cyclodextrin, physical mixture and inclusion complexes obtained in three distinct ways

Formulation and Characterization of a topical gel containing solid inclusion complex

Using Carbopol as the polymer, a topical gel containing freeze-dried inclusion complex (GIC) and also conventional gel was created. The conventional gel was found to be white in colour whereas gel consisting of inclusion complex was found to be transparent, smooth, devoid of grittiness and homogeneous. The pH, viscosity, spreadability, washability, and drug contents were all measured. Tables 3.5 and 3.6 show the final findings.

Fig 10 Conventional gel and Gel using freeze-dried inclusion complex

Table 6 Results obtained from characterisation parameters

Formulation	Measurement of pH	Washability	Spreadability (g/cm^2)	%Drug content
Conventional Gel	4.9	Good	17.9	85.03%
GIC	5.0	Good	14.7	88.07%

CONCLUSIONS

In the present study, a 1:1 molar ratio of solid inclusion complex between tolnaftate & β-CD was successfully prepared. Solid inclusion complex was formulated using three different methods kneading method, co-precipitation method & freeze-drying method respectively. Later this inclusion complex was characterised by using Ultraviolet spectroscopy (U.V), Fourier transform infrared spectroscopy (FTIR) and Differential scanning colourimetry (DSC). After characterisation, it was found that the freeze-drying method showed better complexation comparing to the other two methods. So, a freeze-dried inclusion complex was used for further studies. This freeze-dried inclusion complex was then incorporated into 1% Carbopol 934 gel. Tolnaftate is a synthetic thiocarbamate used as an anti-fungal agent. It belongs to biopharmaceutical class IV drug which is water-insoluble also has the least permeability. A topical gel was prepared using a solid inclusion complex of tolnaftate and β-cyclodextrin in compliance to provide an effective way of improving the drug's solubility, penetration enhancing & delivery of the drug topically. The solid inclusion complex of drug tolnaftate & β- cyclodextrin had shown its effectiveness in improving the solubility of the drug also, the gel formulation comprising solid inclusion complex had shown its usefulness to increase its penetration through the skin, thus decreasing the amount of dose administered and

the resulting side effects. Sustained release of the drug may therefore be accomplished over an extended period. Based on the results and discussions, the following conclusions have been drawn.

- The U.V absorption spectrum of tolnaftate in the water-methanol mixture in 1:1 ratio showed a peak at 257nm.
- FTIR shows all referral major peaks were present.
- The influence of cyclodextrin on the solubility of tolnaftate was carried out by using phase solubility studies.
- Phase solubility diagrams of tolnaftate with β-CD in distilled water showed Because of the formation of inclusion complex tolnaftate solubility increased when the quantity of CD raised. coefficient of determination ($r2$) was found to be 0.9873.
- The solid inclusion complex was prepared by using kneading, co- precipitation & freeze-drying method in a 1:1 molar ratio.
- UV visible spectroscopy, Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) confirmed the formation of inclusion complex and in that freeze-dried inclusion complex showed better complexation.
- The freeze-dried inclusion complex was incorporated into Carbopol gel & the gel formulation was found to be smooth and transparent.
- The pH of gel formulation was found to be in the range of 4.8-5.1 which is closer to the skin pH.
- The rheological properties of the gels within reasonable limits for topical preparation were noticed.
- The release of ex vivo drugs was observed to be slower in comparison.
- .The solution consisting of inclusion complex shows a significant increase in the steady-state flux and permeability coefficients to 3 times than the drug solution.
- The gel formulation showed satisfactory antifungal activity was similar to the standard Tinaderm.
- Based on results obtained for stability tests, the formulation was found to be stable under cool storage conditions in compliance with ICH guidelines may be inferred.

The present study highlights a strategy of improving the drug's solubility, bio- availability & to minimise the side effects by forming a solid inclusion complex with β-cyclodextrin & incorporating them into a gel. By using three different methods solid inclusion complex was produced in which freeze-dried complex was found to be the best. Thus, the current study proved that solid inclusion complex loaded gel was better as compared to that of conventional gel for the treatment of Tinea pedis

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