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Research Article

Formulation And Evalution Of Nanoparticles Loaded Topical Drug Delivery System Of An Anti-Fungal Drug

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ABSTRACT

Ketoconazole is a synthetic antifungal agent belonging to the group of triazole. Itis one of the commonly used antifungal agents for the treatment of local and systemic fungal infections. It is a BCS class II drug (low solubility and high permeability). On oral administration, its bioavailability is low due to poor aqueous solubility. The objective of this work is to prepare Ketoconazole nanoparticles and then incorporated into the freshly prepared gel for transdermal delivery, because patients with Skin infection such as athlete's foot, jock itch, ringworm, and certain kinds of dandruff. The dose is given at a higher level due to its low bioavailability. The nanoparticle transdermal approach was selected to provide prolonged release of Ketoconazole to the affected area that increase bioavailability, reduce the side effects, reduce large doses and increase the therapeutic efficacy

METHOD AND RESULT

Preformulation study was carried out which includes drug estimation method, drug excipients compatibility study and melting point determination. The drug estimation was found to be linear between 50 to 500µg/ml and the melting point was found to be 1460C. The FT-IR spectrum of drug-excipient was found to be satisfactory, which indicated that excipients were compatible. Ketoconazole nanoparticles were prepared by nanoprecipitation method with different ratio of drug to polymer (1:1, 1:2 and 1:3) and stabilizer (Poloxamer 188) (0.1%, 0.425% and 75%). Among the nine formulations F7 was selected as optimized formulation. The particle size, polydispersity index, Zeta

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potential, % Entrapment efficiency and % drug content of all the formulations were found in the range of 48.5 to 83.6 nm, 0.127 to 0.244, -20.1 to -35.7 mv, 85.64% to 93.78% and 57% to 89.38%.. From the in-vitro drug release study, it was revealed that sustained release of same formulation last up to 12 hours.

INTRODUCTION

Nanoparticles are one of the forms of novel drug delivery systems having the capability to release the drug at an optimum rate at the desired site of action. Nano particular formulations provide the liberty to use a wide range of polymers like synthetic, natural, biodegradable and non-biodegradable polymers.1 The size range of the nanoparticles is 1 to 1000nm, but for the purpose of drug delivery, nanoparticles in the range of 50 – 500 nm are acceptable depending on the route of administration Nanoparticles have become one of the most active areas of research in the field of drug delivery due to their ability to deliver the drugs to the right place, at appropriate times, and in the right dosage and in the right dosage. A wide sort of nanoparticles composed of a variety of materials including lipids, polymers and inorganic materials are developed leading to delivery systems that change in their physicochemical properties and their applications. The advantages of nano- encapsulation include the enhanced stability of labile drugs, controlled drug release and an enhanced drug bioavailability owing to the fact that particles in the nano-size range are efficient in crossing permeability barriers. Nanomedicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nanoscale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. Nanomaterials in improving both the efficacy of novel and old drugs (e.g., natural products) and selective diagnosis through disease marker molecules. Depending upon the tactic of preparation, nanoparticles, nanospheres or nano capsules are often obtained``

1. **Nanospheres:**

These have a monolithic type system in (matrix) in which drugs are either adsorbed or dispersed

2. **Nano capsules:**

The system in which the drug is confined to a cavity surrounded by a unique polymer membrane is known as nano capsules Method of preparation of nanoparticles: Several methods have been developed during the last two decades for the preparation of Polymeric nanoparticles. These techniques are classified as follows:

1. Dispersion of preformed polymers.
2. Polymerization of monomers.
3. Ionic gelation or coacervation of hydrophilic polymers.

Nanoparticles obtained from dispersion of preformed polymer: Dispersion of drug in preformed polymers is a common technique used to prepare bio degradable nanoparticles from poly (lactic acid) (PLA), poly (D, L-glycolide) (PLG), poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA). These can be accomplished by different methods described below.

EX: Solvent evaporation method: In this method, polymer solutions are prepared in volatile organic solvents (e.g. dichloromethane and chloroform) and emulsions are formulated by high-speed homogenization or ultrasonication and converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions (e.g. oil-in water (o/w)) or double-emulsions, (e.g. (Water in-oil)-in-water (w/o)/w).

MATERIALS AND METHODS

MATERIALS:

The materials used in the present work are as follows:

Table no:1 List of Materials used and Manufacturers

Sr. No	MATERIALS
1.	Ketoconazole
2.	Eudragit L 100
3.	Ethanol
4.	Methanol
5.	Poloxamer 188
6.	Carbopol 934
7.	Carbopol 940
8.	Glycerin
9.	Propylene Glycol
10.	Triethanolamine (TEA)
11.	Methyl paraben
12.	Propyl paraben
13.	Sodium hydroxide
14.	Potassium dihydrogen phosphate

EQUIPMENT:

The equipment used in the present work as a follow:

Table: 2 List of Instruments Used and Manufacturers

Sr. No.	INSTRUMENTS	MANUFACTURER
1.	Electronic Weighing Balance (0.0001mg to 200g)	Essae-Teraoka Ltd.
2.	UV-Vis Spectrophotometer (UV-1800)	Shimadzu, Japan
3.	FTIR 1700S Spectrophotometer	Shimadzu, Japan
4.	Nano particle Analyzer SZ-100	HORIBA Scientific.
5.	Melting Point Apparatus	SETCO Ltd, Bangalore.
6.	Franz diffusion cell	Sci. Work, Peenya 1st stage, Bangalore.
7.	Brookfield Digital viscometer	Brookfield Digital viscometer
8.	Ultra sonicator	PCI Analytics.
9.	Rotary vacuum evaporator	Digisun Electronics, Hyderabad.
10.	Digital pH Meter 7007	Digisun Electronics, Hyderabad.
11.	Centrifuge	Eppendorf Centrifuge 5430R.
12.	Scanning electron microscope	Zeist International, IISc Bangalore.
13.	Melting Point Apparatus	SETCO Ltd, Bangalore.
14.	Magnetic Stirrer	Remi Pvt. Ltd.
15.	Stability Chamber	Analytical pharmaceutical stability chamber, Bangalore

METHODS:

Preformulation studies:

Determination of λmax and Standard graph preparation:

Accurately weighed 50 mg of Ketoconazole is weighed and transferred into a 50ml volumetric flask, methanol was added to dissolve the drug, then the volume is made up to 50 ml, then from this solution 1 ml is taken and transferred into a 100 ml volumetric flask and made upto100 ml with PH 7.4 Phosphate buffer to get 10 µg/ml solution. Then the prepared solution was scanned in the range of 200 to 400 nm by using pH 7.4 Phosphate buffer as a blank. The λmax was found to be 296 nm.

Preparation of Ketoconazole calibration curve:

50 mg of Ketoconazole was weighed accurately and carefully transferred in 100 ml volumetric flask and dissolved in methanol and the volume is made up to the mark with methanol (500µg/ml). From this solution aliquots of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5ml was pipetted out and diluted to 10ml to get 50, 100, 150, 200, 250, 300, 350, 400, 450 and 500µg/ml by using pH 7.4 phosphate buffer. pH 7.4 phosphate buffer is used as a blank solution. Standard curve was prepared by plotting absorbance vs concentration at 296 nm using UV-Visible spectrophotometer.

Determination of melting point:

Determination of melting point gives an idea about purity of the drug. Melting point of Ketoconazole was determined by capillary method. Fine powder of Ketoconazole was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to assembly was kept on heating and temperature was allowed to increase gradually. Temperature at which the powder melts was noticed. thermometer and the thermometer was placed in tube containing liquid paraffin. The assembly was kept on heating and temperature was allowed to increase gradually. Temperature at which the powder melts was noticed.

Drug-excipients Compatibility study:

A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of more importance.

FT-IR:

The compatibility of the drugs with the excipients was determined by subjecting the physical mixture of the drug and the polymers of the formulation to infrared absorption spectral analysis (FT-IR). Any change in the chemical composition of the drugs after combining it with the polymer was investigated with I.R spectral analysis.

Procedure:

The Ketoconazole nanoparticles were prepared by a nanoprecipitation method. The formulation plan is shown in. Ketoconazole 10mg and Eudragit L 100 10mg, 20mg and 30mg were dissolved in 3ml Ethanol. The internal organic phase solutions were slowly injected at the rate of (1ml/minute) into 20ml of the external aqueous solution containing stabilizing agent (Poloxamer 188) at various concentrations such as (0.1, 0.4 and 0.75% w/v) in double distilled water, and the mixtures were then stirred at 500 rpm for 4 hr at room temperature. Internal organic phase solutions are always composed of solvents, making the drug and Eudragit L 100 soluble completely, and the external aqueous phase comprises aqueous solution, sometimes with or without surfactant in it. The surfactant can penetrate into the Ketoconazole nanoparticles during the nanoprecipitation process to form a stable nanoparticle. The aqueous phase immediately turned into milky bluish opalescence due to the formation of the nanoparticle suspension. Ethanol was completely removed by rotary vacuum evaporation using a water bath maintained at 32°C. The Ketoconazole nanoparticles formed were isolated, washed three times with distilled water, and freeze-dried.

Table no 3 Formulation chart of Ketoconazole nanoparticles (F1- F9)

Formulation Code	Drug: Eudragit L100	Ethanol (ml)	Poloxamer 188 (%)	Distilled water (ml)	Run
F1	1:1	3	0.1	20	2
F2	1:2	3	0.1	20	1
F3	1:3	3	0.1	20	3

F4	1:1	3	0.425	20	8
F5	1:2	3	0.435	20	6
F6	1:3	3	0.425	20	5
F7	1:1	3	0.75	20	9
F8	1:2	3	0.75	20	7
F9	1:3	3	0.75	20	4

Preparation of nano particle-based gel:

Six formulations of Ketoconazole gel were prepared using carbopol 934 & carbopol 940 as a gelling agent with different ratios of 0.3%, 0.5% and 0.7 %. Specified quantity of carbopol 934 and carbopol 940 were soaked overnight as mentioned in the formulation chart shown in Table 4.5. Ketoconazole nanoparticle slurry was prepared by dissolving in a mixture of propylene glycol (penetration enhancer) & glycerine (moistening agent) under continuous stirring. To the carbopol slurry specified quantity of Ketoconazole nanoparticles slurry was slowly added with stirring. Propylene glycol (20 % w/w), Glycerine (10% w/v), Methyl paraben (0.03% w/w) & Propyl paraben (0.01 % w/w) were added slowly with continuous stirring until the homogenous gel was formed. The gel was neutralized with sufficient quantity of Triethanolamine and final volume was made to 50 ml with distilled water.

Table no 4 Formulation chart of Ketoconazole nanoparticles gel.

Formulation code	G1	G2	G3	G4	G5	G6
Ketoconazole nanoparticles equivalent to Ketoconazole=	250mg	250mg	250mg	250mg	250mg	250mg
Carbopol934 (gm)	0.3	0.5	0.7	0	0	0
Carbopol940 (gm)	0	0	0	0.3	0.5	0.7
Ethanol(ml)	2	2	2	2	2	2
Propylene glycol(%)	20	20	20	20	20	20
Glycerin (%)	10	10	10	10	10	10
Methylparaben(%)	0.03	0.03	0.03	0.03	0.03	0.03
Propylparaben(%)	0.01	0.01	0.01	0.01	0.01	0.01
Triethanolamine(ml)	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water	q. s to make 50gm	q. s to make 50gm	q. s to make 50gm	q.s to make 50gm	q. s to make 50gm	q. s to make 50gm

Evaluation of gel

Topical gel evaluated for following characters:

Measurement of pH:

The pH of gel formulations was determined by digital pH meter. 1g of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each Formulation is done in triplicate and average values are calculated.

Drug content studies:

Accurately weighed 1 g of gel was transferred into 10 ml volumetric flask containing 5 ml of saline phosphate buffer (pH 7.4) and stirred for 30 min followed by sonication. The volume was made up to 10 ml with saline phosphate buffer (pH 7.4). 5 ml of the above solution was further diluted to 10 ml with saline phosphate buffer (PH 7.4). The absorbance was measured using Shimadzu 1800 UV Visible spectrophotometer at 296 nm.

Viscosity measurement:

Viscosity of the gel was determined by using Brookfield viscometer. Accurately weighed 25gm of Ketoconazole gel was transferred to 50 ml glass beaker. Spindle no 6 was selected and it is immersed into the gel. The viscometer was operated at 10 rpm until the reading gets stabilized and reading was noted in centipoises. It was noted

from the literature that the formulations after gelling should have a viscosity of 50 – 50,000 cps.

In-vitro diffusion studies:

In-vitro diffusion study was carried out in a Franz diffusion cell using cellophane membrane which is soaked overnight in distilled water. The membrane was tied to the donor compartment and mounted on the reservoir compartment of Franz diffusion cell containing 150 ml of pH 7.4 phosphate buffer. 1 gm of Ketoconazole gel was placed over the cellophane membrane of donor compartment. Whole set was placed on the magnetic stirrer. The study was carried out at 37±0. 5ºC and100 rpm for 12h. Samples were withdrawn from the sampling port of reservoir compartment at regular intervals and absorbance was measured using Shimadzu 1800 UV visible spectrophotometer at 296 nm.

Stability:

Stability testing of drug product is part of drug discovery and ends with the commercial product, to assess the drug and formulation stability, stability studies were done. The stability study was carried out for the optimized formulation (G5), subjecting to a temperature of 40 ± 2°C and 75 ± 5% RH and 4°C in refrigerator for 1 month. After 1 month the samples were analyzed for the physical characteristics, drug content and in-vitro diffusion study.

RESULT AND DISCUSSION:

Preformulation studies:

Determination of Melting Point:

The melting point of Ketoconazole was found to be 146 ˚C.

Determination of wavelength maxima of Ketoconazole:

The solution was scanned in the range of 200-500 nm to fix the wavelength at which maximum absorption of Ketoconazole was observed. The λmax was found to be 296 nm in both methanol and pH 7.4 phosphate buffer.

Standard calibration Curve of Ketoconazole at λmax 296nm in phosphate buffer (pH 7.4):

Ketoconazole obeyed Beer's law in the range from 50-500 µg/ml. The absorbance is shown in the table and standard graph in figure.

Table no 5 Concentration and absorbance of the drug in prepared solutions:

Sr No	Concentration (µg/ml)	Absorbance (MEAN±SD) n=3
1.	0	0±0
2.	50	0.044±0.004
3.	100	0.079±0.001
4.	150	0.115±0.0006
5.	200	0.159±0.0042
6.	250	0.193±0.006
7.	300	0.236±0.0021
8.	350	0.293±0.0043
9.	400	0.332±0.0005
10.	450	0.373±0.0051
11.	500	0.412±0.0065

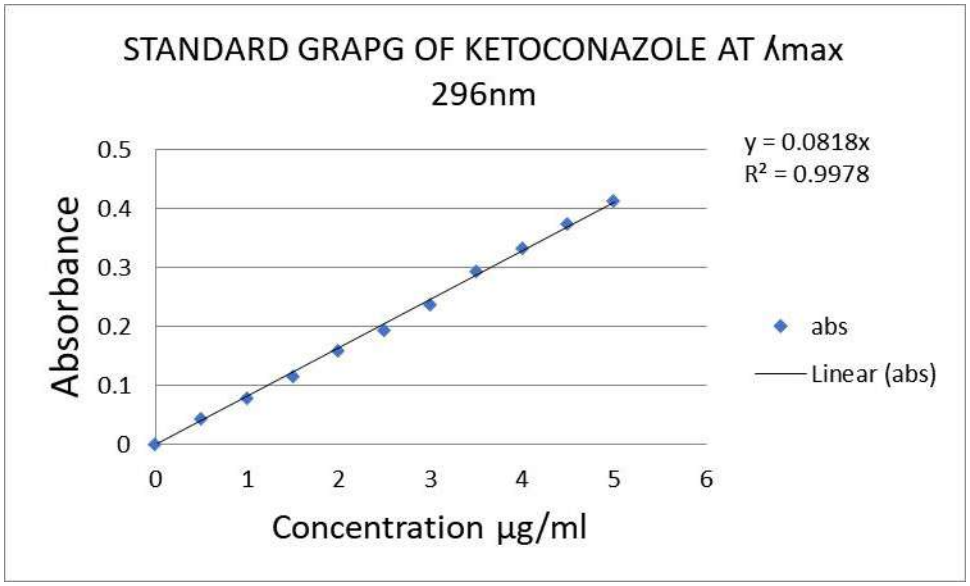


Fig no 1 Standard calibration curve of Ketoconazole.

Drug-Excipient Compatibility Studies:

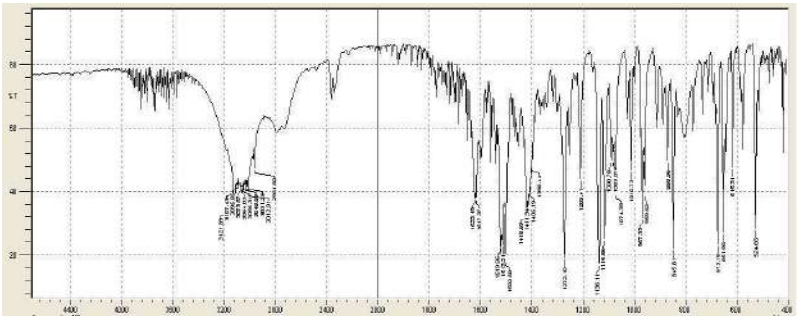


Fig. no 2 FTIR Characteristics Peaks of Pure Ketoconazole Drug

Table no 6 FT-IR Characteristics Peaks of Ketoconazole:

Functional Group	Peak obtained in drug (frequency cm^{-1})	Actual values (cm^{-1})
N-H stretching	3085.89	3550-3200
C-H stretching (Aliphatic)	2927.74	2780-2805
(C=O) carbonyl stretching	1723.53	1705-1725
Aromatic ring	1612	1650-1550
C-O Aromatic group	1238	1050-1150
C=C aromatic stretch	1510	1600-1585
3° amine	1200	1250-1020
C–Cl stretch	814	850-550

Fig no 3 FTIR Characteristics Peaks of Pure Ketoconazole Drug

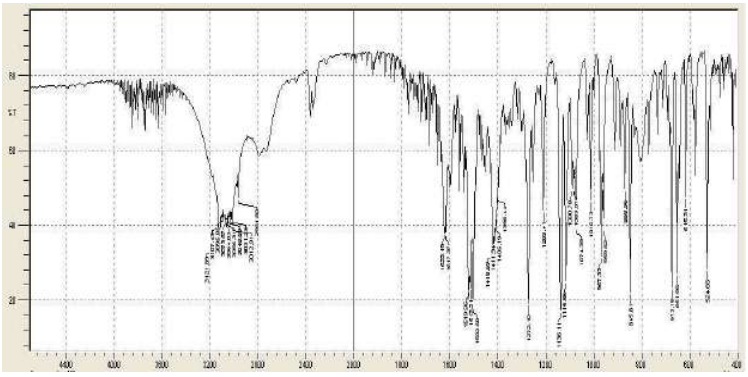
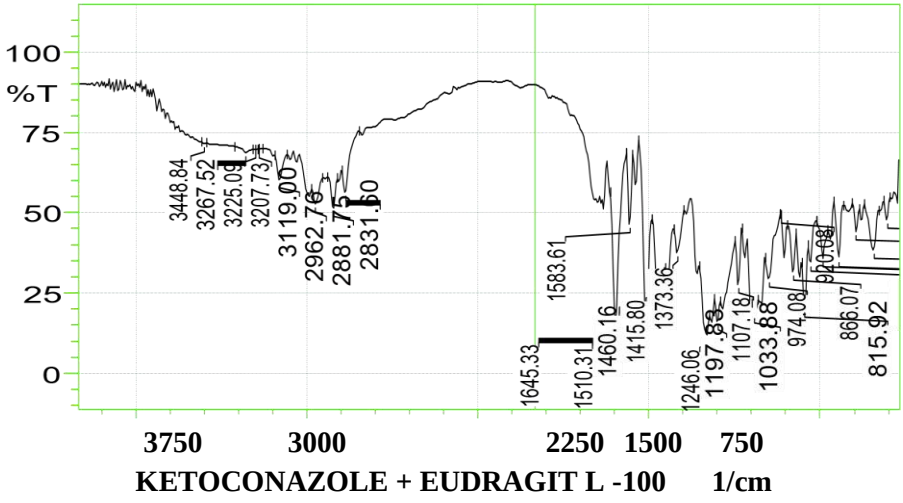


Fig no 4 : FTIR Spectra of Ketoconazole and Eudragit L 100



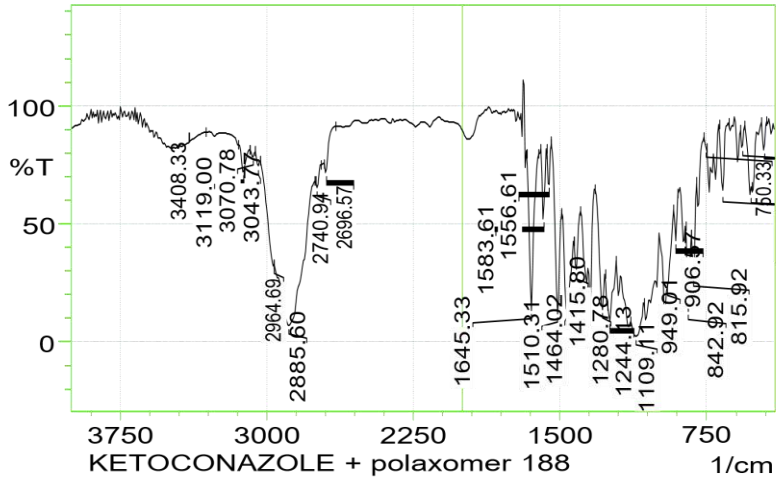


Fig. no 5 FTIR Spectra of Ketoconazole and Polaxomer 188

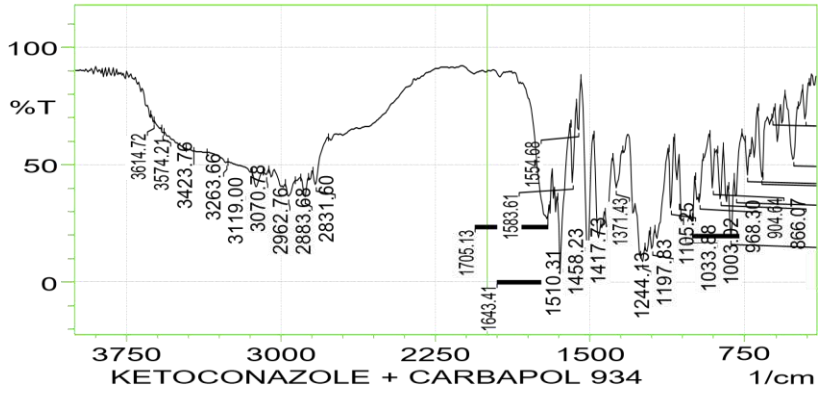


Fig. no 6 : FTIR Spectra of Ketoconazole and Polaxomer 188

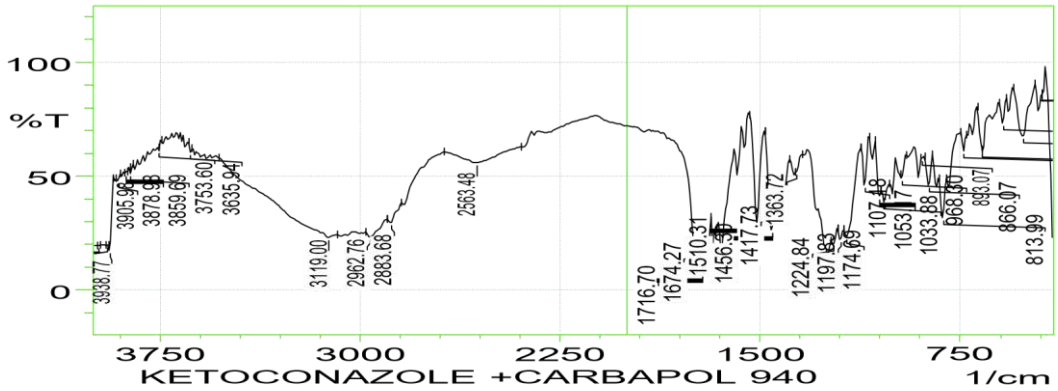


Fig. no 7 FTIR Spectra of Ketoconazole and Carbapol 940

Evaluation of nanoparticles:

Table no 7 Evaluation of nanoparticles by Optimized method (F1 to F9)

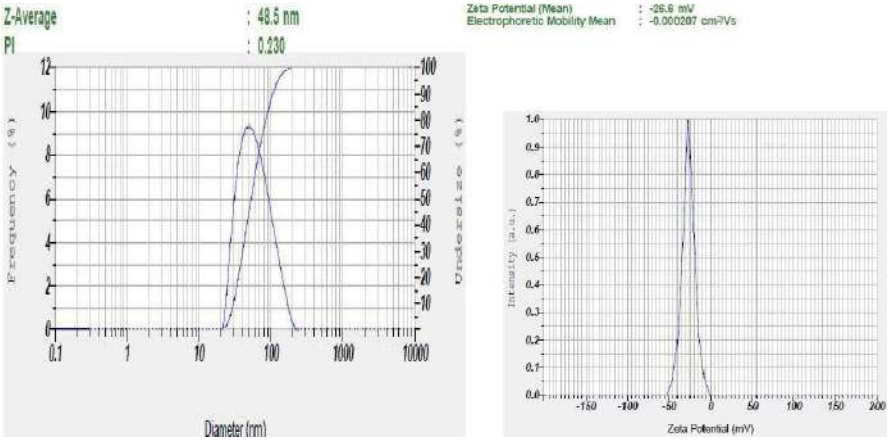
Formulation code	Particle size (nm)	Polydispersity index	Zeta potential (mV)	Entrapment efficiency (%)	% Drug Release	Drug content
F1	83.6	0.127	-20.1	87.69±0.61	85.25	82±1.36
F2	77.5	0.161	-27.1	86.77±0.45	80.01	71±1.94
F3	79.2	0.149	-33.6	83.78±0.03	74.45	57±0.08
F4	69.5	0.234	-26.3	89.55±0.50	86.78	86±1.90
F5	72.8	0.357	-28.3	86.78±0.37	81.87	76±1.29
F6	65.3	0.164	-35.7	86.48±0.23	78.32	62±1.26
F7	50.7	0.253	-26.6	93.78±0.12	89.16	89±1.35
F8	48.5	0.23	-29.4	91.42±0.40	82.13	82±1.40
F9	61.2	0.244	-34.7	85.64±0.23	79.56	70±1.37

Table no 8 Evaluation of nanoparticles of Ketoconazole trial run

Formulation code	Particle size (nm)	Zeta potential (mV)	Ratio of Drug: Polymer	Surfactant
K1	84.2	23.1	1:1	0.1
K2	75.7	22.1	1:2	0.1
K3	81.6	31.6	1:3	0.1
K4	71.3	24.3	1:1	0.425
K5	70.9	26.3	1:2	0.425
K6	63.6	32.7	1:3	0.425
K7	51.1	23.6	1:1	0.75

K8	49.3	25.4	1:2	0.75
K9	63.4	32.7	1:3	0.75
K10	132.4	-25.9	1:4	0.1

Fig no 8 Particle Size Distribution and Zeta potential of Formulation F7.



In-vitro diffusion study:

Table no 9 In-vitro diffusion release of Ketoconazole nanoparticle F1-F5

% cumulative Drug Release of F1 to F5					
Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	29.5±1.86	30.9± 1.92	22.8±0.11	34.8±1.23	31.5±0.06
2	35.3±1.85	42.5±1.57	29.8±0.98	48.3±1.34	43.33±0.32
4	44.9±1.91	48.4±1.36	34.9±1.24	52.6±1.58	50.1±0.051
6	59.4±1.74	56.8±1.24	47.6±1.27	64.4±1.67	59.54±0.22
8	67.6±1.82	65.9±2.01	53.1±1.31	72.7±1.46	67.6±1.65
10	74.8±1.83	74.5±1.86	62.8±1.18	81.1±1.33	77.3±0.8
12	85.25±1.6	80.01±1.97	74.45±1.47	86.78±1.32	81.87±1.21

Table no 10 In-vitro diffusion release of Ketoconazole nanoparticle F6-F9

% Cumulative Drug Release of F6 to F9				
Time (h)	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0
1	25.12±0.4	39.3±0.09	38.02±1.45	29.3±1.01
2	35.3±1.21	46.2±0.12	41.54±1.83	43.8±0.96
4	46.5±1.42	58.5±1.34	56.76±1.03	49.9±1.26
6	55.6±1.01	69.6±1.42	68.34±1.62	58.2±1.34
8	62.2±1.43	78.8±1.94	74.03±1.78	65.3±1.96
10	70.3±2.01	84.1±1.39	79.2±1.88	73.9±1.48
12	78.32±1.19	89.16±1.94	82.13±2.32	79.56±1.96

Fig no 9 In-vitro diffusion release of Ketoconazole nanoparticle (F1 to F5)

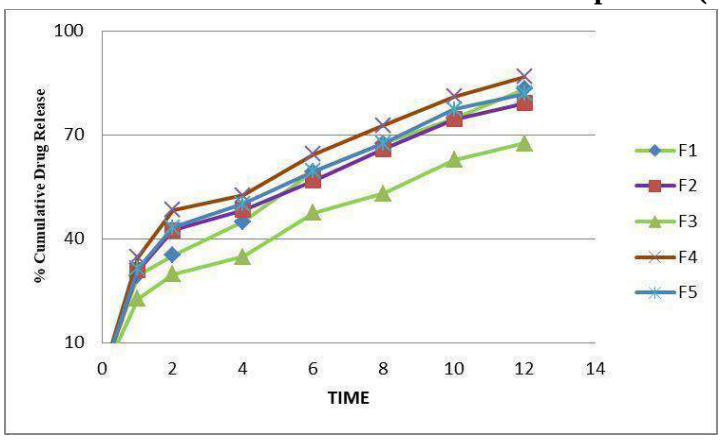
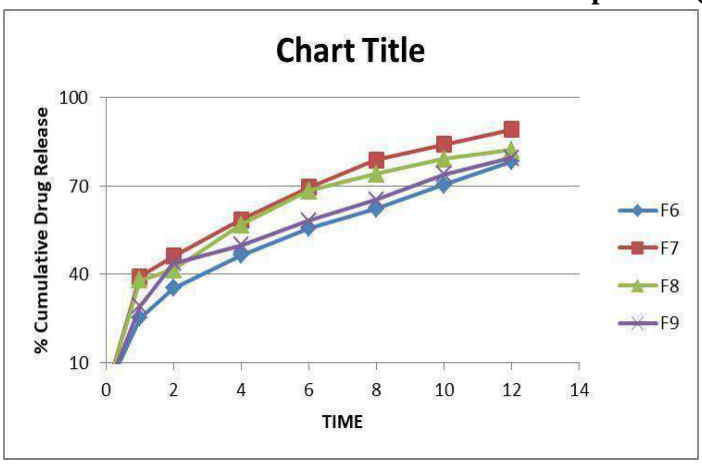


Fig no 10 In-vitro diffusion release of Ketoconazole nanoparticle (F6 to F9)



Stability studies:

Table no 11 Stability studies of Ketoconazole nanoparticles (F7)

At 40°C ± 2°C /75% ±5%RH						
Formulation code	**Particle size (nm)**	**Polydispersity index**	**Zeta potential (mv)**	**Entrapment efficiency (%)**	**Drug content**	**In-vitro drug release (%)**
F7	50.4	0.251	-26.6	91.13	88.76	89.12

At 4 ^{0} C						
Formulation code	**Particle size (nm)**	**Polydispersity index**	**Zeta potential (mv)**	**Entrapment efficiency (%)**	**Drug content**	**In-vitro drug release (%)**
F7	50.1	0.250	-26.5	93.11	88.62	89.05

Evaluation of Ketoconazole nanoparticle gel:

Table no 12 Evaluation of Ketoconazole nanoparticle gel

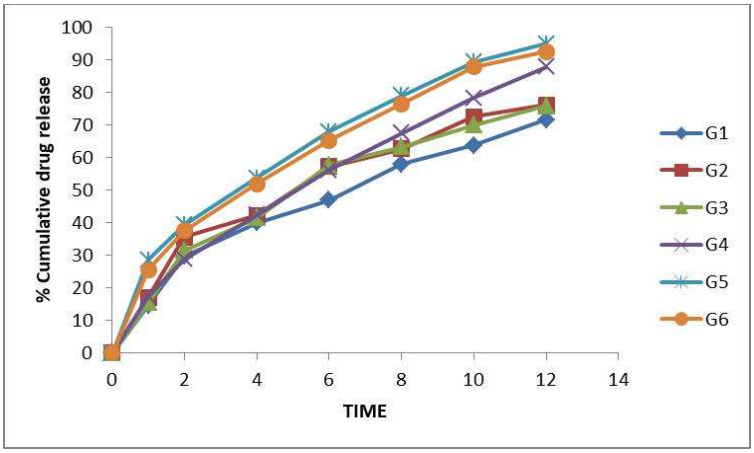
Formulation code	Percentage yield (%)	Drug content (%)	pH	Viscosity (cps)
G1	89.3	84.9±0.900	6.8	6,900
G2	91.8	87.31±0.412	7.1	8,300
G3	93.5	89.10±0.996	6.9	7,115
G4	91.4	90.11±0.339	6.85	9,200

G5	95.6	96.5±0.703	7.0	15,200
G6	93.2	93.0±1.145	7.21	12,100

Table no 13 In-vitro diffusion release of Ketoconazole nanoparticle gel (G5)

% Cumulative Drug Release of G1 to G6						
Time(h)	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**
0	0	0	0	0	0	0
1	14.65±0.015	17.12±0.763	15.35±0.712	17.42±0.669	28.54±0.824	25.56±1.611
2	29.62±1.24	35.54±0.489	31.39±0.834	28.71±0.445	39.32±0.511	37.46±1.21
4	39.89±1.35	42.24±2.322	41.4±1.232	42.37±0.473	53.7±1.011	51.89±2.211
6	46.82±2.205	57.17±1.018	57.6±1.240	56.04±0.714	67.85±0.251	65.1±1.121
8	57.9±1.103	62.67±1.705	63.21±0.313	67.4±0.282	78.92±1.411	76.4±0.285
10	63.67±0.221	72.42±0.706	69.9±0.386	78.21±0.190	89.26±0.339	87.7±0.634
12	71.53±1.269	76.10±1.411	75.82±0.493	89.71±0.200	94.75±0.703	92.4±0.035

Fig no 11 In-vitro diffusion release of Ketoconazole nanoparticle gel (G1 to G6)



Drug release kinetics of formulation G5

Table no 14 Kinetics of drug release of G5 Formulation

Formulation code	**Zero order kinetics**	**First order kinetics**	**Higuchi model**	**Korsemeyer-peppas model**	**Zero order kinetics**	**Mechanism of Drug Release**
	R2	**R2**	**R2**	**R2**	**N**	
F5	0.9222	0.9729	0.94	0.9989	0.4923	Non-Fickian

Fig no 12 Zero order plot for drug release kinetics of G5 formulation.

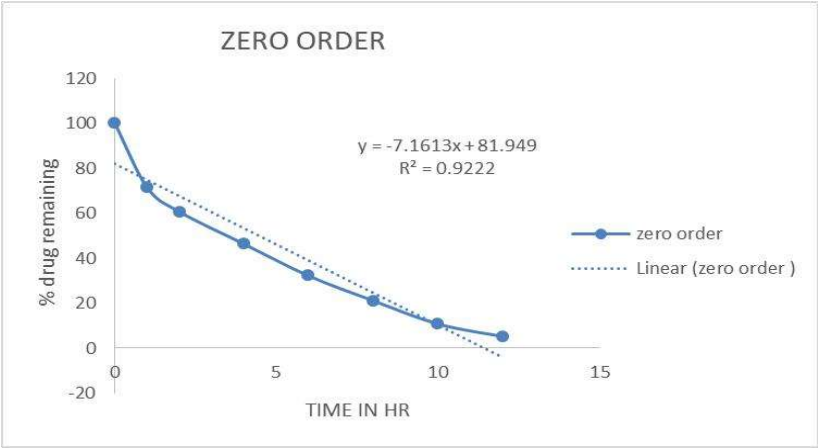


Fig. 13 First order plot for drug release kinetics of G5 formulation.

Fig no 14 Higuchi plot for drug release kinetics of G5 formulation.

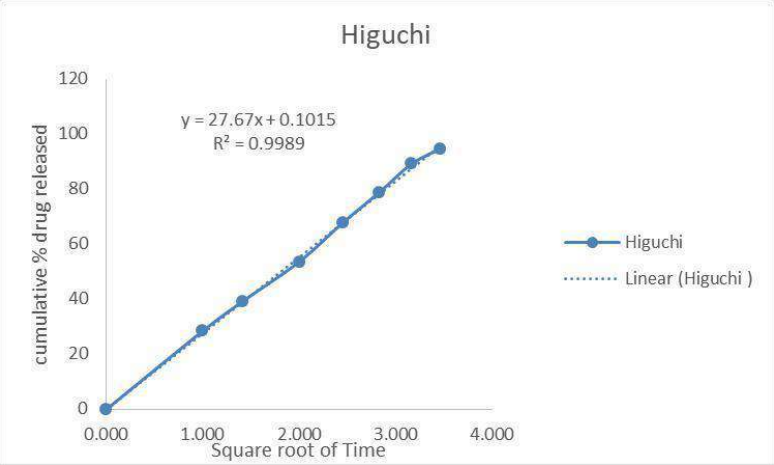
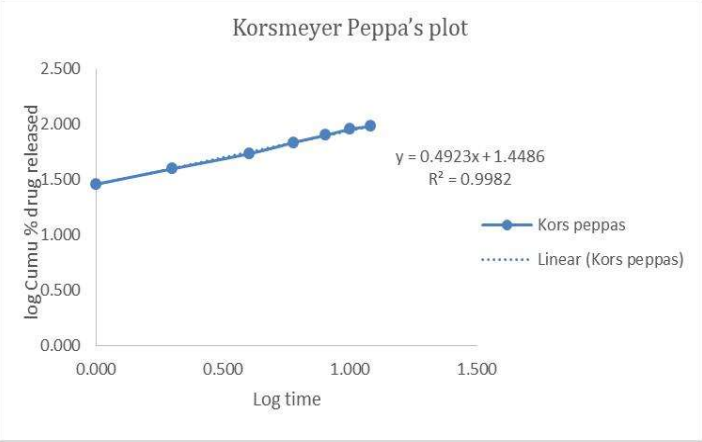


Fig no 15 Korsmeyer Peppa's plot for drug release kinetics of G5 formulation



Stability studies:

Table no 15 stability studies of Ketoconazole nanoparticle gel (G5)

40°C ± 2°C /75% ± 5%RH					
Formulation code	**Percentage yield (%)**	**Drug content (%)**	**pH**	**Viscosity (cps)**	**In-vitro drug release**
G5	95.3	96.2	7.06	15,202	94.63

- In the present study Ketoconazole nanoparticles were prepared by nanoprecipitation method using different ratios of drug and Eudragit L100 and different concentrations of poloxamer 188.

CONCLUSION

- Pre formulation studies were carried out to check the purity of the drug. The standard graph was performed and concluded that the standard graph was found to be linear in the range of 50 - 500 µg/ml.
- FT-IR was performed to study the physical and chemical interaction between the drug and the excipients used. It was observed that there was no interaction between the drug and the excipients.
- F1 to F9 Ketoconazole nanoparticles formulations were prepared by varying the concentration of Eudragit L100 and keeping drug constant and different % of poloxamer 188.
- Based on the particle size, zeta potential, morphology, percentage yield, %drug entrapment efficiency, % drug content and in-vitro drug release studies formulation with 1:1 drug and Eudragit L100 ratios and 0.75% poloxamer 188 was selected to the be best formulation.
- From the above experiments it was confirmed that the drug-polymer ratio was found to influence the particle size, zeta potential, entrapment efficacy and % drug release from the formulation. As the ratio of polaxmer increased, the particle size was found to decrease, whereas the entrapment efficacy and % drug release were found to increase and as the concentration of Eudragit L100 increased there was increase in particle size and decrease in entrapment efficiency and drug release.
- The results obtained from design expert software version 12 in the form of counter plot and 3D-plot graph clearly showed that increase in the factor A i.e. amount of Eudragit L100 increases, the entrapment efficacy and % drug release decreases. As in the factor B i.e. concentration of poloxamer 188 increases the particle size decreases and entrapment efficacy increases.
- The stability studies were also carried out by using the formulation F7 showed closeness in data of in-vitro release and particle size, zeta potential, % entrapment efficiency, % drug content and % yield when compared to data at 40°C ± 2°C /75% ± 5%RH and 4°C.
- The best formulation of Ketoconazole nanoparticles (F7) was formulated into gel using different concentrations of carbopol 934 and carbopol 940 and subjected to physicochemical studies and in- vitro release studies. The pH of all the formulations was in the range of 6.8 to 7.21, which lies in the normal pH range of the skin. From the in-vitro drug release results it was found that, formulation G5 showed highest drug release rate. The mechanism of the drug release for the formulation G5 was found to be Non-Fickian with Zero order kinetics. From the stability study, it is clear that the formulation did not undergo any chemical change and found to be more stable.
- The formulated Naonparticle based topical gel of drug Ketoconazole showed higher stability. The penetration of the drug was increased and as the size was less than 100 nm it shown prolong effect. As a result it was found to have reduced side effects and increased therapeutic efficacy, increased bioavailability. Transdermal route was selected as drug when take oral route shows less bioavailability and gastric emptying was found. Hence nanoparticle-based Ketoconazole topical gel show good potential activity then other dosage form.

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