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FORMULATION AND EVALUATION OF NANOPARTICLES CONTAINING TERBINAFINE

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***Abstract*:** With an aim to formulate and evaluate terbinafine hydrochloride nanosuspension by nanoprecipitation technique and to improve anti-inflammatory therapy, the formulated nanosuspensions were investigated for its characteristics like drug excipients compatibility, particle size distribution, polydispersity index, zeta potential, scanning electron microscopic (SEM) analysis, drug content and *in vitro* release and kinetic studies. In this study, an optimized formulation was presented as an alternative with improved permeability and decreased dosage frequency hence improving compliance and side effects.

***Index Terms* – Nanopartcles, Terbinafine, Drug Delivery, Efficiency, Anti Inflammatory**

1. INTRODUCTION

In recent years, nanotechnology has been embraced by industrial sectors due to its applications in the field of electronic storage systems, biotechnology, magnetic separation and pre concentration of target analytes, targeted drug delivery, and vehicles for gene and drug delivery. As the field of nanotechnology advanced, novel nano materials become apparent having different properties as compared to their larger counterparts. This difference in the physiochemical properties of nano materials can be attributed to their high surface-to-volume ratio. Due to these unique properties, they make excellent candidate for biomedical applications as variety of biological processes occur at nanometer scales. Nanoparticles are being used for diverse purposes, from medical treatments, using in various branches of industry production such as solar and oxide fuel batteries for energy storage, to wide incorporation into diverse materials of everyday use such as cosmetics or clothes.

Nanotechnology and Nano-science studies have emerged rapidly during the past years in a broad range of product domains. It provides opportunities for the development of materials, including those for medical applications, where conventional techniques may reach their limits.

Terbinafine is an allylamine antifungal used to treat dermatophyte infections of toenails and fingernails as well as other fungal skin infections. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Like other allylamines, Terbinafine inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase (also called squalene epoxidase), an enzyme that is part of the fungal cell wall synthesis pathway.

2. MATERIALS AND METHODS

2.1. Pre-formulation study

Evaluation during pre formulation studies was done to assess the colour, odor and taste of the substance.

2.1.1. Solubility

Solubility of drug was determined in water and methanol, ethanol, chloroform, ethyl acetate and DMSO.

2.1.2. Melting point determination

Melting point of drug was determined by Open capillary method.

2.1.3. Determination of partition coefficient

50 mg of drug was taken in three separating funnels. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analysed spectrophotometrically. The partition coefficient of the drug in phases was calculated by using formula:

K_{PC} = Concentration of Drug in Oil Phase/ Concentration of Drug in Water Phase

2.1.4. Determination of λ max

A solution of drug containing the concentration 10 µg/ ml was prepared in 0.1 N HCl. The solution was scanned in the range of 200 – 400 nm UV spectrum using Systronics double beam spectrophotometer.

2.1.5. Standard Calibration Curve of Terbinafine

a) Preparation of Dissolution Medium

0.01N Hydrochloric acid

0.85ml of Hydrochloric acid diluted in1000ml distilled water.

Phosphate buffer pH6.8

50ml of 0.2 M potassium dihydrogen phosphate was placed in 200ml volumetric flask. 22.4 ml of 0.2 M sodium hydroxide was added and make up to the volume with distilled water.

0.2M Potassium dihydrogen phosphate

27.218 gm of potassium dihydrogen phosphate was dissolved and diluted to1000 ml with distilled water.

0.2M Sodium hydroxide

8gm of sodium hydroxide was dissolved and make upto 1000ml with distilled water.

b) Determination of absorption maximum (λmax)

100 mg of Terbinafine was accurately weighted into 100 ml volumetric flask, dissolved in 0.1M HCL and volume was made up with0.1M HCL. Pipette 1ml of this solution into another 10 ml volumetric flask and the volume was made with 0.1M HCL and marked as Stock. The resultant solution was scanned in the range of

(200-400nm) by UV Spectrophotometer (Systronic double beam- 2202) to get absorption maximum (λ max). And, also an absorption maximum was estimated similarly using phosphate buffer pH (7.0)

c) Preparation of calibration curve

From this Terbinafine standard stock solution (1000µg/ml), 1ml solution was diluted to 10 ml using 0.1M HCL solution to get concentrations of 100 µg/ml. from this solution, aliquots of, 0.5 ml, 1.0 ml, 1.5 ml,2.0 ml,2.5 ml,3.0 ml from standard drug solution were diluted to 10 ml with 0.1M. The absorbance of these solutions was measured at 273 nm 0.1 N HCl as a blank.

A standard curve was plotted using concentration on X-axis and the absorbance obtained on Y-axis. And also, a standard curve was prepared similarly using phosphate buffer pH (7.0).

2.1.6. Drug – Excipient Interaction Studies

The compatibility studies were performed for the development of dosage form, preformulation studies is carried out to confirm that there was no interaction between the drug and excipients. Infra spectrophotometer studies used to check the compatibility studies between excipients.

Compatibility was performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight. FTIR spectra matching approach was also used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm-1 in a FTIR spectrophotometer. The FTIR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

2.1.6. Formulation of Terbinafine Nanoparticles Solvent Evaporation Method.

Nanoparticles prepared by polymers like chitosan, ethyl cellulose, hydroxylpropylmethyl cellulose; and polyvinylalcohol by solvent evaporation method. Disperse phase consisting of Terbinafine (100mg) and requisite quantity of polymers dissolved in 20 ml solvent (dichloromethane) was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase. There action mixture was stirred at 1000 rpm for two-three hours on a magnetic stirrer. The nanoparticles formed were collected by filtration through whatman filter paper and dried in oven at 50^0C for 2 hours. The dried nanoparticles were stored in vacuum desicater to ensure the removal of residual solvent.

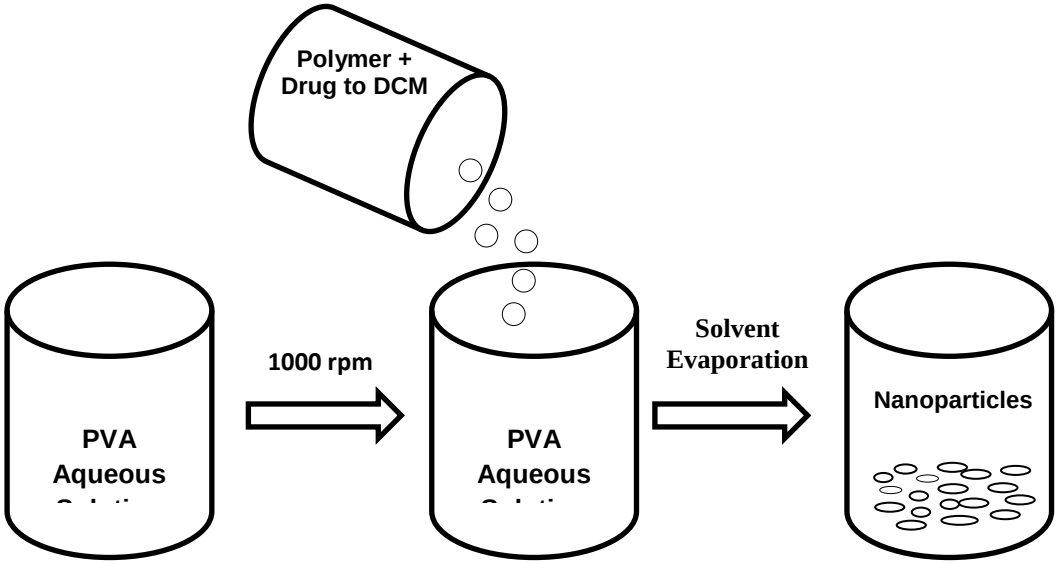

Figure No.1: Schematic Diagram of Preparation of Nanoparticles

Table 1: Schematic Diagram of Preparation of Nanoparticles

Formulation Code	INGREDIENTS						
	Terbinafine (mg)	Ethyl cellulose (mg)	Chitosan (mg)	HPMC K100 (mg)	Polyvinyl alcohol (%w/v)	Dichlro Methane (ml)	Distilled water (ml)
F1	100	300			0.2	20	100
F2	100	600			0.2	20	100
F3	100	900			0.2	20	100
F4	100	1200			0.2	20	100
F5	100		300		0.2	20	100
F6	100		600		0.2	20	100
F7	100		900		0.2	20	100
F8	100		1200		0.2	20	100
F9	100			300	0.2	20	100
F10	100			600	0.2	20	100
F11	100			900	0.2	20	100
F12	100			1200	0.2	20	100

2.2 Characterization of Nanoparticles

All the formulations were evaluated for its production yield, particle size, polydispersity index, zeta potential, drug content, entrapment efficiency, solubilization efficiency and *In vitro* drug release studies and Kinetics of drug release studies.

2.2.1 Production yield

The production yield of the Nanoparticles was calculated for each batch by dividing the total weight of product (M) by the total expected weight of drug and polymer and the weight of nanoparticles (M).

$$\%\ Yield = \frac{Actual\ Yield}{Theoretical\ Yield} \times 100\%$$

2.2.2 Theoretical drug loading

Theoretical drug loading in nano particles was estimated by using the following formula,

$$\text{Drug Loading Content (\%)} = \frac{\text{weight of drug in nanoparticles}}{\text{weight of nanoparticles}} \times 100$$

2.2.3 Determination of Drug content

Sample containing 100mg equivalent Terbinafine Nanoparticles were dissolved and the volume is made upto100ml with pH7.4 phosphate buffer. From the above solution 10ml was pipette out and made up to 100ml with phosphate buffer. The absorbance of resulting solution was determined at λ max (283nm) using UV Spectrophotometer (UV-2202 Systronic) and the drug content is estimated.

2.2.4 Entrapment Efficiency

10 mg of the nanoparticle was analyzed by dissolving sample in 10ml of distilled water. After the drug was dissolved, 10ml of clear layer of dissolved drug was taken.Thereafter, the amount of drug in the water phase was detected by a UV-spectrophotometric method at 273 nm (U.V Spectrophotometer, systronics). The test was repeated with another sample. The amount of the drug in the suspension was analyzed by centrifugation at 500 rpm for 5 minutes and by measuring the concentration of the drug in the clear supernatant layer by the UV-spectrophotometric method. The entrapment efficiency (%) of drug was calculated by the following equation.

%Entrapment Efficiency= Actual content/Therotical content drug×100

2.2.5 Morphological studies of nanoparticles by using Scanning Electron Microscopy (SEM)

Morphological evaluation of the selected Nanoparticles formulation was carried out in scanning electron microscope (SEM) (HitachiX650, Tokyo, Japan).

2.2.6. X-ray Powder Diffraction (XRPD) analysis

The crystalline state of the samples, including the drug and freeze-dried powders were studied in X-ray diffractometer. XRPD was carried out in symmetrical reflection mode using Copper line as the source of radiation .Standard runs using a 40kV and 30m A in this process. Samples were performed with a scanning rate of 0.1000^0/min and the scanning range of the 2 from the initial angle 4˚ to the final angle 90˚.

2.2.7 *In vitro* dissolution studies

In-vitro release studies were carried out by using dialysis membrane bag method and cumulative percentage drug release was calculated.

2.2.8 *In vitro* Kinetic analysis

In order to investigate the drug release mechanism from Controlled release nanoparticles formulations, the percentage cumulative drug release data was analysed with following mathematical model.

1) Zero-order 2) First order 3) Higuchi

4) Hixson-Crowell cube root law 5) Korsmeyer-peppas model.

Table 2: Kinetic Standards for Different Models

Release exponent (n)	Drug transport	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.45< n-0.89	Non-fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II	t^{n-1}

2.2.9. Stability Studies

The nano-particle formulation was subjected to stability studies according to ICH guidelines by storing at 25 C/60% RH for 30 days and 40 C /75% RH for 30 days. These samples were analysed and checked for changes in physical appearance, drug content and Entrapment efficiency, in vitro drug release studies at regular intervals.

3. RESULTS

3.1. Pre-formulation Studies

Table 3: **Description of Terbinafine**

S. No.	Tests	Results
1	Colour	White
2	Odor	odorless
3	Taste	Bitter

3.2 Solubility Study.

Table 4: Solubility Study of Terbinafine

S. No.	Solvent	Solubility
1.	Water	-- - -
2.	0.1 N HCl	+ - --

3.	Phosphate Buffer (6.8 pH)	++++
4.	Methanol	++++
5.	DMSO	++++
6.	Acetone	++++

3.3 Melting point determination

The melting point of Terbinafine was found to be 233° C.

3.4 Determination of λ max

Solution was scanned under UV-Vis Spectrophotometer and λ max was determined. It was found to be as per the monograph.

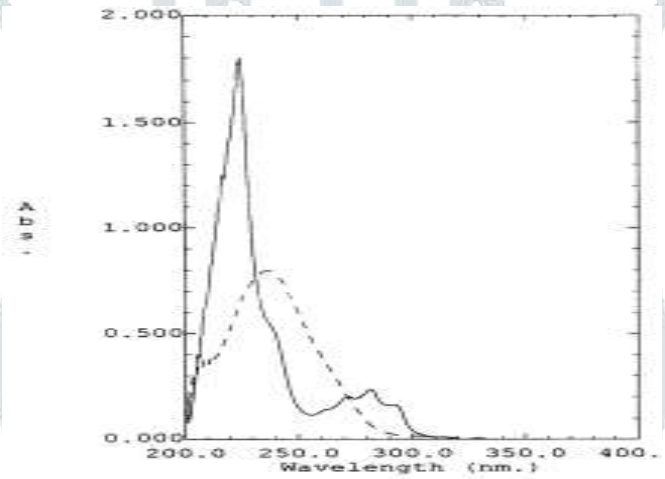

Figure No.2: UV spectra of Terbinafine

Table 5: Wavelength of maximum absorption of Terbinafinein 0.1 N HCl

S. No.	Solvent	λ max
1	0.1 N HCl	283 nm

Table 6: Partition coefficient of Terbinafine in 0.1 N HCl

S. No.	Solvent	Partition coefficient
1	n-octanol	0.999

Table 7: Calibration Curve of Terbinafine in 0.1 N HCl

S. No.	Concentration (µg/ml)	Absorbance (λ_{max} =283nm)
1	5	0.122
2	10	0.184
3	15	0.410
4	20	0.563
5	25	0.762
6	30	0.987

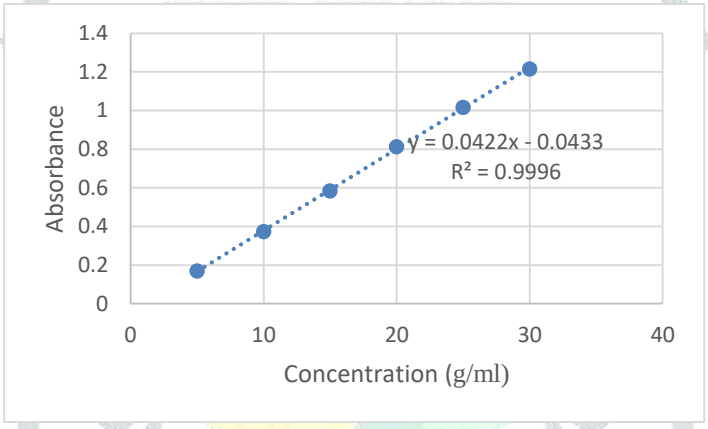

Figure No.3: Graph represents the Calibration Curve of Terbinafine

Table 8: Data for calibration curve in 0.1 N HCl solution

S. No	Parameters	Values in 0.1 N HCl
1.	Absorbance maximum in nm	283nm
2.	Correlation coefficient	0.9996
3.	Equation	y = 0.0422x - 0.0433

3.5 FTIR study

From the spectra of Terbinafine physical mixture of drug and selected ingredients it was observed that all characteristic peaks of Terbinafine were present in the combination spectrum, thus indicating compatibility between drug and selected ingredients. FTIR Spectra shown in Figure 7.

FTIR spectrum of Terbinafine showed absorption bands at 2968.45, 2443.812358.94, 1469.76, 1413.82, 1361.74, 1263.37, 958.62, 808. 17. 792.74. 777.31 and 725.23 cm-1.

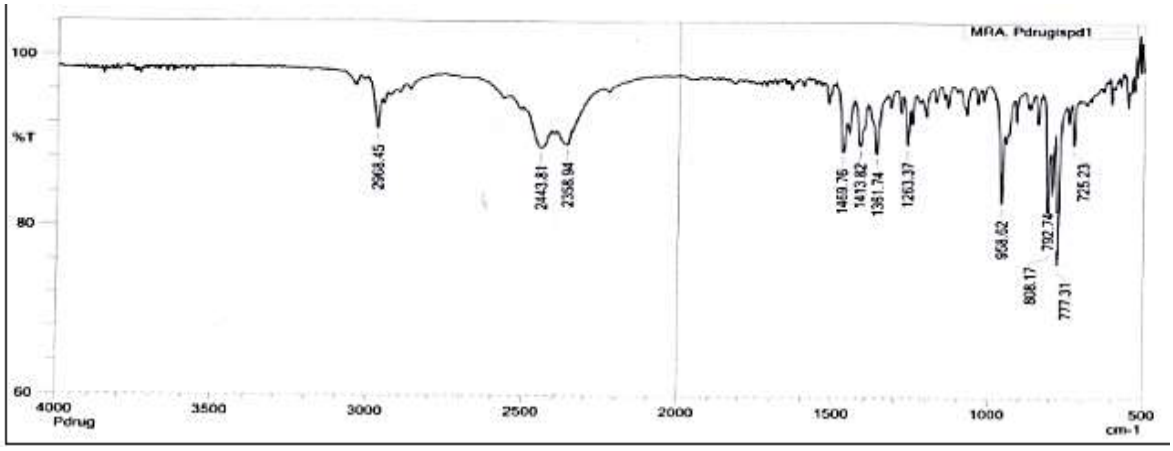

Table 9: Formulation Designing of Terbinafine Nanoparticles

Formulation Code	INGREDIENTS						
	Terbinafine (mg)	**Ethyl cellulose (mg)**	**Chitosan (mg)**	**HPMC K100 (mg)**	**Polyvinyl alcohol (%w/v)**	**Dichlro Methane (ml)**	**Distilled water (ml)**
F1	100	300			0.2	20	100
F2	100	600			0.2	20	100
F3	100	900			0.2	20	100
F4	100	1200			0.2	20	100
F5	100		300		0.2	20	100
F6	100		600		0.2	20	100
F7	100		900		0.2	20	100
F8	100		1200		0.2	20	100
F9	100			300	0.2	20	100
F10	100			600	0.2	20	100
F11	100			900	0.2	20	100
F12	100			1200	0.2	20	100

Table 10: Characterization of Terbinafine Nanoparticles Formulations

S. No.	Formulation Code	Production yield (%)	Drug Loading (%)	Drug Content (%)	Entrapment Efficiency (%)
1.	F1	81.26±1.28	62.07±0.93	91.19±1.37	68.54±1.03
2.	F2	76.20±2.32	43.58±1.62	92.01±1.38	75.93±1.11
3.	F3	84.07±1.16	29.51±0.42	86.55±1.30	64.50±0.95
4.	F4	82.54±1.22	24.40±1.35	85.85±2.25	67.81±1.00
5.	F5	78.53±1.16	65.50±0.93	83.99±1.25	68.61±2.00
6.	F6	81.22±2.20	41.45±2.62	96.20±1.46	91.99±1.31
7.	F7	81.42±1.12	30.42±0.45	88.17±0.37	72.90±1.12
8.	F8	79.35±1.19	23.06±1.38	91.14±1.37	54.36±0.83
9.	F9	80.35±2.21	60.11±0.93	91.03±1.37	68.65±3.03
10.	F10	76.11±1.14	42.79±1.67	94.03±2.43	74.57±1.13
11.	F11	83.16±1.26	30.07±0.47	90.46±1.37	61.13±1.92
12.	F12	80.10±2.32	25.82±2.39	87.13±1.31	58.15±0.89

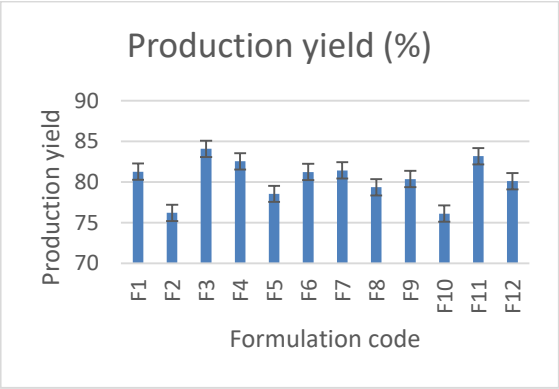

Figure 4: Percentage Production Yield of Terbinafine Nanoparticles Formulations

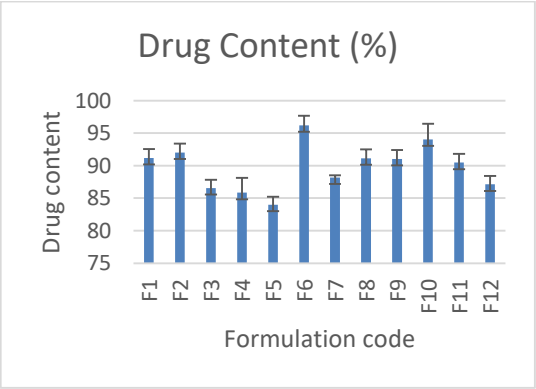

Figure 5: Drug content of Terbinafine Nanoparticles Formulations

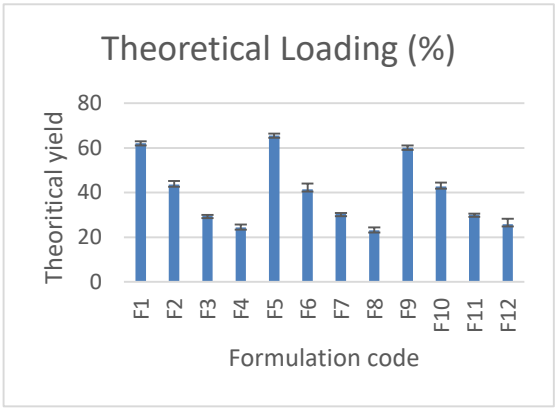

Figure 6: Theoretical Loading of Terbinafine Nanoparticles Formulations

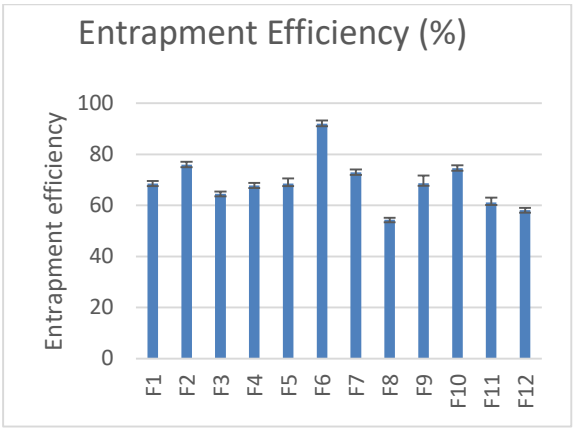

Figure 7: Entrapment Study of Terbinafine Nanoparticles Formulations

Table 11: Solubilisation Study

S. No.	Solvent Used	Pure Drug	F2	F6	F10
1.	Distilled Water	1.46±0.01	8.77±0.14	9.64±0.18	9.19±0.13
2.	0.01N HCl	2.24±0.21	2.56±0.18	3.26±0.25	2.25±0.12
3.	Phosphate Buffer pH6.8	8.65±0.15	9.21±0.11	9.80±0.48	8.53±0.69

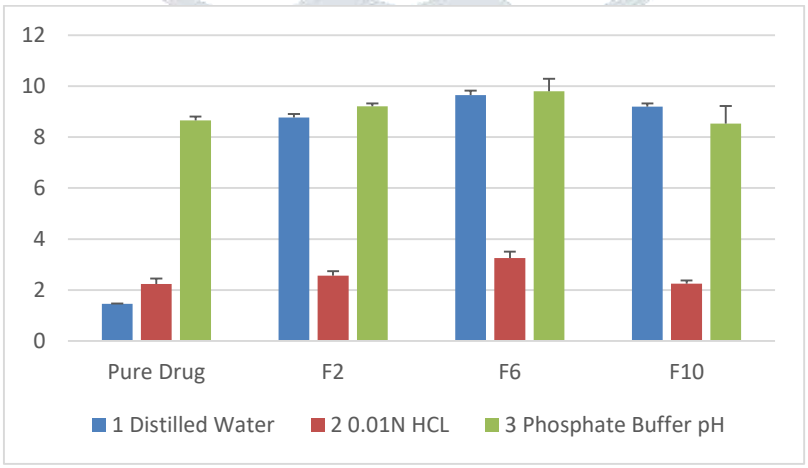

Figure 8: Bar Chart Solubility Study of Drug Formulations

Table 12: Cumulative % Drug Release of Drug and its Formulations

S. No.	Time in hours	Cumulative % Release		
		F2	F6	F10
1.	1	2.86±0.35	2.779±0.25	2.10±0.06
2.	2	12.34±2.05	17.07±0.71	10.67±0.15
3.	3	21.83±0.23	20.93±0.68	22.49±2.02
4.	4	26.97±0.26	29.59±0.33	32.05±0.46
5.	5	32.98±1.48	35.97±0.91	37.11±0.92
6.	6	37.41±1.55	42.98±1.14	43.57±0.94
7.	7	44.89±0.65	49.75±0.81	50.25±0.85
8.	8	52.43±0.93	57.61±1.16	58.48±1.11
9.	9	58.30±0.68	67.53±1.03	65.99±0.85
10.	10	64.40±1.14	77.30±0.47	72.57±1.21
11.	11	80.51±1.84	88.39±1.81	80.50±1.01
12.	12	87.09±1.07	98.09±0.73	90.04±0.77

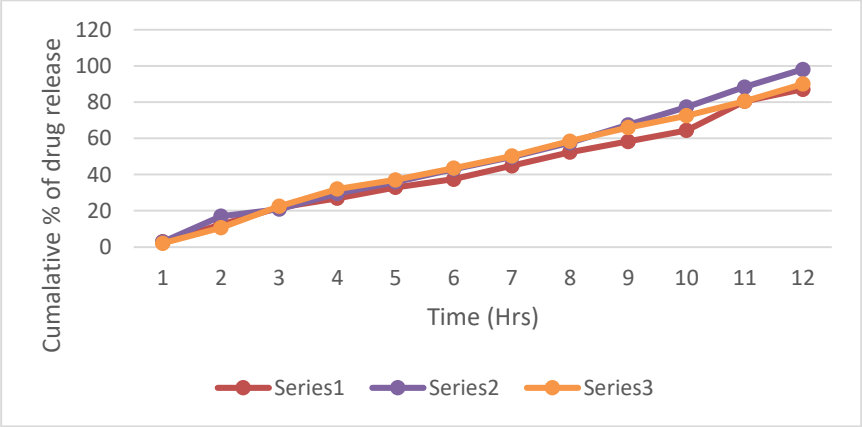

Figure 9: Graph represents Cumulative % Drug Release Study of drugs Nanoparticles Formulations

3.6. FTIR Spectroscopic study:

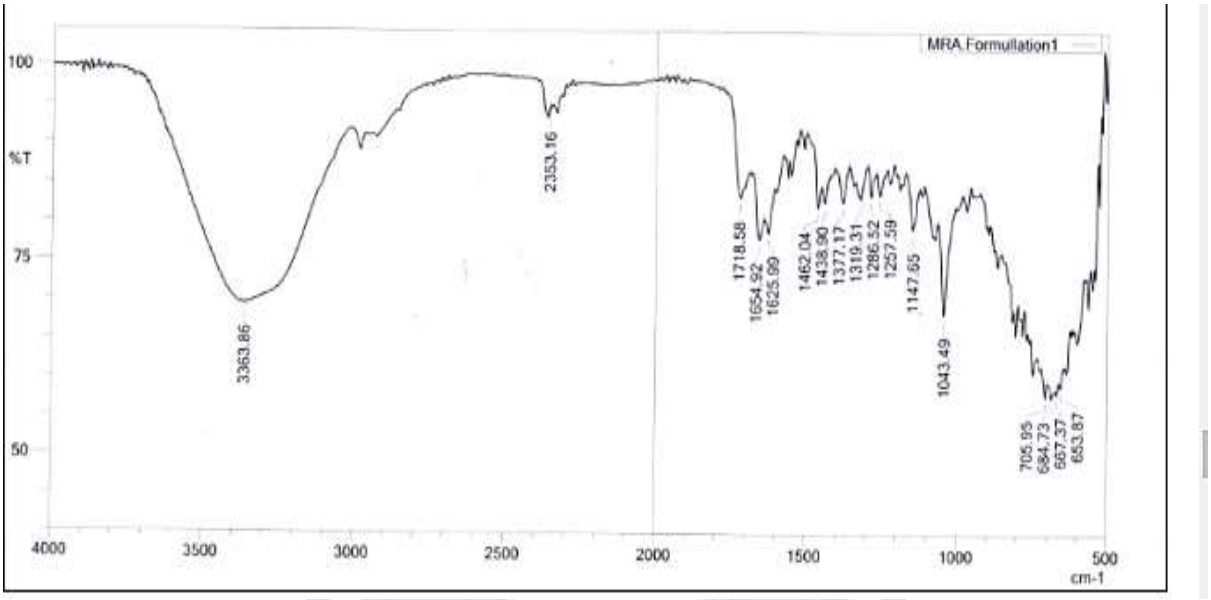

Figure 10: IR Spectra of Formulation

Table 13: Stability Study of Optimized Formulation (F6) of Terbinafine Nanoparticles Formulation

Storage Temperature	**25°C ±20C /65%RH**			**40°C ±20C /70%RH**		
Parameter	**% Drug content**	**% Entrapment efficiency**	**Cumulative % drug Release**	**% Drug content**	**% Entrapment efficiency**	**Cumulative % drug Release**
Initial	97.11 ±1.46	91.68 ±1.38	97.07 ±0.73	97.20 ±1.46	91.88 ±1.38	98.07 ±0.73
30 Days	95.82 ±1.23	91.78 ±1.45	97.51 ±1.16	96.45 ±1.22	90.90 ±1.44	96.62 ±1.15
60 Days	96.81 ±1.16	91.16 ±1.75	97.19 ±1.23	96.38±1.15	90.44 ±1.73	96.24 ±1.22

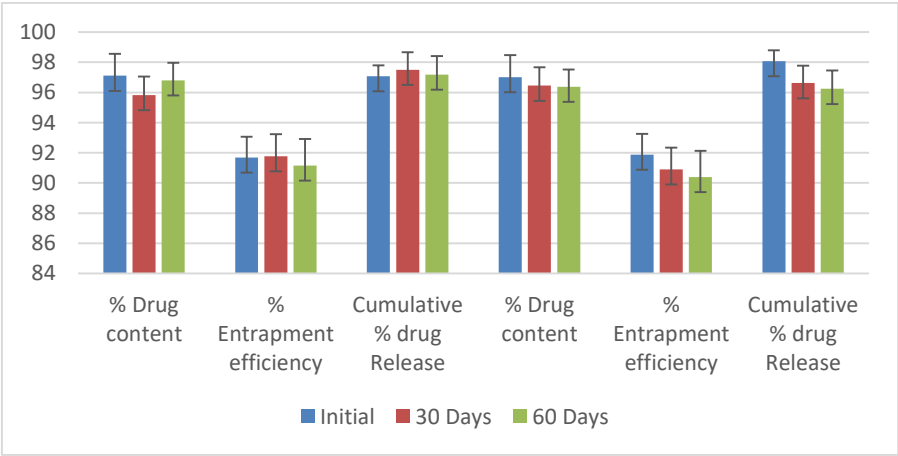

Figure 11: Stability Study of Optimized Formulation (F6) of Terbinafine Nanoparticles Formulation

4. DISCUSSION AND CONCLUSION

Hence, it was concluded that nano-particles ago of approach to release the drug in a controlled manner to the targeted site and enhance the solubility and dissolution property of Terbinafine by solvent evaporation method for the successful incorporation of Terbinafine with high entrapment efficiency. The solubility studies suggested that the nanoparticles formulations enhanced the bioavailability of Terbinafine by improving its solubility and dissolution rate when compared to pure drug. Furthermore, it could be presumed that if then a no meter range of particles was obtained, the bioavailability might be increased. Thus the nanoparticles as controlled release formulations can be useful for delivery of short elimination half-life, low bioavailability through orally. Thus nanoparticles drug delivery system provides site specific drug delivery and prolongs dosage interval and thus improving patient compliance.

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