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REVIEW ARTICLE

DEVELOPMENT AND EVALUATION OF TERBINAFINE HYDROCHLORIDE FOR TABLET FORMULATION

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ABSTRACT

Immediate release tablets prepared by wet granulation method containing drug by using superdisintegrants like Crosscarmellose, Sodium starch glycolate in different concentrations i.e 4.5% and 3% and the selected superdisintegrants were used along with different diluents like microcrystalline cellulose and their combinations. Comparative evaluation of Terbinafine Hydrochloride tablets by wet granulation method as its formulations rapidly disintegrates in the stomach .The *in-vitro* percentage drug release from the formulation F-8 prepared by wet granulation compression containing Microcrystalline cellulose at concentration of 5% was found to be 99.67% drug release.

Keywords: Terbinafine hydrochloride, Crosscarmellose sodium , Immediate release tablets , superdisintegrants

INTRODUCTION:

Among the different routes of drug administration, oral route is mostly preferred. About 90% of drugs are administered orally for systemic effect. Various kinds of solid dosage forms like tablet, capsules, pills, syrups etc are administered through oral route of drug administration. In orally administered dosage forms, tablet represents the preferred choice of class of product. The tablet is convenient, in terms of self medication, ease of administration, compactness, accurate dose, avoidance pain, versatility and most importantly patient compliance. Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either direct compression or molding methods.

The term " Immediate release" pharmaceutical formulati - on includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for modified, controlled, sustained, prolonged , extended or delayed release of drug.

Terbinafine hydrochloride is a synthetic allylamine antifungal agent and it is highly lipophilic in nature and tends to accumulate in skin, nails, fatty tissues, bacterias of the duodenum and viral infections of the stomach. Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell membrane synthesis pathway.So terbinafine prevents conversion of squalene to lanosterol, ergosterol cannot be synthesized. This is thought to change cell membrane permeability, causing fungal cell lysis. It is an anti-fungal which diffuses rapidly into the skin from topical applications and effectively treats athlete's foot i.e.tinea pedis. Terbinafine hydrochloride interferes with the integrity and growth of the fungal cell wall by weakening the cell wall and eventually leading to fungal cell death .It is effective at low levels and diffuses rapidly into the skin to effectively cure tinea.

MATERIALS AND METHODS:

Materials:

Terbinafine hydrochloride was supplied by Arti Chemicals limited and Crosscarmellose sodium from Ferro sigmet chemicals and Microcrystalline cellulose from Accent microcellulose and HydroxyPropyl Cellulose and Sodium

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Starch glycolate from Pharial Chemicals and Cross carmellose Sodium from Prachin chemicals and Colliodal Silicondioxide from Cabot Sanmar limited and Magnesium state from Ferro Sigmet chemicals.

Preformulation Study:

Preformulation studies are the first step in the rational development of dosage form of a drug substance . The objective of preformulation studies are to develop a portfolio of information about the drug substance ,so that this information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Identification of Terbinafine Hydrochloride Infra red spectrum:

The I.R. absorption spectrum of Terbinafine Hydrochloride sample should be in accordance with the I.R. absorption spectrum of standard Terbinafine Hydrochloride.

Identification by UV spectrophotometer:

100 mcg/ml solution of Terbinafine Hydrochloride in methanol shows absorption maximum at about 283 nm.

Solubility Studies:

For crude solubility, equivalent amount of the drug was taken in different test tubes containing the different solvents. Test tubes were shaken vigorously after the addition of each portion of solvent and then crude solubility was observed by visual inspection.

Melting Point Determination:

The melting point of the Terbinafine hydrochloride was determined by using capillary melting point apparatus.

Wavelength Determination:

Wavelength maximum determination in methanol:

10 mg of Terbinafine Hydrochloride was accurately weighed and dissolved in small quantity of methanol into 10 ml of volumetric flask and the volume was made up to 10 ml with methanol to produce stock solution having a concentration of 1000 µg/ml. 1 ml of solution from stock solution was pipette out in 10 ml of volumetric flask and volume was made up to 10 ml with methanol to produce the solution having a concentration of 100 µg/ml. The prepared solution was scanned in the range of 200-400nm by Shimadzu 1700 UV spectrophotometer using methanol as blank solution. The wavelength maximum was observed at 283 nm. The spectrum showing λ_{max} 283 nm is given fig.3.

Calibration Curve Of Terbinafine Hydrochloride:

Preparation of primary stock solution:

10 mg of Terbinafine Hydrochloride was accurately weighed and dissolved in small quantity of methanol in 10 ml of volumetric flask and volume was made upto 10 ml with methanol to produce stock solution having a concentration of 1000 µg/ml.

Preparation of secondary stock solution:

From the primary stock solution, 1 ml of solution was taken in the 10 ml of volumetric flask and diluted upto 10 ml with methanol to produce secondary stock solution having concentration of 100 µg/ml.

Preparation of aliquots:

Aliquots having concentration range of 2-32 µg/ml was prepared by approximately diluting the secondary stock solution with methanol separately. The absorbance of each aliquots was measured at λ max 283 nm using methanol as a blank respectively & standard curve was plotted between concentration in µg/ml on X-axis & absorbance on Y-axis.

Partition Coefficient:

10 mg of the Terbinafine Hydrochloride was accurately weighed and dissolved in 10 ml of distilled water and 10 ml of n- octanol in separating funnel. This mixture was shaken for 10 minutes interval for 1 hour and left it for 24 hours. The two layers were separated out using separating funnel. The aqueous phase was filtered with the help of filter paper and was diluted 100 times with methanol. The absorbance of aqueous phase was taken at 283 nm using methanol as a blank in 1700 Shimadzu UV spectrophotometer and the concentration was determined with the help of standard curve of drug and the partition coefficient was determined by following formula:

$$P_{o/w} = C_{oil}/C_{aq}$$

INFRARED SPECTROSCOPY STUDY:

IR spectroscopy deals with the study of absorption of IR region, which extends from the red end of the visible spectrum to the microwave region. An IR radiation is absorbed by a molecule when the applied IR frequency is equal to the natural frequency of vibration of the molecule. Absorption of IR radiation brings a change in the dipole moment of the molecule.

Drug Excipient Interaction Study By FTIR:

Method- An accurately weighed quantity of KBr was dried in Hot air oven at 600-700 °C .Dried KBr crushed & put in assembly for finding the background. After it 95% of KBr & 5% of blend sample was mixed. Mixture was placed in assembly and then IR spectra

Angle Of Repose:

The angle of repose of Terbinafine hydrochloride was determined by the glass funnel method. The accurately weighed quantity of Terbinafine hydrochloride were passed through the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Bulk Density:

The bulk density was measured by the dividing the mass of a powdered by the bulk volume in cm3.

$$\text{Bulk Density}(\rho b) = \frac{\text{Weight of drug}(W)}{\text{Bulk Volume}(Vb)}$$

Tapped Density:

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm3 .

$$\text{Tapped Density}(\rho t) = \frac{\text{Weight of drug}(W)}{\text{Tapped volume}(Vt)}$$

Compressibility Index:

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation:

$$\text{C.I.} = \frac{(\text{tapped density} - \text{bulk density})}{\text{tapped density}} \times 100$$

Hausner's Ratio:

It provides an indication of the degree of densification which could result from vibration of feed hopper.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Particle Size Determination :

Active pharmaceutical ingredient Terbinafine hydrochloride was analyzed for particle size distribution by means of sieving method using mechanical sieve shaker Electromagnetic sieve shaker EMS8 . A series of standard sieves namely 20#, 40#, 60#, 80# and above were stacked one above the other so that sieves with larger pore size (less sieve number) occupied top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom. Weighed quantity of API was placed in sieve no. 40. Sieve shaker was set for 5 min at amplitude of 60. Remove the set up from the sieve shaker after 5 min and weigh the API retained in each mesh individually. The percentage retained in each sieve was calculated with the following formula.

Instrument used = Electromagnetic sieve shaker EMS8:

50 gm of Terbinafine hydrochloride was taken in sieve no 20 and arrange the sieve in the order of 20,40,60,80,100 and above from top to bottom Then fixed these sieves sets in the electromagnetic sieve shaker and operated for 5 minutes.

pKa Value Determination:

10 mg drug was dissolved in 50 ml of distilled water and then 20ml of drug solution was titrated with 0.1 N NaOH by using phenolphthalein as a indicator and detect the end point till pink colour appeared.Note the volume consumed by titrant when the pink colour appeared and then remaining 20 ml drug solution was further titrated by using half the quantity of 0.1 N NaoH consumed for the determination of endpoint during first titration and determine the pHof the drug solution.

Formulation Of Immediate Release Tablet By Wet Granulation Method:

Sifting: Terbinafine hydrochloride and Microcrystalline Cellulose were sifted through 40 mesh sieve.

Binder Preparation: HydroxyPropyl Cellulose was dissolved in purified water.

Granulation:
Dry mixing: The materials of stage 1 were loaded into the rapid mixer granulator and mixed for 15 min at slowspeed

Granulation: Granules were prepared by adding step 2 in step 3a.
Wet Milling: Wet granules were sifted through 08 mesh sieve.
Drying: The produced Terbinafine Hydrochloride granules were dried in fluidized bed dryer at Inlet Temp.-70^{o} C , Airflow-15% till the Loss on drying of 1.5- 2.0% is achieved at 105^{o}C for 4 minutes.

Sizing: Dried granules were passed through 16 mesh sieve.

Prelubrication: Sodium Starch Glycolate,Cross Carmellose Sodium and Colloidal Silicon dioxide were sifted through 40 mesh sieve and added to step 4.

Lubrication: Sifted granules were transferred to double cone blender.
Magnesium stearate was sifted through 40 mesh sieve and added to step 5 and mixed for 3minutes at 12 RPM.

Evaluation Parameters Of Powdered Blends:
Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Loss on drying:
1 gm of granules was weighed and kept for checking the loss on drying on a moisture sensitive balance at 105°C for 3 mins. Percentage loss of moisture content is determined.

Angle of repose:
This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.The angle of repose of granules was determined by funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The blends were passed through the funnel until it forms a heap. Further adding of granules was stopped as soon as the heap touches the tip of the funnel. A circle was drawn across it without disturbing the pile. The radius and height of the heap was noted down. The same procedure was repeated for three times and the average value was taken. The angle of repose was calculated by using equation.

$$\tan \theta = h/r$$

Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

$$Db = m/Vo$$

Tapped density:
It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$Dt = m/Vi$$

Compressibility (Carr's index):
The flowability of powder can be evaluated by comparing the loose Bulk density (LBD) and Tapped bulk density (TBD) of powder and the rate at which it packed down. Compressibility index of the granules was determined by the Carr's compressibility :

$$CI\ (\%) = \frac{TBD-LBD}{TBD} \times 100$$

Hausner's Ratio:

It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 –1.5, it was determined by the ratio of tapped density and bulk density.

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation Of Tablets:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Shape of Tablet:

Directly compressed tablets were examined under the magnifying lens for the shape of the tablet i.e.round shaped and biconvex.

Thickness:

The thickness of the tablets was determined by Vernier calipers. 3 tablets from each batch were used and the average values were calculated.

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Five tablets were randomly picked and hardness of the tablets was determined.

Friability test:

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Wt) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (WF). The % friability was then calculated :

$$\%F = \frac{W(initial) - W(final)}{W(initial)} \times 100$$

Friability test parameters:-

Number of tablets = 6
RPM(revolution per minute) = 25

Uniformity of weight (weight variation test):

This is an important in-process quality control test to be checked frequently(every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets.The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (± 3%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation: } = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Wetting time:

A conventional method was to measure wetting time and capillary of the prepared tablet.A petri dish of 5.5cm in diameter,containing 10ml of water at room temperature and the double folded absorbent paper was kept in petridish and thoroughly wetted with distilled water.The excess water was drained out of petri dish.Then tablet was placed at the absorbent paper throughout entire tablet was recorded by using stopwatch for complete wetting was recorded.

Drug Content:

Eight tablets of each batches of formulation were weighed and crushed in mortar and 10mg was weighed accurately and dissolved in 10ml of methanol.This was the stock solution from which 1ml sample was withdrawl and diluted to 10ml methanol.The absorbance was measured at wavelength 283nm using double beam UV-Visible spectrophotometer.

$$\%\text{Drug content} = \frac{\text{Practical conc. of drug}}{\text{Theoretical conc. of drug}} \times 100$$

In-vitro Disintegration test:

The disintegration time for immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 20 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

In-vitro Dissolution Studies:

The dissolution studies were carried out in 0.1 N Hydrochloric acid.
Apparatus : Dissolution Apparatus IP Type I (basket)
Medium : 0.1 N HCl 900ml
Speed : 75 RPM
Time : 60 Minutes
Temperature : 37 ± 0.5 0C.

Stability Studies:

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

Result and Discussion:

Infrared spectrum of standard terbinafine and sample:

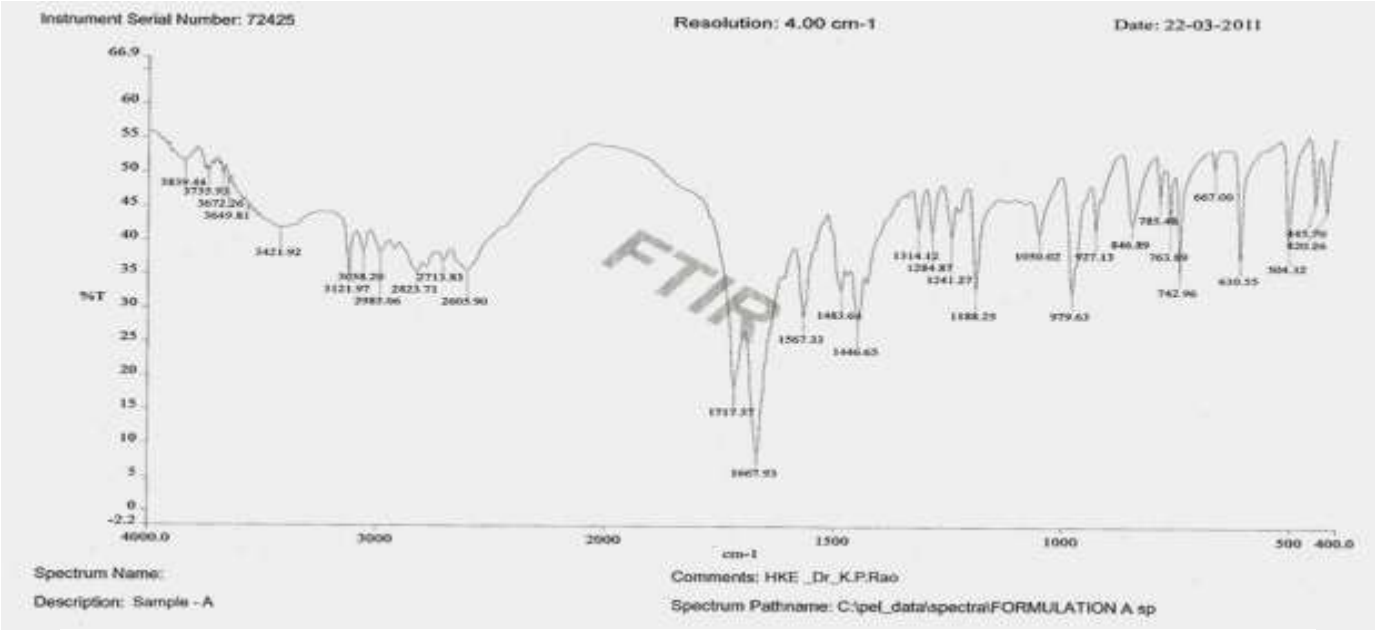

Figure 1: FTIR spectra of standard Terbinafine hydrochloride

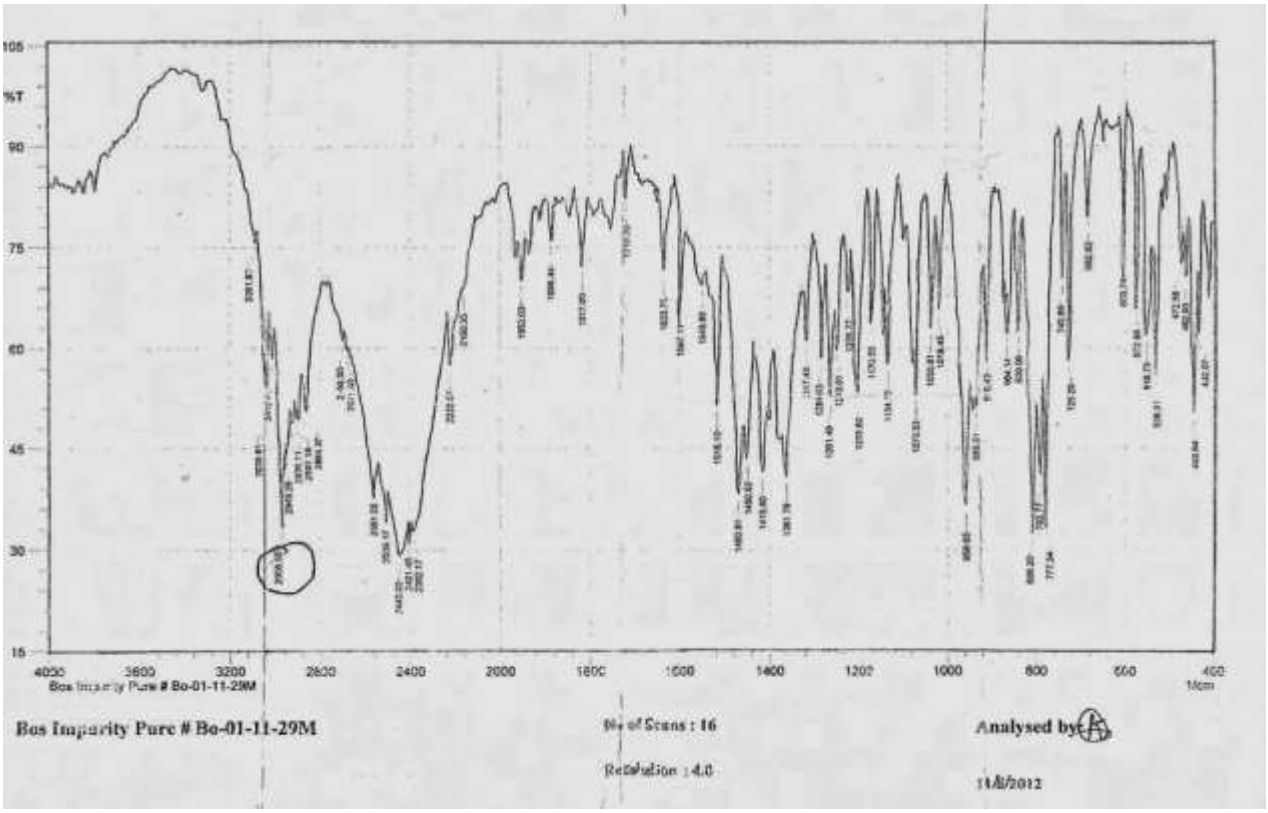

Figure 2: FTIR spectra of sample Terbinafine hydrochloride

Table.1 IR spectra having wave number range which shows signal assignment of drug

S.NO.	FUNCTIONAL GROUP	WAVENUMBER (cm^{-1})	OBSERVATION (cm^{-1})
1.	OH streching	3200-2800	2968
2.	SH streching	2800-2400	2443.89
3.	CN streching	2400-2000	2222.07
4.	C=O streching	1800-1600	1633.76
5.	CH bending	1600-1400	1469.81
6.	COOH streching	1400-1200	1361.79
7.	S=O streching	1200-1000	1070.53
8.	CH bending	1000-800	808.20
9.	C-Cl streching	800-600	777.34

The drug sample was firstly identified spectroscopically by FTIR (Fourier transform infrared) with standard sample. The result showed that the drug Terbinafine hydrochloride was pure and free from impurities because the value of drug sample similar with standard value.

Identification by UV spectrophotometer

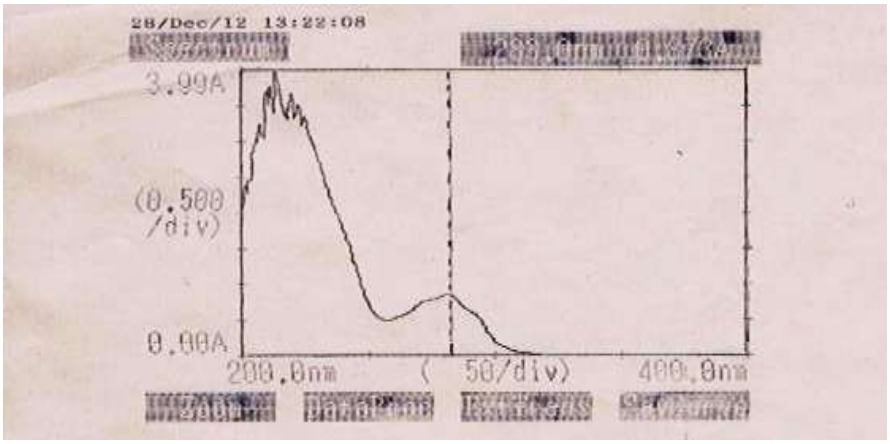

Figure 3: λmax determination of Terbinafine Hydrochloride in methanol

The maximum absorbance of drug was determined by 1700 SHIMDZU UV spectrophotometer and was found the maximum wavelength at 283nm that is similar with the standard absorbance.fig.5

Solubility Studies:

Table: 2. Solubility study of Terbinafine hydrochloride in different solvents.

S.NO.	SOLVENT	INFORM	OBSERVED SOLUBILITY
1.	Methanol	++++	freely Soluble
2.	Ethanol	+++	Soluble
3.	Water	+	Sparingly soluble
4.	0.1 N HCL	+	Sparingly soluble
5.	Chloroform	_ _ _	Insoluble

Qualitative solubility of drug was checked in various solvents and found that the drug was freely soluble in methanol and insoluble in chloroform, sparingly soluble in 0.1N Hcl ,Slightly soluble in water, The result was found that the drug Terbinaine Hydrochloride is lipophillic in nature because it was soluble in organic solvent

Melting Point Determination:

Table: 3. Melting point determination of drug

Sample no.	Melting point (°C)	Average Melting point (°C)
1.	205-206	204-207
2.	206-207	
3.	204-205	

Melting point of drug was determined by digital melting point apparatus. The melting point was found to be in the range of 205-206°C which was matched with standard value of melting point of pure compound.

ASSAY:

Percentage Purity can be calculated by the following formula:

$$\text{Percentage Purity} = \frac{V \times M1 \times EF \times 100}{M2 \times W}$$

Table 4: Assay of Terbinafine hydrochloride

S.No.	Parameters	Value
1.	V (ml)	5.2
2.	M1	0.09591
3.	M2	0.1
4.	EF	0.049
5.	W (gm)	0.25

Percentage purity of Terbinafine Hydrochloride was found to be 98.54%

Callibration Curve Of Terbinafine Hydrochloride:

Table 5: Callibration curve of Terbinafine Hydrochloride in methanol at λ max 283 nm

S.No.	Concentration(µg/ml)	Absorbance
1.	2	0.040
2.	4	0.087
3.	8	0.158
4.	16	0.354
5.	32	0.685

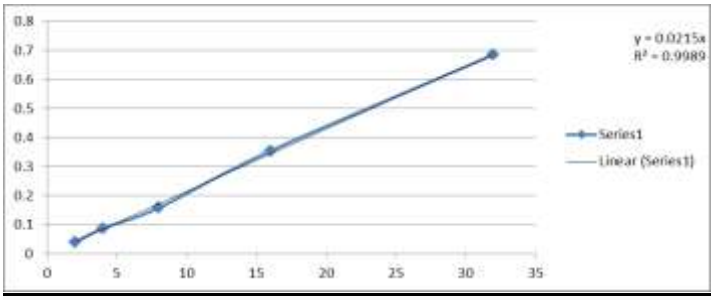

Figure 6: Calibration curve of Terbinafine Hydrochloride in methanol at λ max 283 nm

Standard curve of Terbinafine hydrochloride was prepared using methanol as a solvent by using 1700 UV Shimadzu spectrophotometer. The result showed that Terbinafine hydrochloride follows the Lambert-Beer's law between the concentration ranges of 2-32µg/ml. The R^2 values were found to be 0.998. A straight line was obtain - -ned in all the plots (figure 6).

Partition Coefficient:

Table 6: Absorbance and concentration for determination of Terbinafine hydrochloride

S. No	Solvent	Absorbance	Concentration (µg/ml)
1.	n-octanol	1.644	76
2.	Distilled water	0.516	24

Table 7: Partition coefficient of Terbinafine Hydrochloride

S. No.	Solvent system	Partition cofficient
1.	n-octanol:water	3:1

Partition coefficient of the drug Terbinafine hydrochloride was determined in n- octanol: distilled water, the value of partition coefficient was found to be 3.1. It confirms that the drug Terbinafine hydrochloride shows lipophillic characteristics, because the value of partition coefficient was more than 1. And the concentration of drug in organic portion (n-octanol) was more than the concentration of drug in aqueous portion, which is also an ideal characteristic for preparing of tablet.

Drug Excipient Interaction Study By FTIR:

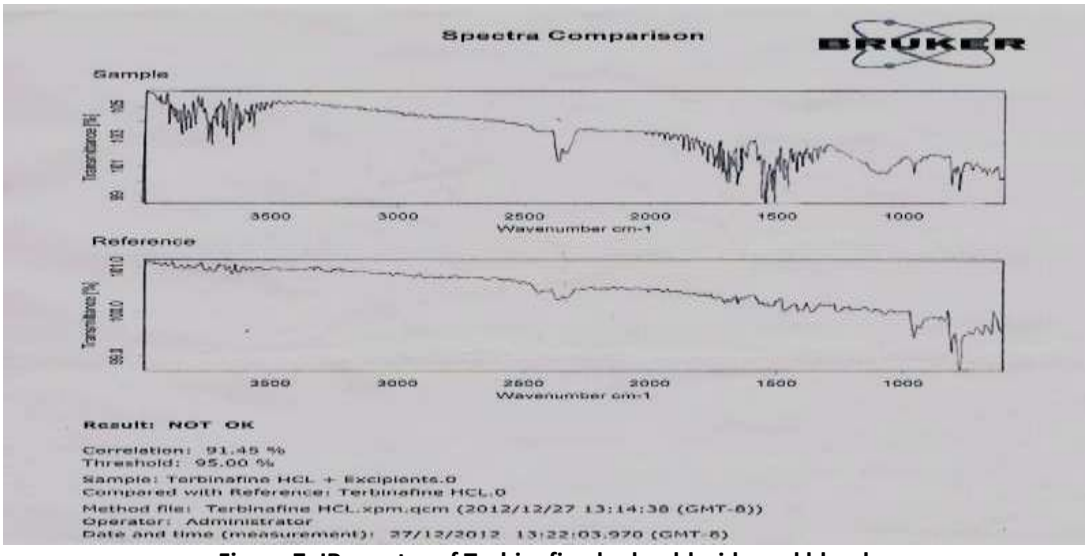

Figure 7: IR spectra of Terbinafine hydrochloride and blend

Drug Excipients Compatibility Study:

S. No.	Name Of Ingredients	Code	Category
1	Terbinafine Hydrochloride	TBH	API
2	Microcrystalline cellulose	MCC	Diluent
3	Colloidal silicon dioxide	CSD	Glidant
4	Cross Carmellose Sodium	CCS	Disintegrant
5	Hydroxy propyl cellulose	HPC	Binder
6	Sodium Starch Glycolate	SSG	Disintegrant
7	Magnesiunm stearate	MGS	Lubricant

Drug with excipients compatibility study 40^0 c

Table 8: Drug with excipients compatibility study at temperature 40°C+ 2°C with 75% +5% Relative Humidity condition

S. No	Ingredients	Ratio(D:E)	Initial observation	1st week	2nd week	3rd week	4th week
1	TBH	1	White coloured powder	NC	NC	NC	NC
2	TBH+ MCC	1:1	White to off white powder	NC	NC	NC	NC
3	TBH+CSD	1:0.5	White to off white powder	NC	NC	NC	NC
4	TBH+CCS	1:0.5	White to off white powder	NC	NC	NC	NC
5	TBH+HPC	1:0.5	White to off white powder	NC	NC	NC	NC
6	TBH+SSG	1:0.5	White to off white powder	NC	NC	NC	NC
7	TBH+MGS	1:0.5	White to off white powder	NC	NC	NC	NC

Drug with excipients compatibility study 25^0 c

Table 9: Drug with excipients compatibility study at temp. 25°C+ 2°C with 60% +5% Relative Humidity condition

S. No	Ingredients	Ratio(D:E)	Initial observation	1st week	2nd week	3rd week	4th week
1	TBH	1	White coloured powder	NC	NC	NC	NC
2	TBH+ MCC	1:1	White to off white powder	NC	NC	NC	NC
3	TBH+CSD	1:0.5	White to off white powder	NC	NC	NC	NC
4	TBH+CCS	1:0.5	White to off white powder	NC	NC	NC	NC
5	TBH+HPC	1:0.5	White to off white powder	NC	NC	NC	NC
6	TBH+SSG	1:0.5	White to off white powder	NC	NC	NC	NC
7	TBH+MGS	1:0.5	White to off white powder	NC	NC	NC	NC

Drug with excipients compatibility study 2-8 ^{0} c

Table 10: Drug with excipients compatibility study at 2-8°C temperature

S. No	Ingredients	Ratio(D:E)	Initial observation	1st week	2nd week	3rd week	4th week
1	TBH	1	White coloured powder	NC	NC	NC	NC
2	TBH+ MCC	1:1	White to off white powder	NC	NC	NC	NC
3	TBH+CSD	1:0.5	White to off white powder	NC	NC	NC	NC
4	TBH+CCS	1:0.5	White to off white powder	NC	NC	NC	NC
5	TBH+HPC	1:0.5	White to off white powder	NC	NC	NC	NC
6	TBH+SSG	1:0.5	White to off white powder	NC	NC	NC	NC
7	TBH+MGS	1:0.5	White to off white powder	NC	NC	NC	NC

Drug-excipient interaction (Drug+excipients) was determined by IR spectrophotometer. The result was found that not any interaction between pure drug and with different excipients so that the drug excipients was pure and effective.

Evaluation of terbinafine Hydrochloride:

Angle Of Repose

θ = tan-1h/r = 35° (acceptable flowability)

Carr's index = 41.0%

(It shows extremely poor flowability)

Bulk Density= 0.3 gm/ml

Hausner's ratio = 1.695

(It shows very poor flow property)

Tapped Density= 0.508 gm/ml

Discussion:

Angle of repose of drug was found to be **35.1°** which shows Acceptable flowability. Bulk density of Terbinafine hydrochloride was found to be **0.3 gm/ml**. Tapped density of drug was found to be **0.508 gm/ml.** Compressibility index of Terbinafine hydrochloride was found to be **41%** which shows that flow ability is poor flowability.Hausner ratio of drug was found to be **1.695** which shows that very poor flow proper

Particle size determination:

Table: 11. Particle size determination of Terbinafine Hydrochloride

Sieve No.	Sieve opening in µm	Mass of each sieve (mm) W_1gm	Mass of each sieve + retained API W_2gm	Mass of API retained $W=(W_2-W_1)$gm	Percentage on each sieve %	Cumulative percent retained
20	850	370.05	390.43	20.28	40.56	40.56
40	425	350.60	374.18	23.58	47.16	87.72
60	250	336.09	339.04	2.95	5.9	93.62
80	180	325.10	327.14	2.04	4.08	97.7
Base		500.72	501.21	0.49	0.98	99.68
				∑W=49.34		

Particle size analysis was carried out by Electromagnetic sieve shaker EMS8 using sieve of different mesh size number which shows that large percentage of particle was obtained on 40 mesh number sieve whose Seive opening is **425 µm**.

Acid Dissociation Constant:

Table: 12. Data for pH value and pKa value of drug

S.No.	Titration with 0.1 N NaOH	RESULT
1.	pH value	5.8
2.	pKa value	5.8

pKa value of drug was determined by pH meter is **5.8** means drug is **weakly acidic** in nature.

Evaluation of blend:

Loss on drying:

Table: 13 Results of loss on drying of Terbinafine HCl bulk drug.

S. NO.	Test	Specification / limits	Observations
1.	Loss on drying	Not more than 2% w/w	1.82%w/w

1 gm of granules were weighed and kept for checking the loss on drying on a moisture sensitive balance at 105°C for 3 mins. Percentage loss of moisture content was **1.82%.**

Flow Property of Blends:

Table 14: Evaluation of granules of Terbinafine Hydrochloride Immediate release

Form.	PARAMETERS				
	Angle of Repose (^{0})	BD (g/ml)	TD (g/ml)	CI (%)	HR
F-1	28.4 ± 0.03	0.69 ± 0.5	0.83 ± 0.21	16.86 ± 1.4	1.20 ± 0.72
F-2	27.5 ± 0.06	0.72 ± 0.48	0.79 ± 0.2	10.12 ± 1.4	1.11 ± 0.7
F-3	27.9 ± 0.03	0.71 ± 0.28	0.80 ± 0.21	11.25 ± 1.4	1.12 ± 0.7
F-4	25.6± 0.06	0.64 ± 0.7	0.73 ± 0.22	12.32 ± 1.5	1.14 ± 0.72
F-5	24.8 ± 0.03	0.60 ± 0.8	0.65 ± 0.2	7.69 ± 0.11	1.08 ± 0.7
F-6	25.3 ± 0.03	0.53 ± 0.9	0.61 ± 0.23	13.11± 1.5	1.15 ± 0.7
F-7	25.3 ± 0.07	0.48 ± 0.8	0.54 ± 0.2	12.09 ±0.07	1.12 ± 0.7
F-8	25.1 ± 0.01	0.47 ± 0.8	0.55 ± 0.2	14.54 ± 1.3	1.15 ± 0.7

Discussion:

The values of angle of repose of blend range from **24.8^o + 0.03 to 28.4^o + 0.03** respectively therefore formulation F-8 value **25.1^o + 0.01** indicates the good flowability. Bulk density of blend ranges from **0.47 + 0.8 to 0.72 + 0.48 respectively therefore** formulation F-8 value **0.47 + 0.8 gm/ml** which shows goodoptimized batch. Tapped density of blend ranges from **0.54 ± 0.2 to 0.83 ± 0.21** respectively therefore formulation F-8 value **0.55 + 0.2 gm/ml** which shows optimized batch. Carr's index of blend ranges from **7.69 ± 0.1 to 16.86 ± 1.4** respectively therefore formulation F-8 value **14.54 ± 1.3%** shows good flow property of optimized batch.Hausner's Ratio of blend ranges from **1.08 ± 0.7 to 1.20 ± 0.7** respectively therefore of formulation F-8 value **1.15 ± 0.7** shows good frictional resistance of optimized.

Sieve analysis:

Table: 15. Sieve analysis of Terbinafine Hydrochloride blend of optimized batch F-8

Sieve No.	Seive opening in µm	Mass of each sieve (mm)W_1gm	Mass of each sieve + retained API W_2gm	Mass of API retained $W=(W_2-W_1)$gm	Percentage on each sieve %	Cumulative percent retained
20	850	370.05	377.23	7.18	14.36	14.36
40	425	350.60	364.70	14.1	28.20	42.56
60	250	336.09	348.99	12.9	25.80	68.36
80	180	325.10	330.83	5.73	4.08	72.44
Base		500.72	510.75	10.03	20.06	99.88
				∑W=49.94		

From the above parameters from formulation F-1 to F-8, F-8 shows optimized batch for Sieve analysis. The maxim-um particles lie between the range from 250-425 µm.

EVALUATION OF TABLETS:

Shape of Tablet:

Figure 8: Shape of tablet

#Directly compressed tablets were examined under the magnifying lens for the shape of the tablet i.e.round shaped and biconvex.

Table: 16. Evaluation of compressed Terbinafine Hydrochloride tablets

S. NO.	TESTS	SPECIFICATION	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Appearance	White coloured oblong shaped tab.	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
2	Identification test	Should pass	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
3	Weight variation(mg)	330 ± 5% from average weight	328-334	327-335	328-334	326-333	325-331	327-334	328-332	325-335
4.	Drug content	95% to 105%	97.92	98.35	96.03	95.86	99.41	98.60	98.67	99.85
6	Thickness (mm)	4.30mm ± 0.2% from average	3.66	3.68	3.67	3.66	3.66	3.76	3.78	3.82
7	Hardness (kg/cm^2)	3-10 kg/cm2	9.4	9.8	8.5	7.4	7.9	7.9	7.5	7.2
8	Friability (%w/w)	NMT 1% w/w	0.63	0.60	0.65	0.45	0.43	0.23	0.21	0.16
9.	Disintegration	NMT 15 min	7-8	5-6	5-6	6-7	3-4	2-3	3-4	2-3

Discussion:

Thickness:

The thickness of the tablets was determined by Vernier calipers. 3 tablets from each batch were evaluated and the average values were calculated in formulation but F-8 is optimized batch F-8 which shows **3.76 ± 0.2mm**

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.. Hardness of the tablets from formulation F-1 to F-8 ranged from **7.2 ± 0.1 to 9.8 ± 0.09** therefore optimized batch formulation F-8 shows **7.2 to 9.8 Kg/cm^2**.

Friability test:

Friability of formulation F-1 to F-8 in the ranged **0.22 to 0.74%**.Therefore friability of optimized batch in formulation F-8 was **0.22%.**

Uniformity of weight (weight variation test):

The Pharmacopoeial limits for deviation for tablets of more than 324mg are ± 5%.The average percentage deviation for all formulations ranged from **-0.1 to + 2.06** therefore optimized batch in F-8 was found to be in range **-0.1 to +1.2** complied with standard.

Wetting time:
Wetting time of formulation F-1 to F-8 ranged from **54sec.to 58sec**.which shows minimum wetting time required in F-8 batch was **54 sec** which shows optimized batch.

Drug Content
The drug content of formulation F-1 to F-8 was found to be in the range **95.86 to 99.85**%.Therefore drug content of optimized batch F-8 was found to be maximum **99.8%**

***In-vitro* Disintegration test:**

Table: 17. Data for Disintegration time of compressed tablets

Formulation codes	Disintegration time (min)	Average +SD (min)
F-1	7-8	6.5 + 0.5
F-2	5-6	5.5 + 0.5
F-3	5-6	5.5 + 0.5
F-4	6-7	6.5 + 0.6
F-5	3-4	3.5 + 0.7
F-6	2-3	2.5 + 0.6
F-7	3-4	3.5 + 0.7
F-8	2-2.5	2.25 + 0.25

Discussion: The time taken for the tablets to *in-vitro* disintegrate of formulation F-1 to F-8 was in the range **2-7 min** therefore the minimum time to disintegrate the tablet of optimized batch F-8 was **2-3 min**.

***In-vitro* Dissolution Studies:**

Table: 18. *In-vitro* dissolution study of Formulation F-8

S. No.	Time (min)	Absorbance	Conc. (µg/ml)	Dilution Factor	Amount Released= $\frac{Cx\ d.f.}{1000}$ (mg)	% Drug Release= Amt.release x100/281.3	Cumulative %drug release
1.	10	0.325	15.47	9000	139.28	49.51	49.51
2	20	0.413	19.6	9000	176.4	62.70	112.21
3	30	0.483	23	9000	207	73.58	185.79
4	40	0.538	25.61	9000	230.49	81.93	267.72
5	50	0.607	28.90	9000	260.1	92.46	360.18
6	60	0.653	31.14	9000	280.26	99.63	459.81

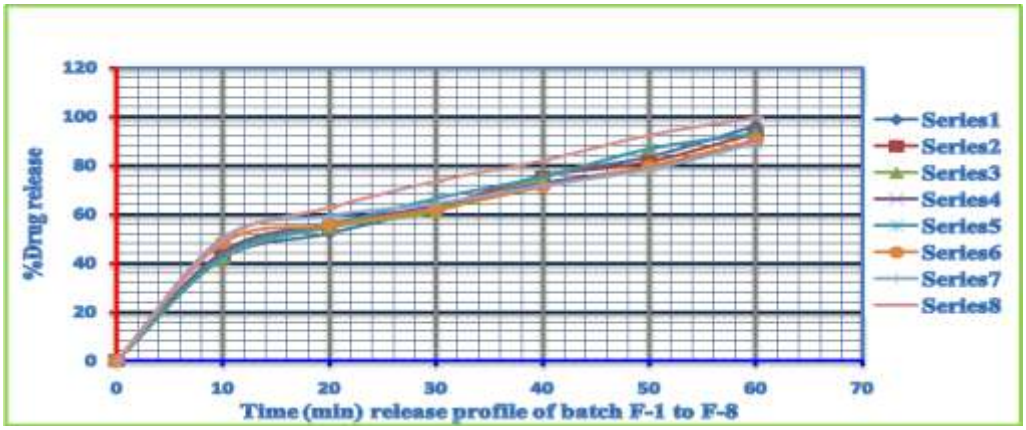

Figure 9: Comparision of *In-vitro* %drug release of formulation F-1 to F-8

#*In-vitro* dissolution study of tablet from formulation F-1 to F-8 ranged from **89.12 to 99.63 %** therefore formulation F-8 was maximum drug release in 60 minutes is **99.63%** .

Stability Study:

Table: 19. Comparative Stability at temperature 25^{0}C ± 2^{0}C with 60% ± 5%Relative Humidity of optimized Formulation F-8

Test	Limits	Initial	Storage Condition at temp. 25^{0}C ± 2^{0}C with 60% ± 5%Relative Humidity		
			1M	2M	3M
Description	**White coloured round tablets**	**Complies**	Complies	Complies	Complies
Moisture content	**3.0%**	**2%w/w**	1.87% w/w	1.95% w/w	2.0% w/w
Disintegration Time	**Not more than 15 minutes**	**2min 50sec**	2min	2min 30sec	2min 50sec
Dissolution Time	**Not less than 70% in 45 min**	**92%**	90%	88%	81%
Related substances	**Not more than 0.1%**	**0.02%**	0.02%	0.03%	0.04%
Assay	**90.0 to 110.0% 0f label claimed**	**98.3%**	97.3%	97.6%	98.1%

Table 20: Comparative Stability at temperature 30^{0}C ± 2^{0}C with 65% ± 5% Relative Humidity of optimized Formulation F-8

Test	Limits	Initial	Storage Condition at temp. 40^{0}C ± 2^{0}C with 75% Relative Humidity		
			1M	2M	3M
Description	**White coloured round tablets**	**Complies**	Complies	Complies	Complies
Moisture content	**5.0%**	**1.6%%**	1.6%	1.7%	2%
Disintegration Time	**Not more than 15 minutes**	**2min 30 sec**	2min 50sec	2min 30sec	2min10sec
Dissolution Time	**Not less than 70% in 45 min**	**93%**	92%	91%	87%
Related substances	**Not more than 0.1%**	**0.01%**	0.02%	0.03%	0.03%
Assay	**90.0 to 110.0% of label claimed**	**97.1%**	97%	96.5%	96.3%

Table 21: Comparative Stability at temperature 40^{0}C ± 2^{0}C with 75% ± 5% Relative Humidity of optimized Formulation F-8

Test	Limits	Initial	Storage Condition at temp. 40^{0}C ± 2^{0}C with 75% ± 5% Relative Humidity		
			1M	2M	3M
Description	**White coloured round tablets**	**Complies**	Complies	Complies	Complies
Moisture content	**5%**	**3%w/w**	2.20%w/w	2.49%w/w	2.65%w/w
Disintegration Time	**Not more than 15 minutes**	**3min**	2 min 15sec	2min 25sec	2min 30sec
Dissolution Time	**Not less than 70% in 45 min**	**95%w/v**	84%	82%	82%
Related substances	**Not more than 0.1%**	**0.01%**	0.02%	0.02%	0.03%
Assay	**90.0 to 110.0% 0f label claimed**	**99.1%**	98.5%	97%	96.7%

By compiling formulation F-8 is considered as optimized batch for stability study for 90 days accelerated ,Intermed -iate and long term stability study and the result was com -pared with that obtained before storage.There was a negligible change in the wetting time,disintegration time, dissolution time, and percentage drug release.

SUMMARY AND CONCLUSION:

The oral route is widely used as it is convenient,safe and offers numerous astonishing advantages over other routes like patient compliance and rapid cessation of drug input and can maintain a suitable plasma concentration.The oral route is the most common way of administering drugs,and among the oral dosage forms tablets of various different types are the most.Sucess of the *In-vitro* drug release studies and disintegration studies recommends the product for further *in-vivo* studies,which may improve patient compliance.From the literature of Terbinafine Hydrochloride individual dosage form was used in the management of fungal infection.Terbinafine hydrochloride as immediate release tablet which improves the patient compliance. The present work involves the formulation ,development and evaluation of Terbinafine Hydrochloride Immediate release tablets.Using microcrystalline cellulose and crosscar- mellose sodium as a superdisintegrant for immediate release tablet along with polymer such as hydroxyl propyl cellulose and lubricant as magnesium stearate.Terbinafine hydrochloride as analternative to the other conventional dosage form for the treatment of fungal infections.To minimize critical process parameters, wet granulation method was selected for the formulation of Terbinafine hydrochloride immediate release tablet.

Under the preformulation studies API (Active Pharma -ceutical Ingredient) characterization, and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.

The polymers and other excipients were selected based on the satisfying results produced during drug-excipient compatibility studies to develop the final formulation.

The *In-vitro* study showed that formulation F-8 was ideally suited to be immediate release formulation.

The final suitable formulation was achieved fruitfully by the wet granulation method. HPC at a concentration of 5% produced desired release profile for Terbinafine HCl immediate release as per specifications.

The results reveal that trial F-8 has met the objective of immediate drug release, patient convenience and cost effectiveness as a once a day dose of the drug

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