CHAPTER-7
DISCUSSION

With the advent of medicated topical applications for transdermal drug delivery, the skin is now viewed as a potential portal of entry. Topical fungal infection can best be treated by application of gels over the skin surface, from which the drug released continuously to the desired site. Many pharmaceutical formulations intended for topical use require the addition of a solubilizer to enhance the solubility of poorly soluble compounds.

PHASE-I
Hydrotropy:

Hydrotropy is a solubilization process whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. In the present study efforts were made to prepare hydrotropic starch gels of Terbinafine HCL using natural polymers corn (10%), potato (10%) starches and hydrotropic salts (Urea and Mannitol) in different concentrations (10, 12.50, 15, w/w).

The calibration of standard curve of Terbinafine HCL obeys the Beers Lambart’s law within the working range with correlation coefficient (r) value 0.9995.

The results were very interesting which are discussed here:

PHASE-II
Solubility:

The solubility of the drug was determined in various solvents, like distilled water, Urea and Mannitol.

The solubility of Terbinafine HCL was found to be more in Urea (15% w/w) as compared to that of Mannitol (15% w/w). Several
mechanisms have been proposed to explain the remarkable increase in the solubility of water insoluble drugs by using hydrotropic salt solution. But the actual mechanism by which this effect occurs is not clear.

**Physical Appearance:**

The hydrotropic starch gels were evaluated for their physical appearance and homogeneity, which was found to be acceptable.

**pH:**

pH of hydrotropic starch gels was found between 6.44 to 6.65, for gels prepared using corn starch with Urea and 7.19 to 7.46 for gels prepared using corn starch with Mannitol. The pH of the hydrotropic starch gels prepared by using potato starch with Urea and Mannitol was 6.29 to 6.41 and 7.35 to 7.46 respectively. Thus indicating suitable for application to the skin. The pH of the formulation containing Mannitol is higher than that of Urea.

**Drug Content:**

Drug content of the formulation was carried out and was found to be within the range between 96.00 to 99.50%.

**PHASE-III**

**In vitro release studies**

The percent drug release of hydrotropically prepared medicated starch gels using corn starch with Urea and Mannitol was TCU-I (25.04%), TCU-II (33.91%), TCU-III (57.94%) and TCM-I (22.86%), TCM-II (25.12%), TCM-III (30.53%) respectively. The percent drug release of hydrotopically prepared medicated starch gels using potato starch with Urea and Mannitol was TPU-I (23.77%), TPU-II (25.26%), TPU-III (29.69%) and TPM-I (20.51%), TPM-II (23.72%), TPM-III (25.13%) respectively.
The percent drug release for marketed Preparation (MP1) was 16.43%. Hydrotropic starch gel TCU-III showed a highest drug release of 57.94% as compared to the other hydrotropic starch gels and marketed cream. To know the release mechanism, the in vitro drug release data were treated to zero order, first order, Higuchi equation, Peppas. Plots were found to be fairly linear indicating the drug release, follows first order kinetic with diffusion controlled.

**PHASE-IV**

**Rheological behaviour:**

Rheological properties help in understanding the physicochemical nature of vehicle and quality control of ingredients, test formulation and final products.

**Viscosity:**

Viscosity is an important parameter for characterizing the gels as it effect the spreadability, extrudability and release of the drug. The viscosity of hydrotropic starch gels prepared by using potato starch and corn starch was determined. The hydrotropic salts Urea and Mannitol has also shown an effect on viscosity, as the concentration of salts was increased there was an increase in the viscosity of the gels. Gels containing Mannitol were found to be more viscous than that containing Urea; as shown in table No.33, 36, 35 and 37. Hydrotropic starch gels TCU-III also evaluated for the rheological behavior by using spindle No SC428/13 R at eight different speeds and the shear stress (dynes/cm²) and shear rate (S⁻¹) was calculated.

The apparent viscosity (cp) value of TCU-III was found to be 105230 and 3054, at low shear rate 0.14 and high shear rate 28.

The rheological data further indicated that hydrotropically prepared starch gels were found to exhibit shear thinning property when shear rate is increased. The ascending and descending rheograms are not supper
imposed and can be concluded as thixotropy in nature with the hysteresis loop as shown in figure-60 & 61. The stress shear rate data was also plotted as casson plots for TCU-III.; the system gave pseudo plastic flow with considerable shear thinning tendency with better spreadability.

**Spreadability:**

Spreadability plays an important role in patient compliance and help in uniform application of gel to the skin. Gels should spread easily. All the formulations were found to have better spreadability.

**PHASE-V**

**IR Studies**

Drug-polymer interaction study was carried out by taking IR spectrum of the pure drug, corn starch, Urea and best formulation (TCU-III).

**Urea:**

The IR spectrum of Urea was recorded; the plain molecule exhibited the carbonyl absorption of urea at 1597 cm⁻¹ as a dominating absorption of characteristics carbonyl group, which is in accordance with the structure of the molecule as shown in figure-62-66.

**TCU-III:**

The drug Terbinafine HCL exhibited number of peaks due to the c-h at 30412 cm⁻¹ to 2862 cm⁻¹. The characteristic peak due to the c≡c is observed at 2444 cm⁻¹, in its structure as shown in figure-62.

In the formulation along with corn starch and Urea and Terbinafine HCL was prepared and IR has been recorded an expected a broad hump is observed at 3444 cm⁻¹ due to OH/CH of starch and drug. A broad peak at 2075 cm⁻¹ were in peak due to the triple bond of the drug has merged to give rise to a broad peak at 2075 cm⁻¹. the carbonyl peak due to the Urea is observed at 31637 cm⁻¹ indicating in this case also drug has remained intact without undergoing any chemical reaction during the formulation.
PHASE-VI

Stability Studies:

Stability studies was carried out for hydrotropic starch gels TCU-III at $28^0\text{C}\pm3^0\text{C}$ for a period of 6 months according to ICH guidelines and all parameter was evaluated at an interval of one month. After six month the result of stability at $28^0\text{C}\pm3^0\text{C}$ was found to be (99.46%) drug content, at 6 hrs 55.40% of drug was released, 105271 cp of viscosity, 6.5 pH, and 14.29 gm c/s spreadability was found. And at $5^0\text{C}\pm3^0\text{C}$ 99.46% of drug content, 55.3% of drug release at 6 hrs, 105210 cp viscosity, 6.5 pH, and 14.2 gmc/s spreadability was found respectively.

PHASE-VII

In-vitro antifungal Activity: In vitro antifungal activity of hydrotropic starch gels TCU-III, TCM-III, TPU-III, TPM-III and MP1 were determined by cup-plate method using candida albicans as test organisms and zone of inhibition was measured.

PHASE-VIII

Skin irritation

The hydrotropic starch gels TCU-III, TCM-III, TPU-III, TPM-III & MP1 were subjected for skin irritation test. The skin irritation tests were performed on healthy white rabbit for a period of 3 days and the visual inspection was done at different time interval. From the results of the study it was clear that there is no (erthrema & edema) found after 72 hours and hence, it was concluded that the hydrotropic starch gels doesn’t produced any irritation on skin after application.