INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received; accepted

HYDROTROPIC MEDICATED STARCH GELS FOR IMPROVED THERAPEUTIC ACTIVITY

K.Purushotham Rao*[1], Aamer Quazi[2], A.Ravindranath[3], D.Jayaprakash[3]

1. H.K.E College of Pharmacy,(M.R.Medical College), Gulbarga (K.S.) . India
2. Dr. Baba Saheb Ambedkar Marathwada University, Aurangabad,(M.S.)-India
3. Dept.Of Pharmacy., Osmania University., Hyderabad.(A.P.)-India

Keywords:
Terbinafine, hydrotropic starch gels

For Correspondence:

K.Purushotham Rao

H.K.E College of Pharmacy,(M.R.Medical College), Gulbarga (K.S.) . India

E-mail:

kprao369@rediffmail.com

ABSTRACT

Hydrotropic phenomenon is one method of preparation of starch gels without the use of heat, with the use of hydrotropical salts and also called as chemical gelling useful for improved bioavailability of poorly soluble drugs in water. The solubility problem can be solved by changing the nature of drug molecule. Terbinafine is characterised by its poor water solubility and low bioavailability. The main objective of present study was to prepare Terbinafine gels by hydrotrotric phenomenon using corn starch as base and urea, mannitol as hydrotropic salts in varied concentrations and characterize systematically for various physico-chemical parameters like spreadability, tube extrudability, pH, drug content estimation etc. All the prepared formulations were subjected for in-vitro drug release parameters by diffusion method for six hours In 100 ml phosphate buffer (pH 7.4) and compared with marketed formulation. Formulation TCU-III containing 15% Urea, 10% corn starch and 1% w/w of drug Showed highest drug release of 57.94 % as compared to marketed preparation 16.43%. IR spectra showed that there was no interaction between the drug and additives, and hence the drug remains intact without undergoing any chemical reaction during the preparation and after its storage.

Introduction:

The skin often has been referred to as the largest of the body organs. An average adult's skin has surface area of about $2m^2$. Its accessibility and the opportunity it affords to maintain applied preparation intact for a prolonged time have resulted in its increasing use as a route of administration whether for local, regional or systemic effects. (1) Fungus infections are extremely common and some of them are serious and even fatal. With the control of most bacterial infections in the developed countries, fungus infections have assumed greater importance. Fungal infections are termed mycoses and in general can be divided into superficial infections (affecting skin, nails, hairs or mucous membranes) and systemic infections (affecting deeper tissues and organs). In the last 20-30 years, there has been a steady increase in systemic fungal infections, not only by known pathogenic fungi but also by fungi previously thought to be innocuous and are termed opportunistic infections. (2) The techniques generally employed to enhance the solubility of poorly water soluble drugs are use of surface active agents, hydrates and solvates, polymorphism, complexation, hydrotropic solubilization and conventional trituration and grinding. Among these techniques, hydrotrope solubilization is considered as easy method of solubilization.Hydrotropes are class of compounds that normally increase the aqueous solubility of insoluble solutes (3,4). .Starches when used with hydrotropic salts (solubilizing agent) in specified concentrations results in hydrotrope gels without the use of heat and at room temperature, which will serve as a vehicle for topical drug delivery (5,6). The present work was focused on the influence of hydrotropic phenomenon on the solubility profile of Terbinafine which belongs to non-steroidal anti-inflammatory drugs (NSAID).

Materials and Methods: Terbinafine was a Gift Sample from Eurodrug labs, Hyderabad. All the chemicals and solvents were of analytical grade.

Formulation of hydrotropic starch gels[7]: Hydrotropic starch gels were prepared by dissolving the weighed quantity of hydrotropic salt (Urea,mannitol) in 40 ml of water along with 1 gm of drug, Starch (corn10%) was weighed and dispersed in remaining quantity of water i.e., 60 ml and was added to the hydrotropic salt solution and the

solution was stirred at 100 rpm for a period of 2 hours until complete gelation was achieved.(Table No 1.)

Evaluation of Hydrotropic Starch Gels: Physical appearance and homogeneity: Hydrotropic starch gel was visually inspected for clarity, color, homogeneity, presence of particles and fibers.

Determination of pH[8,9]: The pH of gels was determined by using a digital pH meter at room temperature. Initially, the pH meter was calibrated using standard buffers of pH 4 and 9.2. Accurately weighed 2.5 gm of gel was dispersed in 25 ml of purified water. The calibrated pH meter was dipped in the gel solution and pH was recorded.

Drug Content Uniformity: The drug content estimation was carried out by dissolving accurately weighed quantity of hydrotropic starch gel equivalent to 50 mg of drug was added to 20 ml of methanol and the volume were made up to 25 ml with methanol. 10 ml filtrate was transferred into another 100 ml of volumetric flask and volume was made up to 100 ml with methanol. The content was assayed at 224 nm against reagent blank by using Shimadzu UV / visible spectrophotometer. The drug content was carried out in triplicate.

Spreadability[10,11] : Spreadability of the formulations was determined by an apparatus suggested by Mutimer et al, which was suitably modified in the laboratory and used for the study. It consists of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on the block. An excess of gels (about 2 gm) under study was placed on the lower plate. The gel was then sandwiched between lower glass plate and another upper glass plate having the same dimensions, provided with the hook. A weight of 1 Kg was placed on the top of the two plates for 5 minutes to expel air and to provide a uniform film of the gel between the plates. Excess of gel was scrapped off from the edges. The upper plate was then subjected to a pull of 50 gm. With the help of a string attached to the hook and the time (in sec) required by the upper plate to cover a distance of 10 cm was noted. A shorter the time interval better the spread ability.

Extrudability[12,13]: In the present study, the method adopted for evaluating gel formulations for extrudability was based upon the quantity in percentage of gel extruded from tube. More the quantity extruded better was extrudability.

***In vitro* Diffusion Study[14,15]:** The drug release from the formulations was determined by using the apparatus, which consist of a cylindrical glass tube (with 22-mm internal diameter and 76 mm height) which was opened at both the ends. 1 gm of gel equivalent to 10 mg of Terbinafine.HCL was spread uniformly on the surface of cellophane membrane (previously soaked in medium for 24 hrs) and was fixed to the one end of tube. The whole assembly was fixed in such a way that the lower end of tube containing gel was just touches (1-2 mm deep) the surface of diffusion medium i.e. 100 ml of pH 7.4 phosphate buffer contained in 100 ml beaker, The assembly was placed on thermostatic hot plate with magnetic stirrer and maintained at temperature 37°±2°c the contents were stirred using magnetic bar at 100rpm for a period of 6 hrs, 5 ml of samples were with drawn at different time intervals and replace with 5 ml of fresh buffer and after suitable dilution the sample were analyzed at 224 nm for Terbinafine.HCL.

Phase IV: Rheological studies: Viscosity[16,17] of hydrotrope-gelled starches was determined by using Brookfield's synchro-electric RVT model digital viscometer. The gel was placed in the sample holder and the suitable spindle selected was lowered perpendicularly into the sample. The spindle was attached to viscometer and then it was allowed to rotate at a constant optimum speed at room temperature. The readings of viscosity of the formulation were measured after 2 minutes.

Gel Strength: The gel strength was measured by apparatus described by Chul Soon et al in which a fixed weight candle (30 g) was placed on the 15 ml gel in a 25 ml measuring cylinder and the time required to travel the candle down to 5 cm was noted.

Drug-polymer Interaction studies [18]: The IR spectra of the pure drug and formulated gels were obtained using Jasio FT/IR 5300 to ensure no interaction has occurred between the drug and polymer.

Stability Studies: The formulated hydrotropic-gelled starches was filled in collapsible tubes and gross visual appearance was observed followed by the initial drug content determination. The sample were divided into two batches and stored at 28°±2°c and

5°±2°c for 24 weeks respectively and samples were withdrawn for their stability analysis.

Results and Discussion: The hydrotropic starch gel was found to be in acceptable limits. pH of hydrotropic starch gel formulations was found between 6.52 to 6.70 .Drug content of the formulation was carried out and was found to be within the range between 96.00 to 99.50%. The percent drug release of hydrotropically prepared medicated starch gels using potato starch with Urea, mannitol was TCU-III (57.94%) ,TCM (30.53%), and whereas for marketed cream (M_1) was 16.43%. Hydrotropic starch gel TCU-III showed a highest drug release when compared to 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 kinetics with diffusion controlled(Table 2,3,4 and fig 1,2,3,) Rheological properties help in understanding the physicochemical nature of vehicle and quality control of ingredients, test formulation and final products. The apparent viscosity (cp) value of TCU-III was found to be 105230 and 3049, at low shear rate 0.14 and high shear rate 28.The rheological data further indicated that hydrotropically prepared starch gels was found to exhibit shear thinning property when shear rate was increased. The ascending and descending rheograms were not supper imposed and can be concluded as thixotropy in nature with the hysteresis. 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 plays an important role in patient compliance and help in uniform application of gel to the skin. As gels should spread easily , all the formulations were found to have better spreadability. Drug-polymer interaction study was carried out by taking IR spectrum of the pure drug and formulation (TCU-III). Drug has remained intact without undergoing any chemical reaction during the formulation. These observations support that during the formulation, the drug has not undergone any chemical change, it has remained intact in its original form for the required biochemical effects or action(fig 3,4,5) Stability studies was carried out for hydrotropic starch gel TCU-III at 28°C±3°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°C±3°C was found to be (99.43%) drug

content, at 6 hrs 55.40% of drug was released, 105371 cp of viscosity, 6.6 pH, and 14.9 gm c/s spreadability was found. And at 5°C±3°C 99.46% of drug content, 53.6% of drug release at 6 hrs, 105210 cp viscosity, 6.4 pH, and 14.2 gmc/s spreadability was found respectively.(Table 5,6).

Conclusion: It was observed that hydrotropic starch gels offer a suitable vehicle for topical delivery of Terbinafine.HCL. The hydrotropic starch gels were found to be white opaque to white translucent in appearance and have good homogeneity. The drug content, pH, spreadability, extrudability was found to be within acceptable range. The starch (corn) showed an impact on the viscosity of gel formulations. Formulation TCU-III containing 15% Urea, 10% Potato starch and 1% w/w of drug showed highest drug release of 57.94 % as compared to marketed preparation 16.43%. IR spectra showed that there is no interaction between the drug and additives, and hence the drug remains intact without undergoing any chemical reaction during the preparation and after its storage.

Acknowledgments: The authors are very much thankful to Dr Babasaheb Ambedkar Marathwada University Management Council for encouragement and management, K.T.Patil College of Pharmacy, Osmanabad for providing necessary facilities for this project work.

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Table-1: Formulation of Hydrotropic starch gels by using Corn-starch

Ingredients (% w/w)	Formulation code					
	TCU-I	TCU-II	TCU-III	TCM-I	TCM-II	TCM-III
Terbinafine.HCL	1.00	1.00	1.00	1.00	1.00	1.00
Corn-starch	10.00	10.00	10.00	10.00	10.00	10.00
Urea	10.00	12.5	15.00	-	-	-
Mannitol	-	-	-	1000	12.5	15.00
Water (ml) up to	100.00	100.00	100.00	100.00	100.00	100.00

C = Corn starch; U = Urea; M = Mannitol; T = Terbinafine.HCL

Table- 2 : Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TCU-I, II & III

Time (hrs)	Cumulative percent drug released		
	TCU-I	TCU-II	TCU-III
0	0	0	0
1	6.28	4.98	7.04
2	11.21	9.76	13.84
3	14.91	19.12	28.33
4	21.38	21.38	39.50
5	28.44	23.18	44.95
6	33.91	25.04	57.94

*Average of three replicates

*1 gram. sample containing 10 mg of drug.

Figure-1 : Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TCU-I, II & III

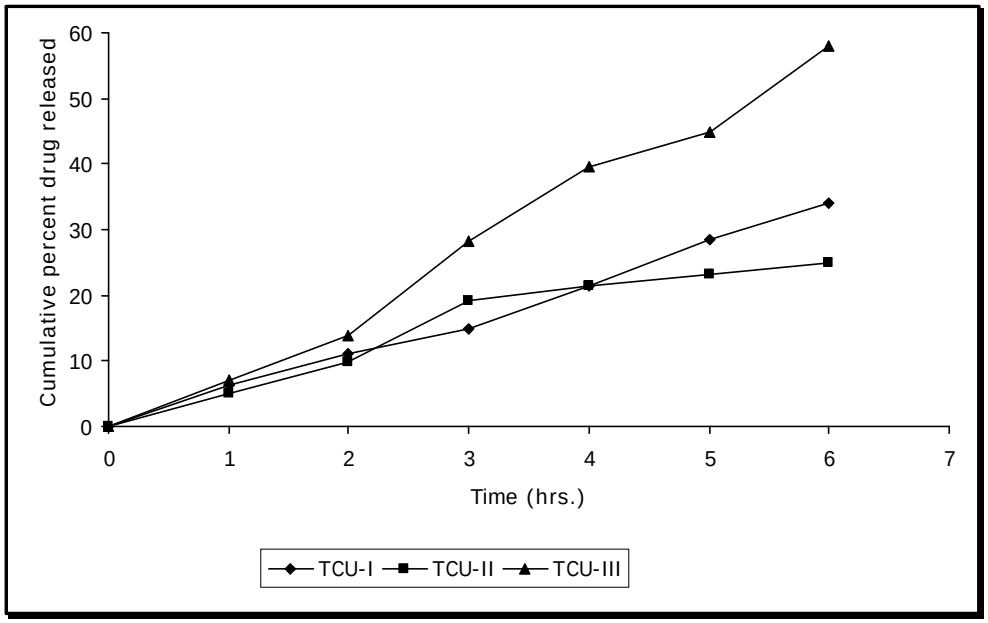

Table- 3 : Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TCM-I, II & III

Time (hrs)	Cumulative percent drug released		
	TCM-I	TCM-II	TCM-III
0	0	0	0
1	4.86	5.32	5.62
2	9.25	9.58	12.17
3	13.41	14.61	20.31
4	17.32	20.47	22.17
5	19.81	21.49	25.13
6	22.86	25.12	30.53

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

Figure- 2 : Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TCM-I, II & III

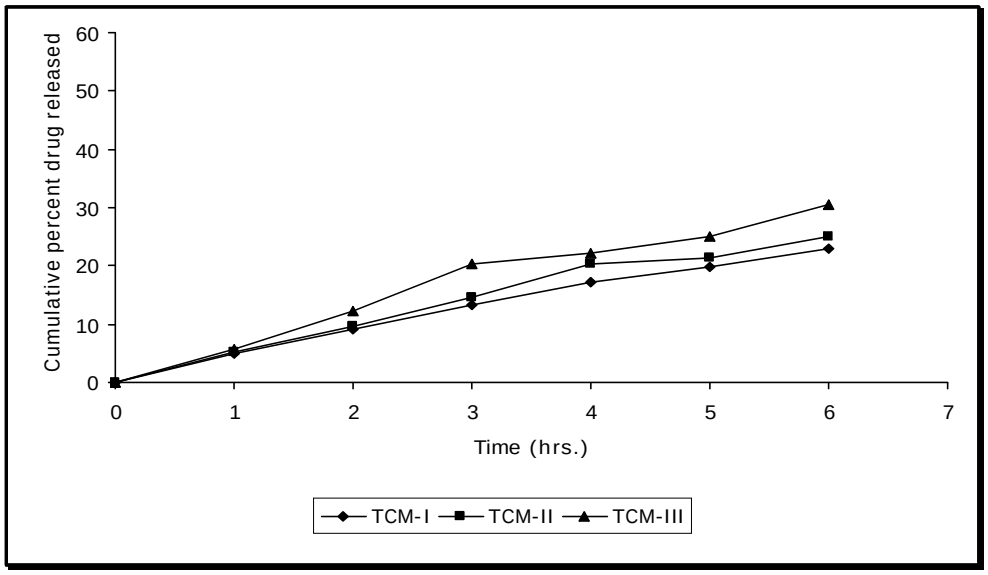

Table-4: *In vitro* percent drug release of Terbinafine HCL from Marketed cream M-I

Time (hrs)	Square root of time	Log time	Cumulative percent drug released	Cumulative % drug remaining	Log percent drug released	Log percent drug remaining
0	0	0	0	100	0	2.00
1	1.000	0	6.12	93.88	0.78	1.97
2	1.414	0.301	8.41	91.59	0.92	1.96
3	1.732	0.477	9.99	90.01	0.99	1.95
4	2.000	0.602	13.71	86.29	1.13	1.93
5	2.236	0.698	14.91	85.09	1.17	1.92
6	2.449	0.778	16.43	83.57	1.21	1.92

* Average of three replicates

* 1 gram sample containing 10 mg. of drug.

Figure-3:
IR Spectra of Terbinafine HCL (Pure Drug)

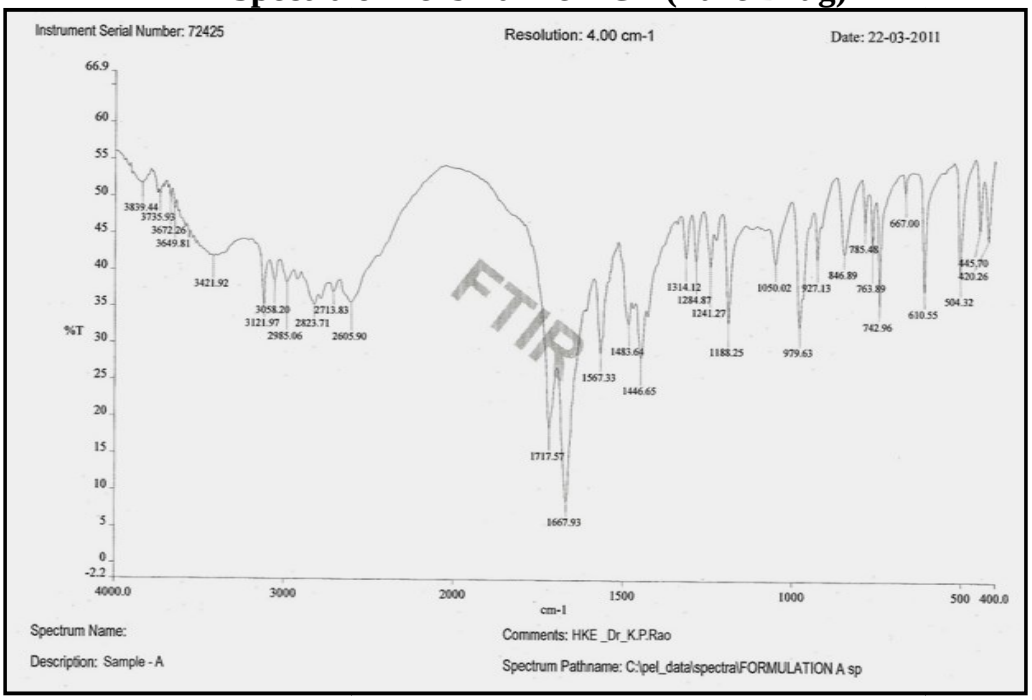

Figure-4:
IR Spectra of hydrotropic starch gels containing Terbinafine HCL (TCU-III)

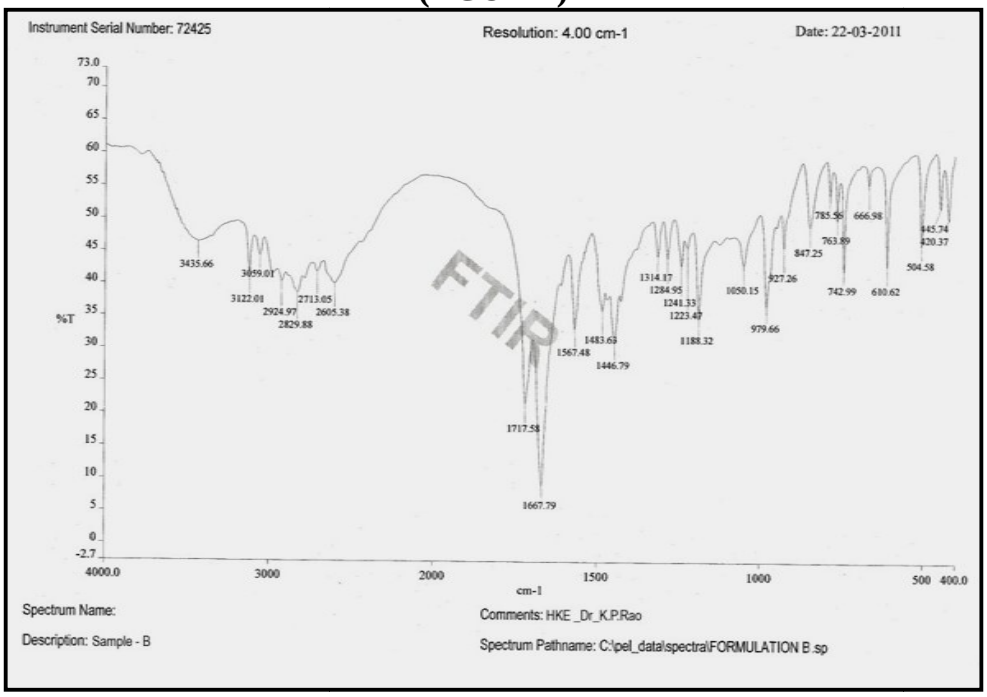

Figure-5:
IR Spectra of hydrotropic starch gels containing Terbinafine HCL (TCM-III)

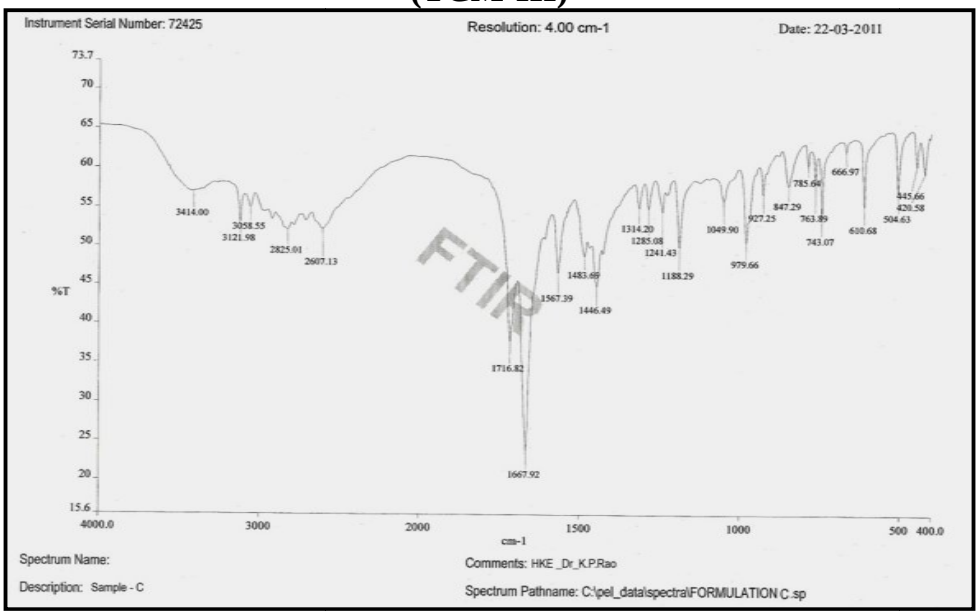

Table-5: Stability studies of hydrotropic starch gel TCU-III at Temperature 28±3ºC and Relative Humidity (RH) 65±5%

Sl. No	Drug Content (%)	In-vitro diffusion study (%) 6 hrs	Viscosity (cps)	pH	Spreadability (gm c/s)	Extrudability
1.	99.46	55.3	105210	6.4	14.2	++
2.	99.35	55.1	150277	6.4	14.2	++
3.	99.24	55.0	105339	6.3	14.3	++
4.	99.14	54.8	105237	6.5	14.1	++
5.	99.01	54.7	105208	6.4	14.3	++
6.	98.87	54.3	105271	6.5	14.4	++

Average of three replicates
++ Good

Table-6: Stability studies of hydrotropic starch gel TCU-III at Temperature 5±3ºC

Sl. No.	Drug Content (%)	diffusion study (%) 6 hrs	Viscosity (cps)	pH	Spreadability(gmc/s)	Extrudability
1.	99.43	52.11	105371	6.6	14.9	++
2.	99.42	55.13	105349	6.6	14.9	++
3.	99.40	54.59	105329	6.6	14.8	++
4.	99.39	54.71	105231	6.7	14.7	++
5.	99.33	54.79	105201	6.3	14.8	++
6.	99.21	52.77	105217	6.6	14.6	++

Average of three replicates

++ Good