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REVIEW ARTICLE

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1. INTRODUCTION

1.1 Topical dosage form

Topical dosage forms are those which are applied directly to external body surface either by inunciting it (spreading and rubbing in a semi-solid with the fingers), by spraying or dustingit on, or by instillingit (applying a liquid as drops). Topical dosage form are applied to the skin either for their physical effects, that is for the ability to act as skin protectants, lubricants, emollients, drying agents, etc. or for specific effect of medicinal agents present. Preparations sold over the country frequently contain mixtures of medical substances used in the treatment of such conditions as minor skin infection, itching, bruise, acne, psoriasis and eczema. Topical dosage forms have been used since very ancient times. The application of medicinal substance to skin or to various body orifices is a concept as old as humanity. Various ointments, creams, gels, lotions, pastes, powders and plasters have been used for many years.

Advantages of topical systems

- Avoidance of first pass metabolism of drugs.
- Peak plasma levels of drug are reduced, leading to decreased side effects.
- Reduction of fluctuation in plasma levels of drugs.
- Utilization of drug candidates with short half-life and low therapeutic index.
- Reduction of dosing frequency and patient compliance.
- Avoid the risk and inconvenience of intravenous therapy.
- They eliminate the variables, which influences gastrointestinal absorption such as food intake, stomach emptying and intestinal motility and transit time.
- Topical drug delivery systems are relatively inexpensive compared to conventional dosageforms.

Limitations

- The route is not suitable for drugs that irritate or sensitize the skin.
- The route is restricted by the surface area of delivery system.
- Limited drug permeability through skin.
- Percutaneous absorption is a slow process, thus a drug must be pharmacologically active.

Fungal infections

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 andorgans). In the last 20-30 years, there has been a steady increase insystemic fungal infections, not only by known pathogenic fungi but also by fungi previously thought to be innocuous. These last are termedopportunistic infections.

Superficial fungal infections

Superficial fungal infections can be classified into thedermatomycoses and candidiasis.

Dermatomycoses

Dermatomycoses are infections of the skin, hair and nails, causedby dermatophytes. The commonest are due to Tinea organisms, which cause various types of ringworm. Tinea capitis affects the scalp, tinea crusis, the groin, Tinea pedis, the feet (causing athlete's foot) and Tinea Corporis, the body. In superficial candidiasis, yeast – like organisminfects the mucous membrane of the mouth (thrush) or vagina, or skin. Some of the surface fungal infections and cutaneous fungal infections which fall into superficial mycoses groups are:

Pityriasis versicolor: Pityriasis versicolor (Tinea versicolor) is a chronic usually asymptomatic, involvement of the stratum corneum, characterized by discrete or confluent macular areas of discoloration or depigmentation of the skin. The area involved is mainly the chest, abdomen, upper limbs and back. The causative agent is lipophilic, yeast like fungus, Pityrosporum arbiculare (*Malassezia furfur*).

1.2 Type of fungal disease

Individuals who are experiencing diabetes mellitus or different maladies related with debilitated resistant framework will have more prominent possibility of having parasitic contaminations in light of their debilitated insusceptibility. Additionally, people who have poor sustenance and cleanliness, come across impediment of the skin and live in locations with warm, sticky atmospheres are some other inclining factors for contagious

contaminations. There are several types of fungal disease found in humans shown below.

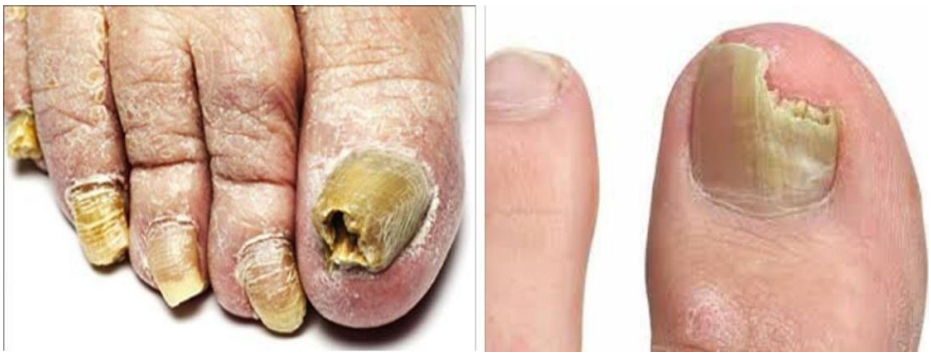


Fig. 1.2: Fungal nail infection (Fingernails are become thickened, discolored, Curledand Brittle).

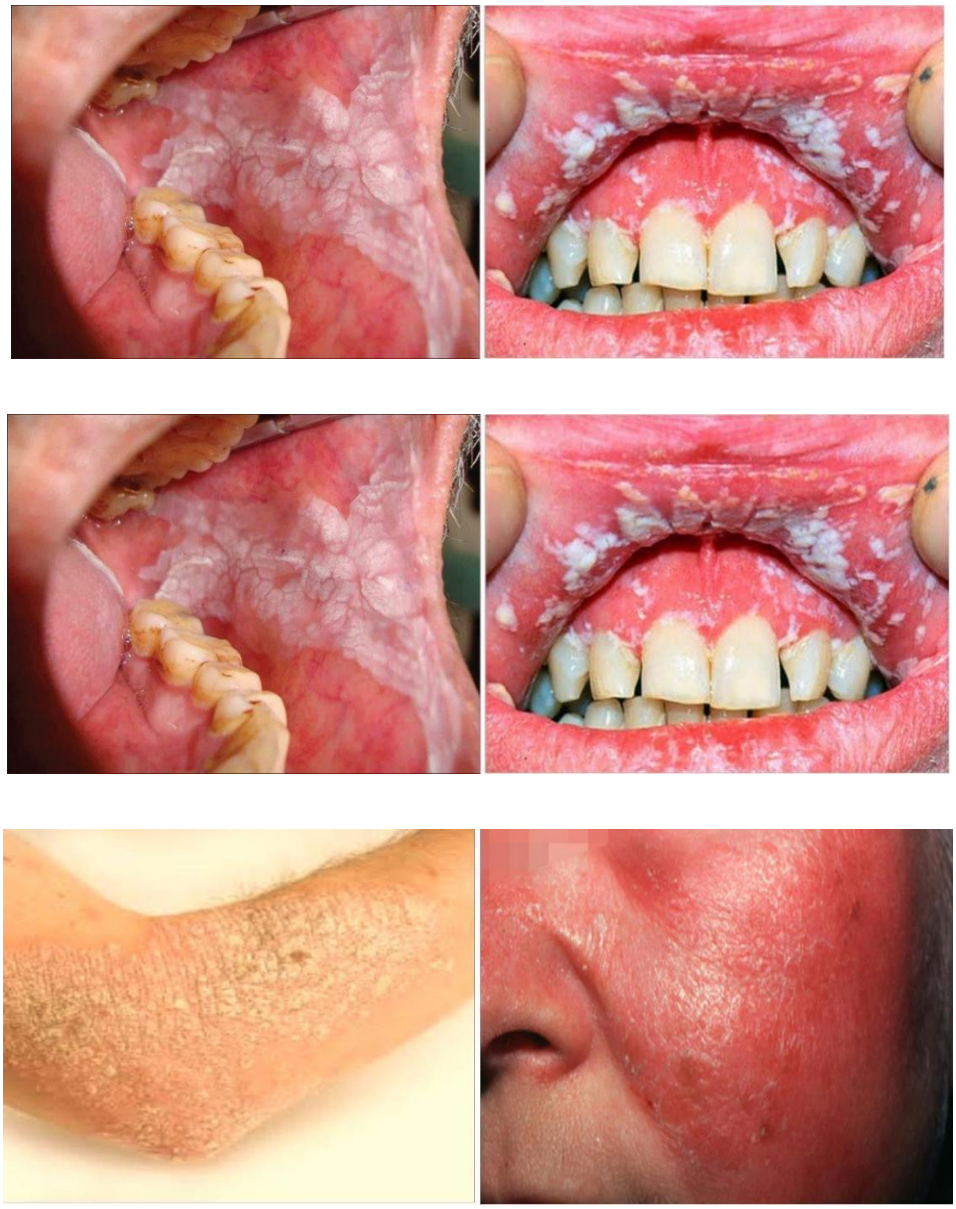


Fig. 1.3: Mucosal infections (Observed in oral cavity).

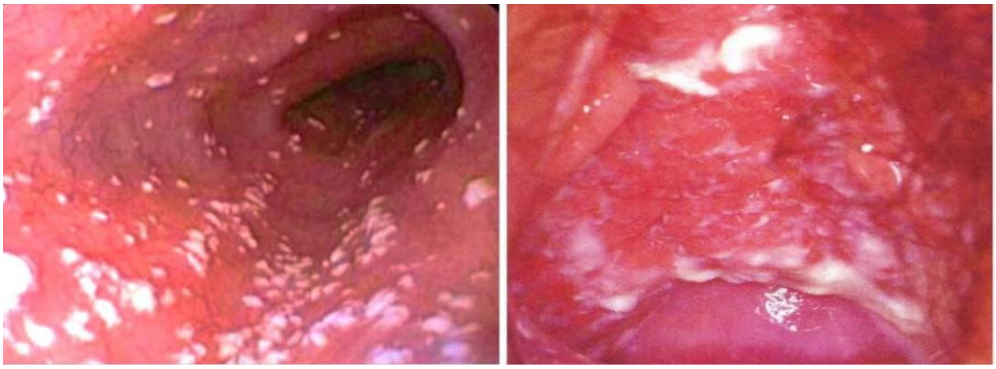


Figure: 1.4: Vaginal thrush (Irritation and Swelling of vagina).

Gels

The word ‘gel’ is derived from ‘gelatin’ and both ‘gel’ and ‘jelly’ can be traced back to the Latin gelu for ‘frost’ and gelare, meaning ‘freeze’ or ‘congeal’. This origin indicates the essential idea of a liquid setting to a solid-like material that does not flow, but is elastic and retains some liquidcharacteristics.[28]

Definition

The term ‘gels’ is broad, encompassing semisolids of a wide range of characteristics from fairly rigid gelatin slabs, to suspensions of colloidal clays, to certain greases. Gels can be looked on as being composed of two interpenetrating phases.[29] The United States Pharmacopoeia defines gels as semisolids, being either suspensions of small inorganic particles or large organic molecules interpenetrated with liquid.

Classification of gels

Gels are classified in the BP according to the characteristics of hydrophobic or hydrophilic characteristics of the gelled liquid.

Hydrophobic gels

The bases of hydrophobic gels (oleogels) usually consist of liquid paraffin with polyethylene orfatty oils gelled with colloidal silica or aluminium or zinc soaps.

Hydrophilic gels

The bases of hydrophilic gels (hydrogels) usually consists of water, glycerol or propylene glycol gelled with suitable gelling agents such as tragacanth, starch, cellulose derivatives, carboxy vinylpolymers and magnesium aluminum silicates.

Characteristics of gels

Ideally, gelling agents for pharmaceutical and cosmetic use should be inert, safe and non-reactive with other formulation components. The inclusion of a gelling agent in a liquid formulation should provide a reasonable solid like matrix during storage that can be broken easily when subjected to the shear forces generated in shaking a bottle or squeezing a tube, or during topical application. The gel should exhibit little viscosity, changes under the temperature variation of normal use andstorage. A topical gel should not be tacky. Too high a concentration of gel former or the use of an excessive molecular weight may producea gel difficult to dispense or apply. The gel characteristicsshould match the intended use. The aim is to produce a stable, elegant, economical gel product adequately suited for its intended use.

1.3 Types of antifungal medicines

Antifungal medicines can be used as different form as per the targeted area such as

- **Topical anti fungal medicines:** Most of the drug available in the form of cream, gel, ointment and spray form.
- **Oral antifungal medicines:** Tablet, capsules, dusting powder and liquid dosage form mint for oral route.
- **Parenteral medications:** Injections are available for vain or muscle.
- **Pessaries and Suppositories:** Small soft tablets insert into body cavity and

Vagina

There are few common antifungal medicines are mentioned below:

- Amphotericin
- Clotrimazole
- Oxiconazole
- Econazole
- Miconazole
- Terbinafine
- Fluconazole
- Ketoconazole

1.4 Recent advances in topical drug delivery system

Medicine movement systems are methodologies which are used to ensure that drugs get into the body and accomplish the district where they are required. These systems must think about

different prerequisites, stretching out from straightforwardness of movement to suitability of the drugs. Atthe point when a medication is directed, the dose must be deliberately figured so the body can utilize the medication, which requires a drug delivery system framework which considers exact dosing. Drug delivery system frameworks additionally need to consider the manner by which a medication is utilized by the body. For instance, a few medications are wrecked in the intestinal tract, which implies that they can't be acquainted with the body thusly. Others might be unsafe in huge sums, which imply that a period discharge strategy ought to be utilized to convey the medication for quiet security. Topical drug delivery system frameworks include the acquaintance of a medication with the surface of the body, in a plan which can be ingested. Topical medication transport structures skin fills in as a champion among the most successfully open courses for sedate association. Stratum corneum has been seen as the genuine limit to invasion of substances in to and through the skin. These frameworks are regularly simple for patients to utilize, which makes them engaging. In all cases, the objective of a drug delivery system framework is to get the correct measurement to the perfect place. Patients have a tendency to incline toward strategies which areeffortless and simple, which is the reason numerous pharmaceuticals come as topical and enteral techniques which can be taken by mouth or connected specifically to the skin Topical medication association is a limited drug transport structure wherever in the body through ophthalmic, rectal, vaginal and skin as topical courses. Skin is a standout among the most immediately open organs on human body for topical association and is essential course of topical medicine movement system. Topical arrangements are associated with the skin for surface, adjacent or key effects. Now and again, the base may be used alone for its therapeutic properties, for instance, emollient, alleviating or cautious action. The conveyance of medications through most normally utilized customary arrangements, for example, creams, gels, salves, emulsion, and soon limits the adequacy of actives because of obstruction properties i.e. epidermis of the skin which ruin the medication testimony. Subsequently choice of appropriate transporter's critical by considering the view in the mind that they should expand sedate statement through topical definition.

In any case, starting late it has ended up being clear that the advancement of new medication alone isn't adequate to guarantee in advance in tranquilize treatment. Present day's topical conveyance of medications especially if there should be an occurrence of skin issue, for example, psoriasis, skin contagious disease (dermatiatis) and so forth is picking up significance and furthermore has loads of difficulties. Drug delivery system by topical course

is powerful just by better skin infiltration to the required layer of skin. In this way, choice of appropriate transporter is critical. Infiltration of medication will rely upon the molecule measure and thus nanocarriers are promising conveyance framework. The 21st century will witness ocean changes in the region of medication conveyance offering ascend to items more intense and more secure. The regular drug delivery system frameworks and strategies for organization have changed definitely. Covering of particles, improvement of polymers, infiltration enhancers, nanoparticles, microspheres, liposome, niosome, iontophoresis, sonophoresis, are for the most part adding to this up and coming method of drug delivery system.

1.5. Recent advances in topical drug delivery system

Medicine movement systems are methodologies which are used to ensure that drugs get into the body and accomplish the district where they are required. These systems must think about different prerequisites, stretching out from straightforwardness of movement to suitability of the drugs. Atthe point when a medication is directed, the dose must be deliberately figured so the body can utilize the medication, which requires a drug delivery system framework which considers exact dosing. Drug delivery system frameworks additionally need to consider the manner by which a medication is utilized by the body. For instance, a few medications are wrecked in the intestinal tract, which implies that they can't be acquainted with the body thusly.

2. LITERATURE REVIEW

2.1 Arslan A et al., (2018) contemplated on Evaluation of a novel oxiconazole nitrate definition. The shallow infectious defilements brought about by Candida species are ordinary skin sicknesses. Thusly, this examination expected to develop another enumerating containing oxiconazole nitrate, which is an azole total subordinate forantifungal treatment, as a thermosensitive gel since there has been no reviewing examination to this point. Thermosensitive gel definition containing oxiconazole nitratewas seen to be effective on shallow infectious defilements. Researcher trusts it in likemanner fits for in vivo usage, yet it is vital to perform animal besides, human research. **Soliman G.M** et al., **(2017)** studied on nanoparticles as safe and viable delivery systemsof antifungal agents. Meddling parasitic defilements are transforming into a vital prosperity stress in a couple of social events of patients inciting outrageous dismalness and mortality. Despite the openness of a couple of incredible masters in the antifungal medicine field, their accommodating outcome isn't as

much as perfect as a result ofrequirements related to sedate physicochemical properties and peril. Understanding of these nanoformulations from the lab to the office could be supported by focusing the examination on overcoming issues related to nanoparticle soundness, steady stacking andamazing cost of creation and organization.

Iizhar S. An et al., **(2016)** studied on *In-vitro* assessment of the pharmaceutical capability of ethosomes entrapped with Terbinafine Hydrochloride. The present examination inquires about the capture of Terbinafine Hydrochloride (TH) in ethosomal vesicles by methods for unsonicated and sonication procedure. Carbopol 934P was participated in the best definition, F6, got by sonication system. It revealed that F6 showed distinctive deterioration profiles. Transdermal movement and motivation for F6 and MR was seen to be 144.61±1.28 µg/cm2/hr and 121.6±1.16 µg/cm248/hr, independently. This examination revealed that F6 lives at an engaged site for a by and large longer time span accordingly suggesting the upgraded patient consistency.

Marto J et al., **(2016)** studied on ethosomes for improved skin delivery of griseofulvin. Purpose of this work was to set up another GRF definition for a topical application using lipid-based nanosystems; to think about its invasion and passage, cell common sense and to survey its supportive action. Ethosomal structures made out of soybean phosphatidyl choline, ethanol and water were set in the mood for joining GRF. After the depiction of the vesicles, Cell sensibility at different combinations of the picked definition was settled. Skin balanced agar scattering test was performed to assess the medicinal reasonability of the definition. The skin scattering test affirms the ability of the made an arrangement to target skin dermatophytes. The results gained in this examination add to another perspective in the topical treatment of infectious illnesses.

Mayur Gandhi et al., **(2014)** studied on niosomes as a novel drug delivery system. Niosomes are non-ionic surfactant vesicles procured on the hydration of built nonionic surfactants, with or without wire of cholesterol or diverse lipids. They are vesicular systems like liposomes that can be used as transporters of amphiphilic and lipophilic meds. Niosomes are minor lamellar structures running between 10 to 1000 nm comprise of non-ionic surfactant and cholesterol. Niosomes are supported over liposome due to manufactured substances solidness and more economy.

Kumar J.R et al., **(2014)** studied on Antifungal operators: another methodology for novel

delivery systems. The present treatment grasped by specialists for the treatment of infectious joins the fundamental association and topical association of antifungal agents. Therefore, consideration has been centered on novel medication transport of antifungal agents which is the most by and large recognized methodology.

Accurate (intra-day: CV= 1.57% and between day: CV= 1.50%) and definite (mean recoveries: 99.69%). The results differentiated emphatically and those of the HPLC strategy.

Gugnanih C et al., **(1993)** studied on Oxiconazole in the treatment of tropical dermatomycoses. A 1% cream detailing of oxiconazole, an imidazole subordinate, was used to treat 50 instances of tropical dermatomycoses, including 30 cases of pityriasis versicolor, 9 of tinea pedis, 5 everyone of tinea corporis and tinea cruris all caused by T rubrum, also, one of foot and crotch disease because of Trichosporon cutaneum. The author concluded that oxiconazole is prescribed as a successful treatment for shallow parasitic diseases of the skin.

Saleh AM et al (1916) described the term hydrotropic agents, which was first introduced by Neuberg to designate anionic organicsalts which at high concentration considerably increase the aqueous solubility of poorly soluble solutes. El-Khordagui LK[33] studied some physicochemical properties of hydrotrope-gelled starch. A starch gel has been prepared without heat treatment or chemical modification, using a typical hydrotropic salt (sodium salicylate) as a gelling agent. This gel has the advantage of retaining the marked solubilizing capacity of sodium salicylate. Badwan AA et al[34]investigated the influence of simple structural modification on the solubility of a seriesof poorly soluble benzodiazepines in sodium salicylate solution. Results of solubility and spectral studies indicate that an electrostatic force of the donor-acceptor type plays an important role in the solubilization of these compounds by hydrotrophy. The remarkable increase in the solubilizing effect of sodium salicylate was probably associated with aggregate formation. Inclusion of the benzodiazepine molecules in the sodium salicylate aggregates was thought to be the mechanism responsible for the solubilization of these poorly soluble drugs.

Shivakumar HN et al investigated hydrotropically gelled maize starch as granulating agent for preparing tablets of diclofenac sodium. Granular and tablet properties were determined and compared with those obtained using conventionally prepared starch paste. Hydrotropically gelled starch exhibited good stability as compare to that of conventionally prepared starch paste. Saida Khalilet al[38] studied the solubility and stability of diazepam in

sodium salicylate solution, it was observed that as the concentration of sodium salicylate increases, the solubility of diazepam (practically insoluble in water) also increases. Thus, the author believed that the mechanism of solubilization by hydrotropic salts may involve change in water structure; diazepam in sodium salicylate was completely stable against photodecomposition.

3. AIM AND OBJECTIVE OF THE STUDY

The skin often has been referred to as the largest of the bodyorgans. An average adult's skin has surface area of about 2m². Itsaccessibility and the opportunity it affords to maintain applied preparation intact for a prolonged time have resulted in its increasing use as a routeof administration whether for local, regional or systemic effects.

The extensive studies on release properties have revealed that the active ingredients in gel based formulations are better percutaneouslyabsorbed than cream or ointment bases. Terbinafine HCL is effectivetopically for the management of cutaneous candidiasis and tineainfection.

The major drawback of this drug is its low aqueous solubility.Increasing the water solubilityof insoluble or slightly soluble compounds is a major concern for pharmaceuticalresearchers. The techniques generally employed to enhance the solubility ofpoorlywater soluble drugs are use of surface active agents, hydrates andsolvates, polymorphism, complexation, hydrotropic solubilization andconventional 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.

Starches when used with hydrotropic salts (solubilizing agents)such as urea and mannitol results in hydrotrope gels, which will serve asa vehicle for topical drug delivery and also improve stability, solubility and bioavailability of poorly insoluble drugs. Hydrotrope-gelled starch offers promise as a vehicle for topical drugdelivery. The solubility of terbinafine HCL can be enhanced by using hydrotropic salts; these are the solubilizing compound which will enhance solubility of poorly soluble drugs.

Hence, in the present investigation an attempt was made to develop terbinafine HCL hydrotropic starch gels using potato and corn starch along with urea and manitol as hydrotropic salts, which will be a potential vehicle for delivering topically the drug directlyto

the site of action.

4. MATERIAL AND METHOD

Sl. No.	Materials/ Chemicals	Batch No.	Source
1.	Terbinafine HCL	24586A/2	Eurodrug Laboratories, Hyderabad
2.	Ketoconazole	13567D&B	Eurodrug Laboratories, Hyderabad
3.	Urea	G240107	Loba Chemical Pvt. Ltd., Mumbai
4.	Mannitol	V0086/2	Loba Chemical Pvt. Ltd., Mumbai
5.	Potato Starch	60679	SD Fine Chemicals Ltd.
6.	Corn starch	61604	SD Fine Chemicals Ltd.
7.	Methanol	R152102	Ranbaxy Fine Chemicals Limited
8.	Cellophane membrane	0706119	Himedia Laboratories Pvt.Ltd., Mumbai (India).
9.	Aluminum collapsible tubes	--	Digvijay Containers & Closures, Mumbai
10.	Agar	103Y/0303	SD Fine Chemicals Ltd.
11.	Malt extract	1095-171056	SD Fine Chemicals Ltd.
12.	Peptone	A02p/3730/120	SD Fine Chemicals Ltd.
13.	Glucose	0802	Bentley Nova

Sl. No.	Equipment	Source
1.	UV/ Visible spectrophotometer	Shimadzu 1700, Shimadzu Corporation, Japan
2.	Electronics balance	Shimadzu Corporation- BL-220H
3.	pH meter	Elico II-122
4.	Brookfield synchroelectric-RVT modeldigital viscometer	Sanjay Technologies, Mumbai
5.	Digital stirrer	Remi Motors, Mumbai
6.	Magnetic stirrer	Remi Equipment Ltd., Mumbai
7.	Sonicator	Flexit Jour Laboratories Pvt.Ltd.
8.	Spreadability apparatus	Fabricated
9.	Extrudability apparatus	Fabricated
10.	Autoclave	Oswal Companies
11.	Incubator	Rotex Instruments

Phase I

Construction of calibration curve[105,106]

Construction of calibration curve in phosphate buffer pH 7.4: A spectrophotometric method based on measurement of absorbance at 224nm in phosphate buffer pH 7.4 was used

for estimation of Terbinafine HCL.

Stock solution: Accurately weight quantity (100 mg) of Terbinafine HCL was dissolved in 100 ml of phosphate buffer pH 7.4.

Sub-stock solution: From above stock solution, 5 ml of solution was taken in 100 ml volumetric flask and the volume was made up to 100ml with phosphate buffer pH 7.4. Aliquots of 1, 2,3,4,5,6,7,8 ml of sub-stock solution was pippetted out into 10 ml volumetric flask and adjusted up to mark of 10 ml to achieve a concentrationsof 5,10,15, 20,25,30,35,40 mcg/ml respectively. The absorbance was measured at 224 nm using phosphate buffer pH 7.4 as blank. All the absorbancewas recorded using UV-visible spectrophotometer. The absorbance was plotted against concentration of Terbinafine HCL.

Preparation of calibration curve of Terbinafine HCL in methanol stock solution: Accurately weighed (100 mg) of Terbinafine HCL was dissolvedin 100 ml of methanol, which gives the concentration of1 mg/ ml.

Sub-stock solution: From above stock solution, 5 ml of the solutionwas takenin 100 ml of volumetric flask and the volume was made upto 100 ml with methanol.

From these aliquots of 0.2, 0.4, 0.6, 0.8 and1 ml of sub-stock solution was pippetted out into 10 ml volumetricflask and the volume was made up to the mark with methanol. This dilution gives 2, 4, 6, 8 and 10 mcg/ml concentration of Terbinafine HCL. The absorbance was measured at 224 nm using UV/Visiblespectrophotometer against methanol as blank. The study was carried out in triplicate. The absorbance was plotted against concentration of Terbinafine HCL.

Solubility

The solubility of Terbinafine HCL in various solvents was carried out. Excess amount of Terbinafine HCL (100 mg) was addedto 10 ml of each solventin a 25 ml stoppered conical flask and the mixture was shaken for 24 hours at room temperature (28±1ºC) on a rotary flask shaker. 2 ml aliquots were withdrawn at 1 hour interval and diluted suitably and assayed at 224 nm by UV/Vis spectrophotometer; shaking was continued until two consecutiveestimations were found same. The solubility experiments were conducted in triplicate.

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	12.50	15.00	-	-	-
Mannitol (%)	-	-	-	10.00	12.50	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: Formulation of Hydrotropic starch gels by using Potato-starch.

Ingredients (% w/w)	Formulation code					
	TPU-I	TPU-II	TPU-III	TPM-I	TPM-II	TPM-III
Terbinafine HCL	1.00	1.00	1.00	1.00	1.00	1.00
Potato-starch (%)	10.00	10.00	10.00	10.00	10.00	10.00
Urea (%)	10.00	12.50	15.00	-	-	-
Mannitol (%)	-	-	-	10.00	12.50	15.00
Water (ml) up to	100.00	100.00	100.00	100.00	100.00	100.00

P = Potato starch; U = Urea; M = Mannitol; T = Terbinafine HCL

Formulation of hydrotropic starch gels

Hydrotropic starch gels were prepared by dissolving the weighed quantity of hydrotropic salt (Urea) in 40 ml of water along with 1 gm of drug, which was finely powdered and passed through mesh # 100. Starch (corn 10%) was weighed and dispersed in the 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. The aboveprocedure was repeated for the preparation of gels with different hydrotropic salts and starch as shown in table No 1 and 2.

Phase II:

Evaluation of hydrotropic starch gels

1. Physical Appearance and Homogeneity

Hydrotropic starch gels were visually inspected for clarity, color, homogeneity, presence of particles and fibers.

2. Determination of pH[107,108]

The pH of gels was determined by using a digital Elico pHmeter 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.

3. Drug content uniformity[109]

The drug content was carried out by dissolving accurately weighed quantity of hydrotropic starch gels equivalent to 50 mg ofdrug 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 usingShimadzu UV/ visible spectrophotometer. The drug content was carried out in triplicate.

4. Spreadability

Spreadability of the formulation 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 groundglass 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 for5 minutes to expel air and to provide a uniform film of the gel betweenthe 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 plateto cover a distance of 10 cm was noted. A shorter the time interval better the spreadability.

The spreadability was calculated using the formula:

$$U = \frac{ml}{t}$$

Where

U = Spreadability

m = Weight tide to upper side

l = Length moved on the glass slide

M = timetaken in seconds.

Results are shown in Table-32.

5. Extrudability[110,111]

In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity in percentage of gel extruded from tubeon application of certain load. More the quantity extruded better was extrudability. The formulation under study was filled in a clean, lacquered aluminum collapsible one- ounce tube with a nasal tip of 5 mm opening. It was then placed in between twoglass slides and was clamped. Extrudability was determined by weighing the amount of gels extruded through the tip when a constant load of 1 Kg was placed on the slides and gels extruded was collected and weighed. The percentage of gel extruded was calculated and grades were allotted (+++ good; ++ fair and +poor).

Phase III

In vitro diffusion study[112]

The drug release from the formulation 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 theends. 1 gm of gel equivalent to 10 mg of Terbinafine HCL was spread uniformly on the surface of cellophane membrane (previously soakedin 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 gelwas just touched (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 2^0c the contents were stirred using magnetic bar at 100rpm for a period of 6 hrs, 5 mlof samples were with drawn at different time intervals and replacewith 5 ml of fresh buffer and after suitable dilution the sample were analyzed at 224 nm for Terbinafine HCL.

Phase IV

Rheological studies

1. Viscosity[113,114]

The viscosity of hydrotrope-gelled starch 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.

2. Rheological Behavior of Terbinafine HCL Gel Formulations

Formulations TCS -III were evaluated for rheological behavior. The viscosity of gels was

determined by using Brookfield synchro-electric RVT model digital viscometer at room temperature with the following variables. Spindle No. SC4 28/13R was used with 12 ml volume adapter. Eight spindle speeds (rpm) 0.5, 1.0, 2.5, 5.0, 10.0,20.0, 50.0 and 100 was used. The shear stress (dynes/cm^2) and shearrate (sec-1) was calculated.

3. Rheogram

In the present work, the shear rate (sec^{-1}) was considered as independent variable and shear stress dynes/ cm^2 as dependentvariable.

Stress-Shear Rate Rheogram: Both ascending and descending rheograms were drawn for low and high shear rate values to ascertain whether gels systems show thixotropy. The data was plotted as Casson plots[115] in which square root of shear stress are plotted against the square root of shear rate. The intercepts on the stress axis gives theyield values in (dynes/cm^2).

4. 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 15ml gel in a 25 ml measuring cylinder and the time required to travelthe candle down to 5 cm was noted.

Phase V

Drug-polymer Interaction studies.[115,116]

The IR spectra of the pure drug, potato starch, corn starch, hydrotropic salts and formulated gels with drug were obtained using Jasco FT/IR 5300 to ensure no interaction has occurred between thedrug and polymer.

Phase VI

Stability studies

The formulated hydrotropic-gelled starch was filled incollapsible 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 2^0c and 5 2^0c for 24 weeks respectively and samples were withdrawn for their stability analysis.

Phase VII

Microbial Studies

1. *In vitro* antifungal activity[117,118]

The anti fungal studies was carried out for hydrotropic starchgels TCU- III, TCM-III, TPU-III TPM-III gel base and marketed preparation by cup-plate method using *Candida Albicans* as test organism.

Materials and Method: Sabouraud's dextrose agar[119] composition

Dextrose 4%
Peptone.....1%
Agar.....2%
Chloramphenicol.....50 mg/L
Amoxicillin .....500 mg/L
Distilled water.....up to 100 ml
This medium has acidic pH 5.6.

Preparation of solution

1. **Reference solution:** 10mg of Terbinafine HCL and plain corn gel base was addedto 20 ml of methanol and shaken for 2 hrs, and filtered. The filtrated was further diluted with phosphate buffer pH 7.4 to achieve 100mcg/0.1 ml.
2. **Hydrotropic starch gels:** hydrotropic starch gels TCU-III equivalent to 10 mg of drug was dispersed in 20 ml of methanoland shaken for 2 hrs on roto-shaker, after 2hrs the solution was filtered and filtrated was further diluted with phosphate buffer pH7.4 to achieve a concentration of 100 mcg/ 0.1 ml.

Marketed formulation: Marketed preparation (MP_1) containing 10 mg. of Terbinafine HCL was added to 20 ml of methanol and shaken on roto shaker for 2 hrs, after 2hrs the solution was filtered and the filtrate and diluted with phosphate buffer pH 7.4 to getconcentration of 100.

Method of testing: Organism and Inoculums 0.1 ml.

The cultures of *Candida albicans* were cultivated on Sabouraud's dextroseagar maintained on slants in the refrigerator (4±2ºC).

Cup-plate method: The composition of Sabouraud's dextrose agar was taken in a250 ml of conical flask and was dissolved in 100 ml of distilled water. The pH wasadjusted to 5.6. The medium was sterilized in an autoclave at 15 lbs for 20 minutes. After the completion of sterilization, the medium was kept asideat room temperature. 0.5 ml diluted suspension culture in NaCl 0.9% were added to 100 ml of medium at 47±2ºC and used as inoculatedlayer. The medium (20 ml) waspoured into a sterilized petridish togive a depth of 3-4 mm, and was assured thatthe layer of medium is uniform in thickness by placing petridish on a leveled surface.After solidifying the medium at room temperature, with the help of a sterile cork borer, cups of each 6 mm diameter were punched and scoopedout from the petridish. Using sterile pipettes sample solutions (0.1 ml) of known concentrationwere fed into the cup. The petridish was then incubated for 24 hours at 37ºC. After incubation the zone of inhibition was measured.The order of the solutions was as follows:

Cup-1: Market product (MP_1) Cup-2: Reference solution (R) Cup-3: TCU-II(F)

5. RESULT AND DISCUSSION

Results

Phase-I

Table-3: Standard calibration data of Terbinafine HCL in pH 7.4 phosphate buffer (221nm).

Sl. No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.102
3	10	0.240
4	15	0.364
5	20	0.445
6	25	0.507
7	30	0.754
8	35	0.889
9	40	0.906

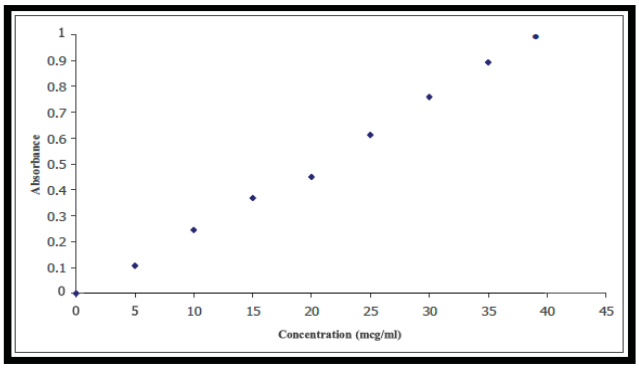


Figure-1:

Table 4: Standard calibration data of Terbinafine HCL in methanol.

Sl. No.	Concentration (mcg/ml)	Absorbance (average of three)
1	0	0.000
2	2	0.216
3	4	0.445
4	6	0.638
5	8	0.845
6	10	1.087

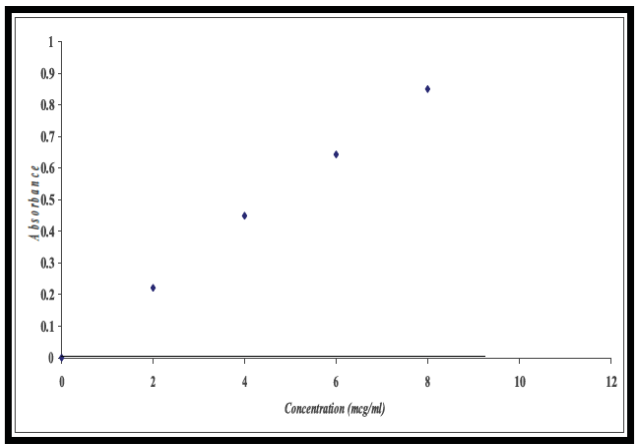


Figure 2

Solubility study of Terbinafine HCL in Urea

The addition of 10% and 12.50% w/v of Urea produced a 28 and 66-fold increase in solubility of Terbinafine HCL respectively as compared to its solubility in water (0.0866 mg/l). There was further increase in the solubility of Terbinafine HCL as the concentration of Ureawas increased to 15% w/v and was found to be 85-fold increaseas shown in table.

Table 5: Solubility study of Terbinafine HCL in Urea.

Sl. No	% w/v of Urea	Solubility in folds
1.	10%	28
2.	12.50%	66
3.	15%	85

Solubility study of Terbinafine HCL in Mannitol

It was observed that the solubility of Terbinafine HCL increased with an increase in concentration (% w/v) of Mannitol. The additionof 10% and 12.50% w/v of Mannitol produced 12 and 26-fold increase in solubility of Terbinafine HCL respectively as compared to its solubility in water (0.0866 mg/l). There was a further increase in the solubility of Terbinafine HCL as the concentration of Mannitol was increased to 15%w/v and was found to 35-fold increase as shown in table.

Table-6: Solubility study of Terbinafine HCL in Mannitol.

Sl. No	% w/v of Mannitol	Solubility in folds
1.	10%	12
2.	12.50%	26
3.	15%	35

Phase-II

Evaluation of Hydrotropic starch gels

Table 7: Physical Appearance and Homogeneity of hydrotropic starch gelscontaining corn starch, Urea and Terbinafine HCL.

Sl. No.	Formulation code	Physical appearance	Homogeneity
1.	TCU-I	White translucent	++
2.	TCU-II	White translucent	++
3.	TCU-III	White translucent	++
4.	TCM-I	White opaque	++
5.	TCM-II	White opaque	++
6.	TCM-III	White translucent	++

++ Good

Table 8: Physical appearance and homogeneity of hydrotropic starch gel containing potato starch, Mannitol and Terbinafine HCL.

Sl. No.	Formulation code	Physical appearance	Homogeneity
1.	TPU-I	White translucent	++
2.	TPU-II	White translucent	++
3.	TPU-III	White translucent	++
4.	TPM-I	White opaque	++
5.	TPM-II	White opaque	++
6.	TPM-III	White opaque	++

++ Good

Table 9: pH of Hydrotropic starch gel containing corn starch, Urea and Terbinafine HCL.

Sl. No.	Formulation Code	pH
1.	TCU-I	6.44
2.	TCU-II	6.55
3.	TCU-III	6.65

Table 10: pH of Hydrotropic starch gel containing corn starch, Mannitol and Terbinafine HCL.

Sl. No.	Formulation Code	pH
1.	TCM-I	7.19
2.	TCM-II	7.35
3.	TCM-III	7.46

Table 11: pH of Hydrotropic starch gel containing potato starch, Urea and Terbinafine HCL.

Sl. No.	Formulation Code	pH
1.	TPU-I	6.29
2.	TPU-II	6.36
3.	TPU-III	6.41

Table 12: pH of Hydrotropic starch gel containing potato starch, Mannitol and Terbinafine HCL.

Sl. No.	Formulation Code	pH
1.	TPM-I	7.35
2.	TPM-II	7.42
3.	TPM-III	7.46

Table 13: Drug content uniformity.

Sl. No.	Formulation code	% Drug content (mean ±SD)
1.	TCU-I	96.16±0.11
2.	TCU-II	96.93±0.23
3.	TCU-III	96.51±0.14
4.	TCM-I	96.52±0.26
5.	TCM-II	99.218±0.02
6.	TCM-III	96.58±0.21
7.	TPU-I	97.26±0.14
8.	TPU-II	96.45±0.12
9.	TPU-III	96.33±0.21
10.	TPM-I	98.38±0.23
11.	TPM-II	98.16±0.21
12.	TPM-III	96.51±0.16
13.	MP1	97.37±0.12

Phase-III

Table 14: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TCU-I.

Time (hrs)	Square root of time	Log time	Cumulative percent drug released	% Amount of drug remaining	Log percent drug released	Log percent drug remaining
0	0	0	0	100	0	2.000
1	1.000	0	4.98	95.02	0.697	1.978
2	1.414	0.301	9.76	90.24	0.989	1.955
3	1.732	0.477	19.12	80.88	1.281	1.908
4	2.000	0.602	21.38	78.62	1.330	1.896
5	2.236	0.698	23.18	76.82	1.305	1.885
6	2.449	0.778	25.04	74.96	1.399	1.875

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

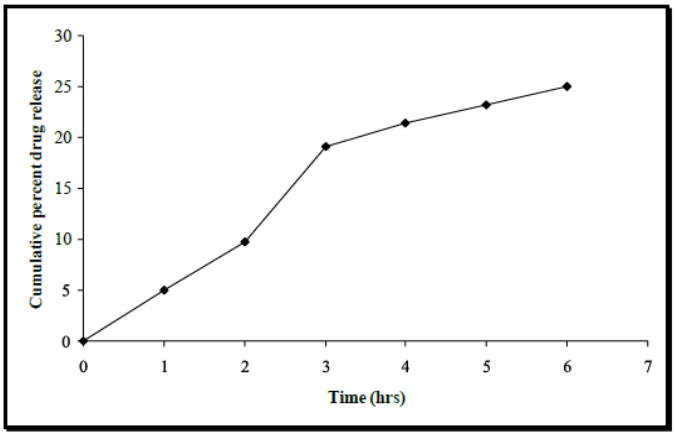


Figure 3: Cumulative percent drug release of Terbinafine HCL from hydrotropic starch gel TCU-I.

Table 15: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TCU-II.

Time (hrs)	are root of time	Log time	Cumulative percent drug released	% Amount of drug remaining	Log percent drug released	Log percent drug remaining
0	0	0	0	100	0	2.00
1	1.000	0	6.28	93.72	0.79	1.97
2	1.414	0.301	11.21	88.79	1.04	1.94
3	1.732	0.477	14.91	85.09	1.17	1.92
4	2.000	0.602	21.38	78.62	1.33	1.89
5	2.236	0.698	28.44	71.56	1.45	1.85
6	2.449	0.778	33.91	66.09	1.53	1.82

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

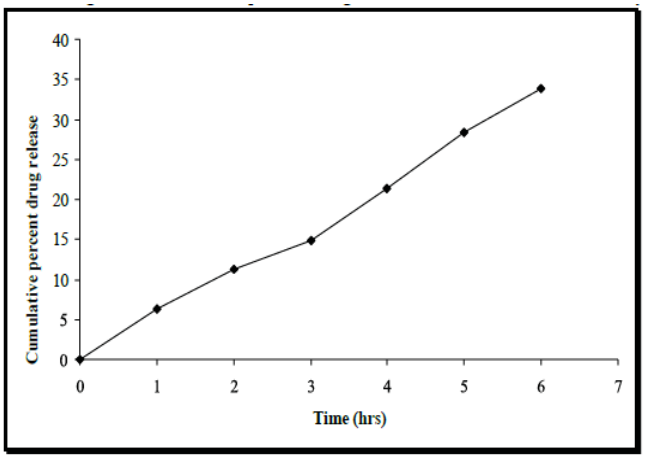


Figure 7: Cumulative percent drug release of Terbinafine HCLfrom hydrotropic starch gel TCU-II.

Table 16: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TCU-III.

Time (hrs)	Square root of time	Logtime	Cumulative percent drug released	Amount of drug remaining	Log percent drugreleased	Log percent drug remaining
0	0	0	0	100	0	2.00
1	1.000	0	7.04	92.96	0.84	1.96
2	1.414	0.301	13.84	86.16	1.14	1.93
3	1.732	0.477	28.33	71.67	1.45	1.85
4	2.000	0.602	39.50	60.50	1.59	1.78
5	2.236	0.698	44.95	55.05	1.65	1.74
6	2.449	0.778	57.94	42.06	1.76	1.62

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

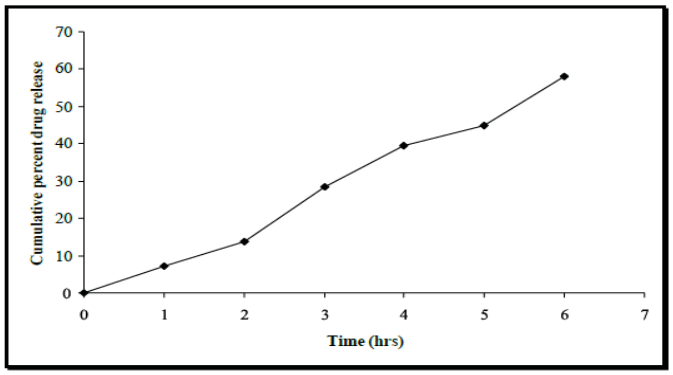


Figure 11: Cumulative percent drug release of Terbinafine HCLhydrotropic starch gel TCU-III.

Table 17: 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	4.98	6.28	7.04
2	9.76	11.21	13.84
3	19.12	14.91	28.33
4	21.38	21.38	39.50
5	23.18	28.44	44.95
6	25.04	33.91	57.94

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

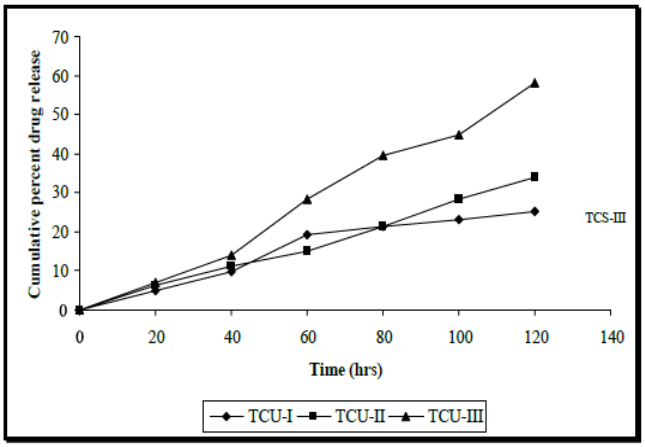


Figure-15

Table 18: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TCM-I.

Time (hrs)	Square rootof 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	4.86	95.14	0.68	1.97
2	1.414	0.301	9.25	90.75	0.96	1.95
3	1.732	0.477	13.41	86.59	1.12	1.93
4	2.000	0.602	17.32	82.68	1.23	1.91
5	2.236	0.698	19.81	80.19	1.29	1.90
6	2.449	0.778	22.86	77.14	1.35	1.88

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

Table 19: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TCM-II.

Time (hrs)	Square root of time	Log time	Cumulative percent drug released	Cumulative % drug remaining	percent drug released	Log percent drug remaining
0	0	0	0	100	0	2.00
1	1.000	0	5.32	94.68	0.71	1.97
2	1.414	0.301	9.58	90.42	0.98	1.95
3	1.732	0.477	14.61	83.39	1.16	1.93
4	2.000	0.602	20.47	79.53	1.31	1.90
5	2.236	0.698	21.49	78.51	1.33	1.89
6	2.449	0.778	25.12	74.88	1.40	1.87

* Average of three replicates
* 1 gram sample containing 10 mg. of drug.

Table 20: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TCM-III.

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	5.62	94.38	0.74	1.97
2	1.414	0.301	12.17	87.83	1.08	1.94
3	1.732	0.477	20.31	79.69	1.30	1.90
4	2.000	0.602	22.17	77.29	1.35	1.88
5	2.236	0.698	25.13	74.87	1.40	1.87
6	2.449	0.778	30.53	69.47	1.48	1.84

* Average of three replicates
* 1 gram sample containing 10 mg of drug.

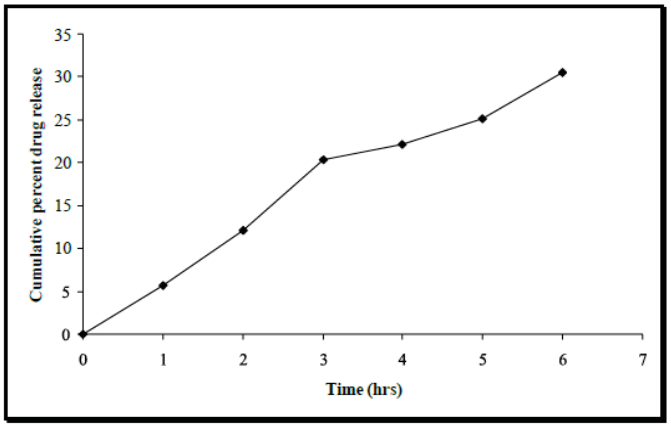


Figure 24: Cumulative percent drug release of fromhydrotropic starch gel TCM-III.

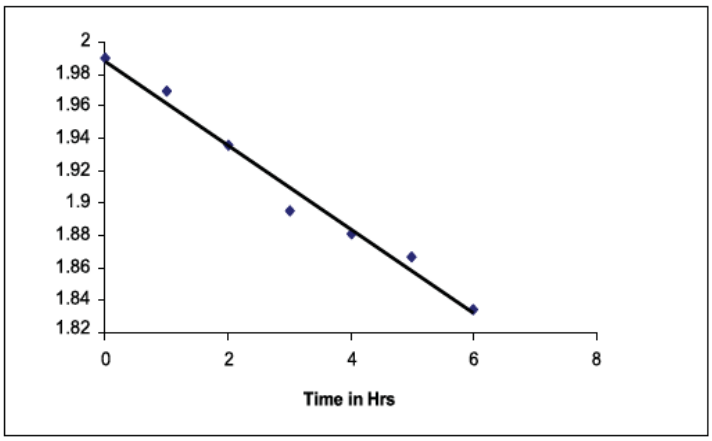


Table 21: Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TCM-I, II & III.

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.

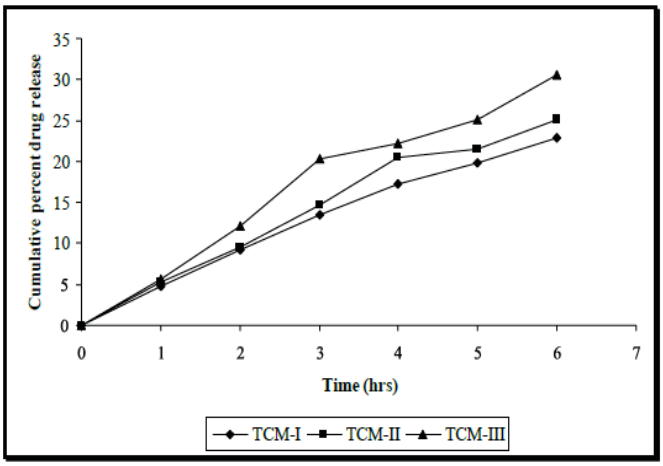


Figure-28

Table 22: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TPU-I.

Time (hrs)	Square root oftime	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	4.93	95.07	0.69	1.97
2	1.414	0.301	9.51	90.49	0.97	1.95
3	1.732	0.477	13.75	86.2	1.13	1.93
4	2.000	0.602	16.12	83.88	1.20	1.92
5	2.236	0.698	20.47	79.53	1.31	1.90
6	2.449	0.778	23.77	76.23	1.37	1.88

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

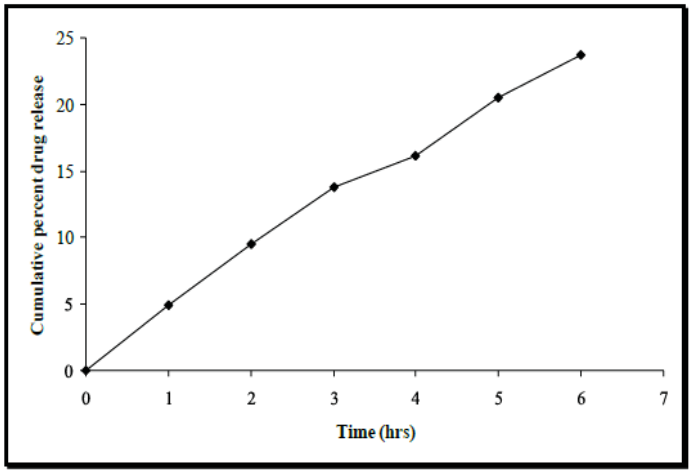


Figure 29: Cumulative percent drug release of Terbinafine HCL from hydrotropic starch gel TPU-I.

Table-23: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TPU-II.

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	5.62	94.38	0.74	1.97
2	1.414	0.301	9.91	90.09	0.99	1.95
3	1.732	0.477	18.89	81.11	1.27	1.90
4	2.000	0.602	20.32	79.68	1.30	1.90
5	2.236	0.698	23.77	76.23	1.37	1.88
6	2.449	0.778	25.26	74.74	1.40	1.87

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

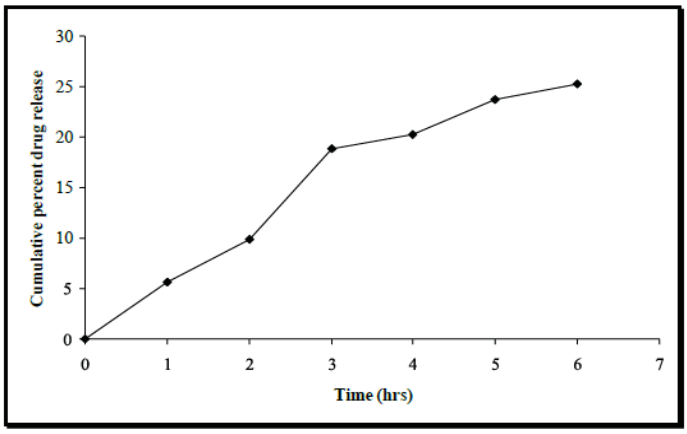


Figure 33: Cumulative percent drug release of Terbinafine HCL from hydrotropic starch gel TPU-I.

Table-24: *In vitro* drug release of Terbinafine HCL from hydrotropic starch gel TPU-III.

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	8.51	91.49	0.92	1.96
2	1.414	0.301	12.14	87.86	1.08	1.94
3	1.732	0.477	22.29	77.71	1.34	1.89
4	2.000	0.602	23.31	76.69	1.36	1.88
5	2.236	0.698	25.12	74.88	1.40	1.87
6	2.449	0.778	29.69	70.31	1.47	1.84

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

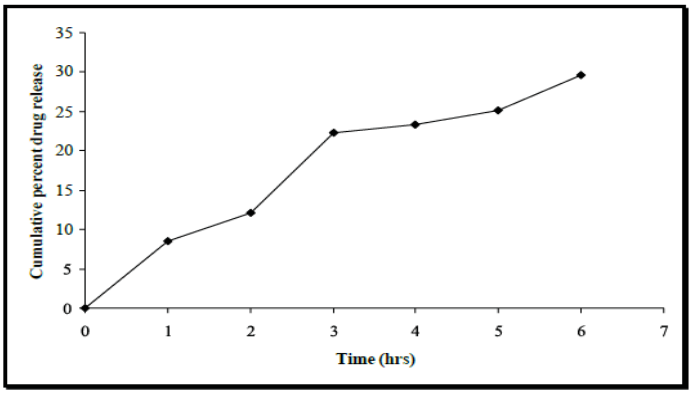


Figure 37: Cumulative percent drug release of Terbinafine HCL from hydrotropic starch gel TPU-III.

Table 25: Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TPU-I, II & III.

Time (hrs)	Cumulative percent drug released		
	TPU-I	TPU-II	TPU-III
0	0	0	0
1	4.93	5.62	8.51
2	9.51	9.91	12.14
3	13.75	18.89	22.29
4	16.12	20.32	23.31
5	20.47	23.77	25.12
6	23.77	25.26	29.69

*Average of three replicates

*1 gram sample containing 10 mg of drug.

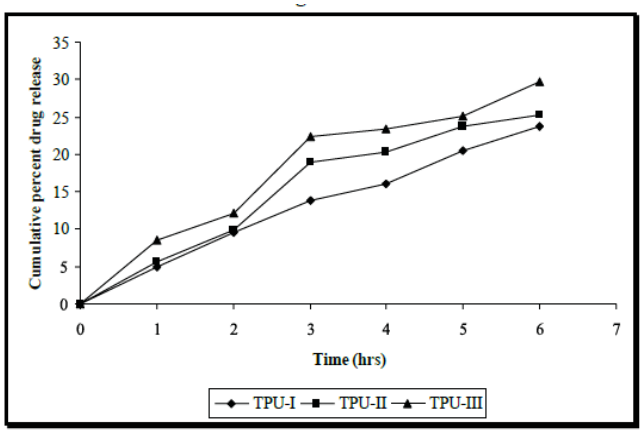


Figure-41

Table 26: *In vitro* % drug release of Terbinafine HCL from hydrotropic starch gel TPM-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	3.14	96.86	0.49	1.98
2	1.414	0.301	6.32	93.68	0.80	1.97
3	1.732	0.477	10.44	89.56	1.01	1.95
4	2.000	0.602	12.32	87.68	1.09	1.94
5	2.236	0.698	16.26	83.74	1.21	1.92
6	2.449	0.778	20.51	79.49	1.31	1.90

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

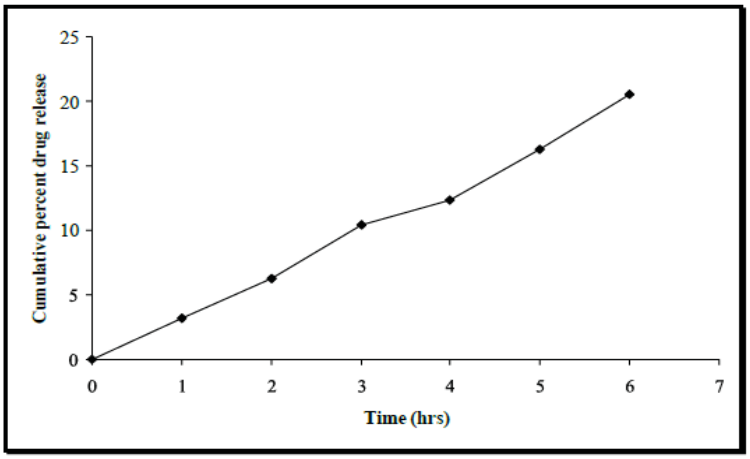


Figure 42: Cumulative percent drug release of Terbinafine HCLfrom hydrotropic starch gel TPM-I.

Table 27: *In vitro* % drug release of Terbinafine HCL from hydrotropic starch gel TPM-II.

Time (hrs)	Square rootof 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	4.40	95.60	0.64	1.98
2	1.414	0.301	7.21	92.79	0.85	1.96
3	1.732	0.477	11.52	88.48	1.00	1.94
4	2.000	0.602	13.61	86.39	1.13	1.93
5	2.236	0.698	17.12	82.88	1.23	1.91
6	2.449	0.778	23.72	76.28	1.37	1.88

* Average of three replicates
* 1 gram sample containing 10 mg of drug.

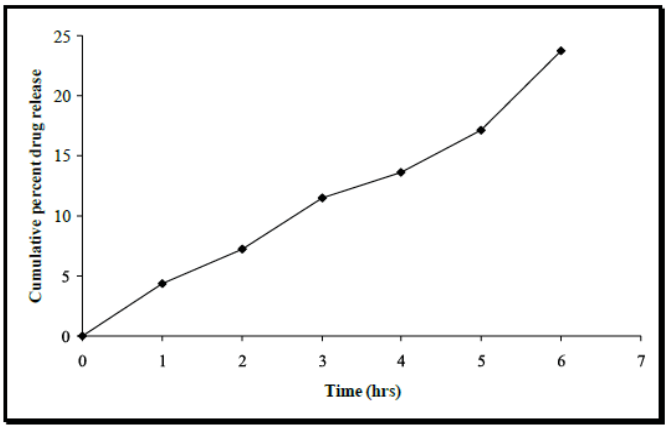


Figure 46: Cumulative percent drug release of Terbinafine HCL from hydrotropic starch gel TPM-II.

Table 28: *In vitro* % drug release of Terbinafine HCL from hydrotropic starch gel TPM-III.

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	7.44	92.56	0.87	1.96
2	1.414	0.3010	10.21	89.79	1.00	1.95
3	1.732	0.477	18.42	81.58	1.26	1.91
4	2.000	0.602	19.81	80.19	1.29	1.90
5	2.236	0.698	21.36	78.64	1.32	1.89
6	2.449	0.778	25.13	74.87	1.40	1.87

* Average of three replicates
* 1 gram sample containing 10 mg of drug.

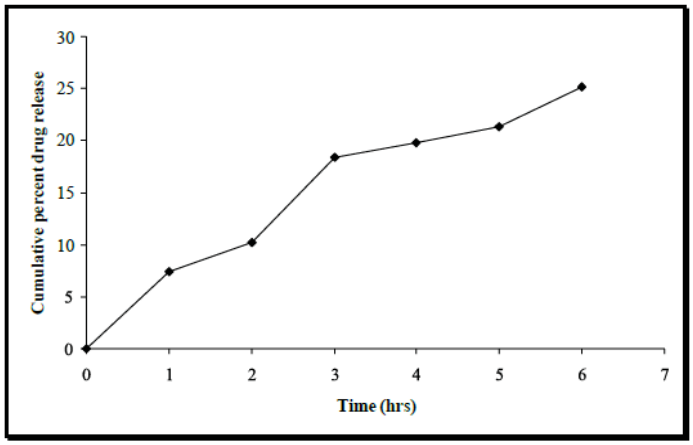


Figure 50: Cumulative percent drug release of Terbinafine HCL from hydrotropic starch gel TPM-III.

Table 29: Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TPM-I, II & III.

Time (hrs)	Cumulative percent drug released		
	TPM-I	TPM-II	TPM-III
0	0	0	0
1	3.14	4.40	7.44
2	6.32	7.21	10.21
3	10.44	11.52	18.42
4	12.32	13.61	19.81
5	16.26	17.12	21.36
6	20.51	23.72	25.13

* Average of three replicates
* 1 gram sample containing 10 mg of drug.

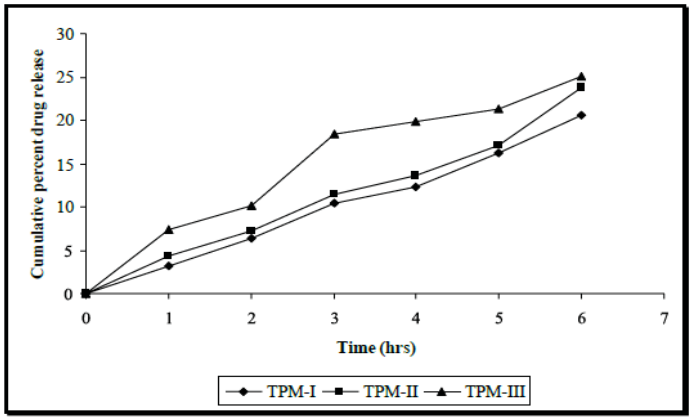


Figure-54

Table 30: *In vitro* % drug release of Terbinafine HCL from Marketed Formulation MP1.

Time (hrs)	Square rootof 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.

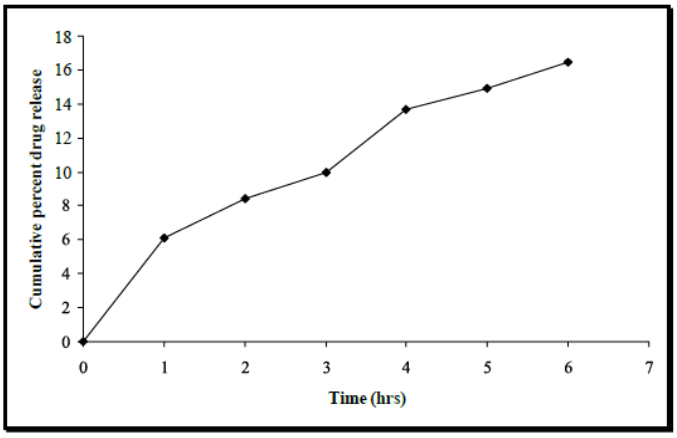


Figure 55: Cumulative percent drug release of Terbinafine HCLmarketed formulation (MP1).

Table 31: Comparative Cumulative percent drug release of Terbinafine HCL hydrotropic starch gels TCU, TPU, TCM, TPM-III & Marketed Formulation (MP1).

Time (hrs)	Cumulative percent drug released				
	TCU-III	TCM-III	TPU-III	TPM-III	MP-I
0	0	0	0	0	0
1	7.04	5.62	8.51	7.44	6.12
2	13.84	12.17	12.14	10.21	8.41
3	28.33	20.31	22.29	18.42	9.99
4	39.50	22.17	23.31	19.81	13.71
5	44.95	25.13	25.12	21.36	14.91
6	57.94	30.53	29.69	25.13	16.43

* Average of three replicates

* 1 gram sample containing 10 mg of drug.

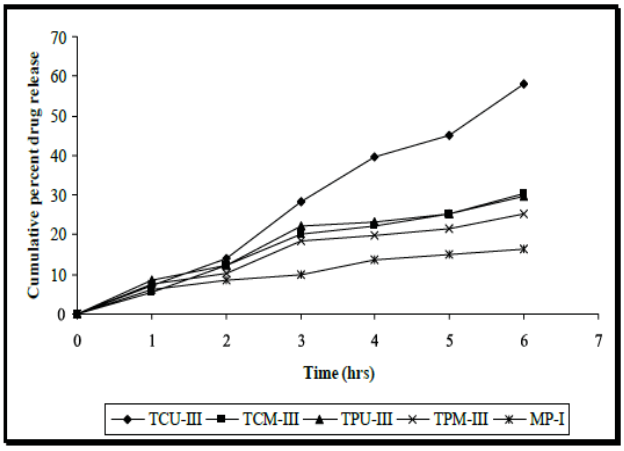


Figure-59

Phase-IV

Rheological properties

1. Spreadability

The prepared hydrotropic starch gel and marketed Preparatoin creams were evaluated for spreadability and was found to be in the range of 13.62 to 15.88 gm-cm/sec for formulations (TCU-I, TCU-II, TCU-III , TCM-I, TCM-II, TCM-III, TPU-I, TPU-II, TPU-III, TPM-I, TPM-II, TPM-III), 14.09 gm-cm/sec for marketed formulation (MP1). Spreadability of individual formulation is shown in table-32.

Table 32: Spreadability.

Sl. No.	Formulationcode	Time taken to travel the distance (sec)	Extrudability	Spreadability gm-cm/sec
1.	TCU-I	59	++	15.51

2.	TCU-II	61	++	15.09
3.	TCU-III	64	++	14.29
4.	TCM-I	60	++	15.29
5.	TCM-II	62	++	14.76
6.	TCM-III	67	++	13.69
7.	TPU-I	58	++	15.88
8.	TPU-II	59	++	15.53
9.	TPU-III	60	++	15.26
10.	TPM-I	62	++	15.79
11.	TPM-II	63	++	14.51
12.	TPM-III	66	++	13.62
13.	MP1	65	++	14.09

Table 33: Viscosity of hydrotropic starch gels containing corn Starch andUrea.

Sl. No.	Formulation Code	Viscosity (cps)
1.	TCU-I	34506
2.	TCU-II	83394
3.	TCU-III	127450

Table 34: Viscosity of hydrotropic starch gels containing corn starch andMannitol.

Sl. No.	Formulation Code	Viscosity (cps)
1.	TCM-I	3846
2.	TCM-II	10841
3.	TCM-III	163740

Table 35: Viscosity of hydrotropic starch gels containing potato starch andUrea.

Sl. No.	Formulation Code	Viscosity (cps)
1.	TPU-I	3321
2.	TPU-II	9821
3.	TPU-III	134172

Table 36: Viscosity of hydrotropic starch gels containing potato starch andMannitol.

Sl. No.	Formulation Code	Viscosity (cps)
1.	TPM-I	6423
2.	TPM-II	15432
3.	TPM-III	227665

Table 37: Viscosity (cps) for hydrotropically gelled starch TCU-III.

Speed (rpm)	Shear Rate (sec^{-1})	Square Rootof Shear Rate	Apparent Viscosity up curve (cps)	Shear Stress up curve ($dynes/cm^2$)	Square Rootof Shear Stress up	Apparent Viscosity down (cps)	Shear Stress down curve ($dynes/cm^2$)
0.5	0.14	0.37	105230	15146	116.51	118000	17050
1.0	0.28	0.52	70064	18538	130.06	75364	20302
2.5	0.7	0.83	35367	24423	148.68	38867	26873
5.0	1.4	1.18	20157	28664	161.44	23657	33564

10	2.8	1.67	12063	35506	180.22	14563	42776
20	5.6	2.36	8064	44110	211.53	17014	55611
50	14	3.74	4431	62451	241.00	5837	82051
100	28	5.29	3049	84321	281.12	4064	105800

Average of three replicates

Phase-V

Drug-Polymer Interaction (IR Studies)

IR spectrum of selected hydrotropic starch gels weredetermined and shows that the Terbinafine HCL had only physicalentrapment in the polymer and no drug-polymer interaction have taken as shown in figure-62-66.

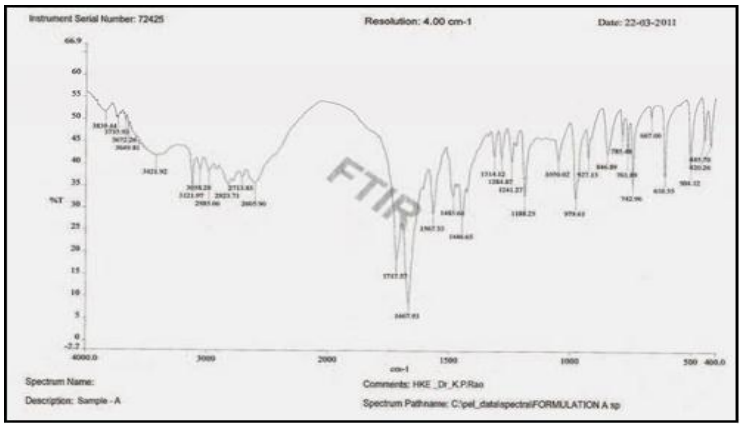


Figure 62: IR Spectra of Terbinafine HCL (Pure Drug).

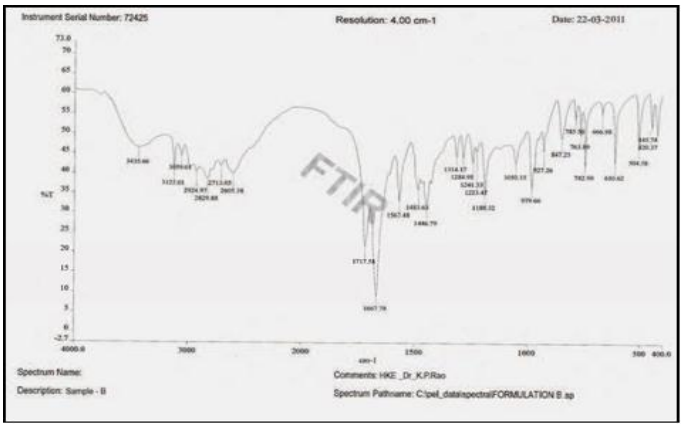


Figure 63: IR Spectra of hydrotropic starch gels containing Terbinafine HCL (TCU-III).

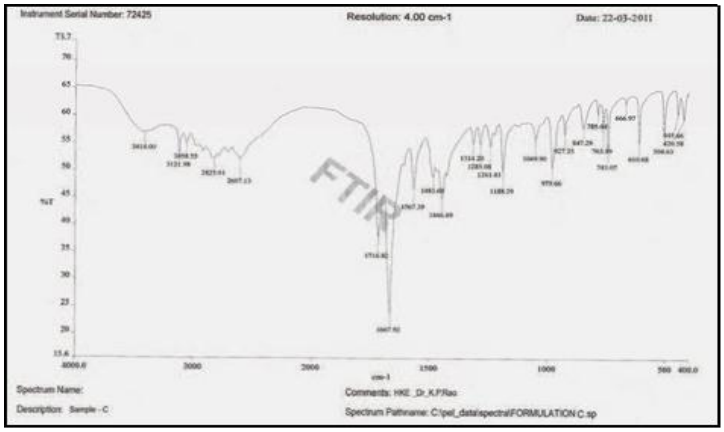


Figure 64: IR Spectra of hydrotropic starch gels containing Terbinafine HCL (TCM-III).

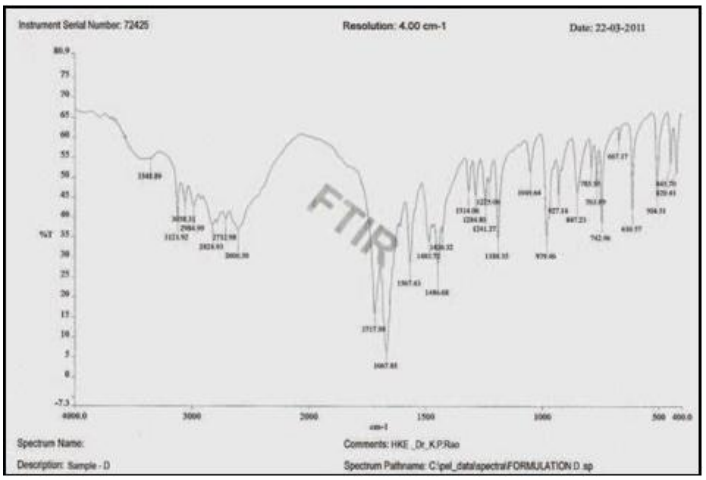


Figure 65: IR Spectra of hydrotropic starch gels containing Terbinafine HCL (TPU-III).

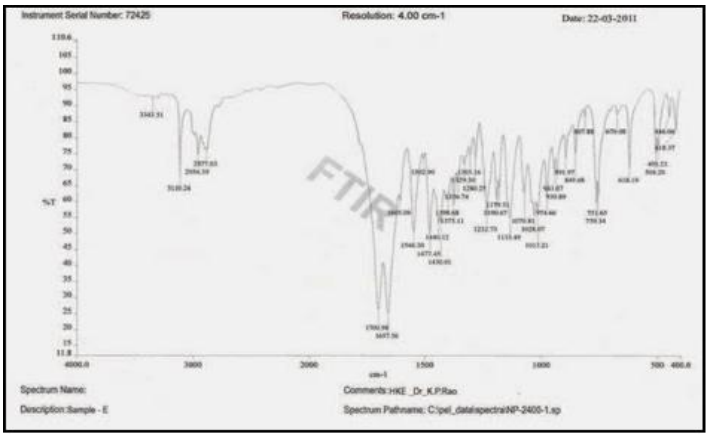


Figure 66: IR Spectra of hydrotropic starch gels containing Terbinafine HCL (TPM-III).

Phase-VI

Stability studies

Hydrotropic starch gel containing Terbinafine HCL were found to be stable at the temperatures andparameters tested are as shown in table-38-39.

Tabl 38: Stability studies of hydrotropic starch gel TCU-III at Temperature 28±3ºC and RelativeHumidity (RH) 65±5%.

Sl. No	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 39: Stability studies of hydrotropic starch gel TCU-III at Temperature 5±3ºC.

Time	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

Phase-VII: Antifungal activity

Photograh-1: Antimicrobial studies showing the comparative zone of inhibition of drug as Pure and Informulation (TCU -III).

Pure drug

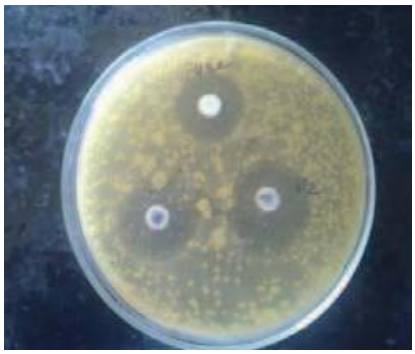


Plate-1

Pure drug

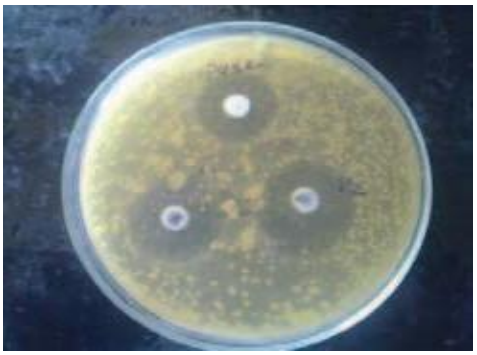


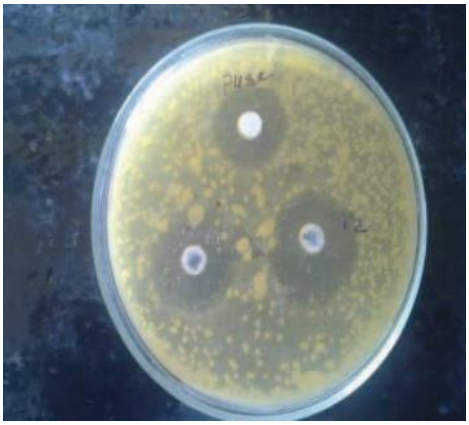
Plate- 2

Pure drug

Plate- 3

Formulationcode	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	24	25	23.66±0.57
TCU-III (plate 1)	24	21	22	22.33±1.53
TCU-III (plate 2)	21	20	23	21.33±1.53
TCU-III (plate 3)	22	23	21	22.00±1.00

Photograh 2: Antimicrobial studies showing the comparative zone of inhibition of drug as Pure and Informulation (TCM-III).



Pure drug

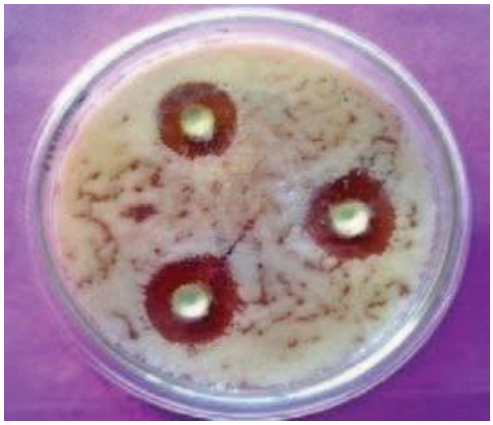
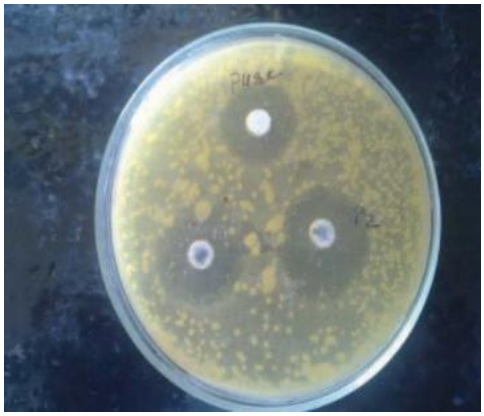
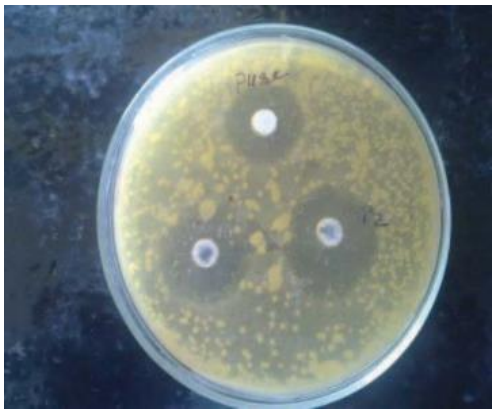


Plate-1



Pure drug

Plate2



Pure drug

Plate-3

Formulation code	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	24	25	23.66±0.57
TCM-III (plate1)	23	20	22	21.66±1.52
TCM-III	20	22	22	21.33±1.54

(plate2)				
TCM-III (plate3)	21	23	22	22.00±1.00

Photograh 3: Antimicrobial studies showing the comparative zone of inhibition of drug as Pure and Informulation (TPU-III)

Pure drug

Plate-1

Pure drug

Plate-2

Pure drug

Plate-3

Formulation code	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	24	25	23.66±0.57
TPU-III (plate 1)	23	23	22	22.66±0.57
TPU-III (plate 2)	22	21	22	21.66±0.57
TPU-III (plate 3)	23	21	20	21.33±1.52

Photograh 4: Antimicrobial studies showing the comparative zone of inhibition of drug as Pure and inFormulation (TPM-III).

Pure drug

Plate-3

Pure drug

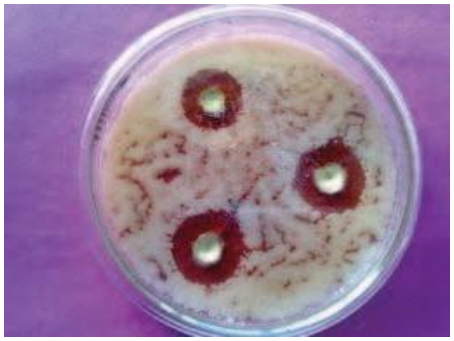
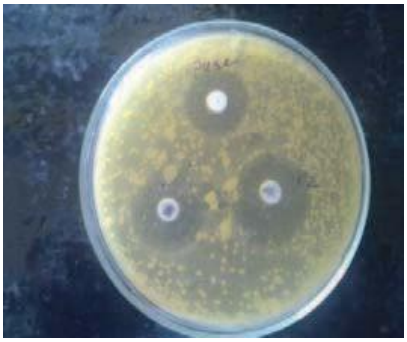


Plate-2

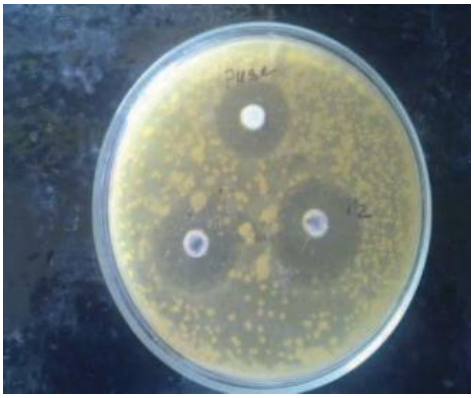


Pure drug

Plate-3

Formulationcode	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	24	25	23.66±0.57
TPM-III (plate 1)	20	22	19	20.33±1.52
TPM-III (plate 2)	23	21	21	21.66±1.15
TPM-III (plate 3)	22	21	19	20.66±1.52

Photograh 5: Antimicrobial studies showing the comparative zone of inhibition of drug as Pure andMarketed formulation (MP-1).



Pure drug

Plate-1

Pure drug

Plate-2

Pure drug

Plate-3

Formulation Code	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	24	25	23.66±0.57
MP-1 (plate 1)	20	23	21	21.33±1.52
MP-1 (plate 2)	22	21	19	20.66±1.53
MP-1 (plate 3)	20	22	21	21.00±1.00

Table 40: Antimicrobial studies showing the comparative zone of inhibition of drug as Pure and In formulations.

	Statistical Zone inhibition (mm) after 36 hrs			Mean± S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug(plate1)	23	24	23	23.33±0.57
Pure Drug(plate2)	22	24	22	22.66±1.15
Pure Drug(plate3)	23	23	21	22.33±1.16
TCU-III(plate 1)	24	21	22	22.33±1.53
TCU-III(plate 2)	21	20	23	21.33±1.53
TCU-III(plate 3)	22	23	21	22.00±1.00
TCM-III(plate1)	23	20	22	21.66±1.52
TCM-III(plate2)	20	22	22	21.33±1.54
TCM-III(plate3)	21	23	22	22.00±1.00
TPU-III(plate 1)	23	23	22	22.66±0.57
TPU-III(plate 2)	22	21	22	21.66±0.57
TPU-III(plate 3)	23	21	20	21.33±1.52
TPM-III(plate 1)	20	22	19	20.33±1.52
TPM-III(plate 2)	23	21	21	21.66±1.15
TPM-III(plate 3)	22	21	19	20.66±1.52
MP-1 (plate 1)	20	23	21	21.33±1.52
MP-1 (plate 2)	22	21	19	20.66±1.53
MP-1 (plate 3)	20	22	21	21.00±1.00

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 additionof 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, likedistilled 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. Butthe actual mechanism by which this effect occurs is not clear.

Physical appearance

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

pH

pH of hydrotropic starch gels was found between 6.44 to 6.65, forgels 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 gelsprepared by using potato starch with Urea and Mannitol was 6.29 to 6.41and 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 ofUrea.

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 starchgel 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 andfinal products.

Viscosity

Viscosity is an important parameter for characterizing the gels as it effect the spreadability, extrudability and release of the drug. The viscosityof hydrotropic starch gels prepared by using potato starch and corn starchwas determined. The hydrotropic salts Urea and Mannitol has also shownan effect on viscosity, as the concentration of salts was increased there wasan increase in the viscosity of the gels. Gels containing Mannitol were foundto be more viscous than that containing Urea; as shown in table No.33, 36,35 and Hydrotropic starch gels TCU-IIIalso evaluated for the rheological behavior by using spindle No SC428/13 R at eight differentspeeds and the shearstress (dynes/cm^2) and shear rate (S^{-1}) was calculated.

The apparent viscosity (cp) value of TCU-III was found to be 105230and 3049, at low shear rate 0.14 and high shear rate 28.

The rheological data further indicated that hydrotropically preparedstarch gels werefound to exhibit shear thinning property when shear rate isincreased.

The ascending and descending rheograms are not supper imposed and can be concluded as thixotropy in nature with the hysteresisloop as shown in figure-60 & 61. The stress shear rate data was also plottedas casson plots for TCU-III.; the system gave pseudo plastic flow withconsiderable shear thinning tendency with better spreadability.

Spreadability

Spreadability plays an important role in patient compliance and helpin 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 spectrumof 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 absorptionof 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-hat 30412 cm $^{-1}$ to2862 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 28^0C±3^0 C for a periodof 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 28^0C±3^0 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 14.29gm c/s spreadability was found. And at 5^0C±3^0 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.

SUMMARY

Increasing attention has been focused on achieving systemic delivery of drugs by means of dermatological application of semi-solid dosage forms. Among the various semi-solid dosage forms, a much more tendency has been shown towards the gel formulation because of itsesthetic value, controlled release of drugs, etc.

In the present study, Terbinafine HCL hydrotropic starch gel were prepared using corn and potato starches along Urea and Mannitol as a hydrotropic salts and Terbinafine HCLas model drug. Hydrotropic salts produce swelling and gelatinization of starch without the uses of heat i.e., decreases the gelatinization temperature, the effect being concentration dependent.

Hydrotropes are recognized as a class of compounds, which in fairly high concentrations increases the solubility of a variety of poorly soluble drugs in water.

Terbinafine HCL, an antifungal drug used in the treatment of fungal infection caused by the organism like *Candida albicans*, Tinea, etc. The drug is slightly soluble in water with low bioavailability due to first pass metabolism. The oral administration of Terbinafine HCL causes gastric upset, and many other side effects, so Terbinafine HCLwas used as a drug of choice in the research work.

The present investigation was done to explore new pharmaceutical application of hydrotropy and the present work reports on some properties of hydrotropic starch gels, particularly the release of Terbinafine HCL.

The need and objective of the present work is presented in chapter-3.

Standardization of all materials used in formulation of hydrotropic starch gels was done. The hydrotropic starch gels were prepared using different starches & hydrotropic salts in varying concentration. The effect of hydrotropic salts (Urea and Manitol) on solubility of Terbinafine HCL was determined. It was observed that the solubility of Terbinafine HCL increase as the concentration of salts was increased.

The prepared hydrotropic starch gels were evaluated for physico chemical characterization and were found acceptable. In-vitro drug release of hydrotropic starch gels was significant

when compared to marketed creams.

The hydrotropic starch gels were also subjected for drug polymer studies andwere found that there was no interaction between the drugand polymer.

Stability studies were performed to assure that the formulationretains itsactivity.

CONCLUSION

The data obtained from the study of development and evaluation of starch basedhydrotropic gels, the following conclusions were made. It was observed that hydrotropicstarch gels offer a suitable vehicle for topical delivery of Terbinafine HCL. The hydrotropic salts Urea was observed to improve the solubility of Terbinafine HCL as compared to Mannitol. The hydrotropic starch gels were found to be white opaque to white translucent in appearance and have good homogeneity. The drug content, pH, spreadability, was found to be within acceptable range. The starches (corn & potato) showed an impact on the viscosity of gel formulations. Gels prepared using potato starch was more viscousthan gels prepared using corn starch. Hydrotropic salts has also showed an impact on the viscosity ofgels Gels containing Mannitol were more viscous than that containing Urea. The in vitro release of hydrotropic starch gels containing Terbinafine HCL were found to be in the following order TCU-III>TCU- II> TCM-III>MP1.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 other formulation and marketed preparation.IR spectra showed that there is no interaction between the drug and additives, and hence the drug remains intact without undergoing anychemical reaction during the preparation and after its storage.

Skin irritation study was conducted on white rabbits and guineapigs for a period of 3 days, and was observed regularly. The results of the study concludes that there was no (erthrema & edema) found after 3 days on the skin of rabbit and guinea pig on application of prepared gel. The obtained results were confirmed on application of formulations in healthy human volunteers in clinical studies.

The antifungal activity manifested that the mean zone of inhibition of the hydrotropic starch gel (TCU-III) was larger than that of the reference and marketed cream (MP1).Theexperiment was reproduced with another drug ketoconazoleand the results obtained were reproducible.

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