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Formulation and Evaluation of Topical Hydrogel of Terbinafine HCL for Effective Management of Dermatophyte.

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ABSTRACT: In this research work an attempt has been made to formulate the topical drug delivery system of Terbinafine HCl in the form of hydro gel. The gel was prepared for topical use so the bioavailability if drug is increased and prevent the loss of drug from first pass metabolism. Hydrogel is a Topical drug administration drug delivery system anywhere in the body of ophthalmic, rectal, vaginal and skin. Hydrogel based micro valves have a number of advantages over conventional micro valves, including relatively simple. Fabrication, no external power requirement no integrated electronics. Hydrogel having good oxygen permeability and superior biocompatibility, low protein adsorption and cell adhesion. Antifungal drug is widely used for the treatment of the fungal infection such as itching, redness, and fungal infection. Hydrogel show good homogeneity, drug content, Spredability and stability and has a wider prospect for Topical preparation. Terbinafine HCl is widely used antifungal agent mostly used to treat fungal infection. Pre-formulation studies were carried out using polymer like HPMC, CMC, Carbapol and Guar gum. The literature survey indicates that Carbapol and HPMC an excellent gelling agent during the formulation of Hydro gel preparation. As Carbapol and HPMC is chief, easily availableand have a wide regulatory acceptance, it was chosen as a gelling agent in the present study.

KEYWRODS: Terbinafine HCL, Topical Drug Delivery System, Carbapol, Polymer.

INTRODUCTION:

1.Skin

A. Structure of Skin

The human skin is multilayered organ composed of many histological layers. Skin is most accessible organ in body. Its major function is protection of major or vital internalorgans from the external influences, temperature regulation, control of water output andsensation.[1] The skin of an average adult body covers approximately surface area of twosquare meters and receives about one- third of the blood circulating through the body. Skin is the complex organ and allows the passage of various chemicals into and acrossthe skin. Drugs that are systemically active are administered via the skin, where they are absorbed, introduced into the bloodstream, and then delivered to the desired tissues.[2]

Layers of Skin:

Three Major Layers of The Skin Are:

a) Epidermis

b) Dermis

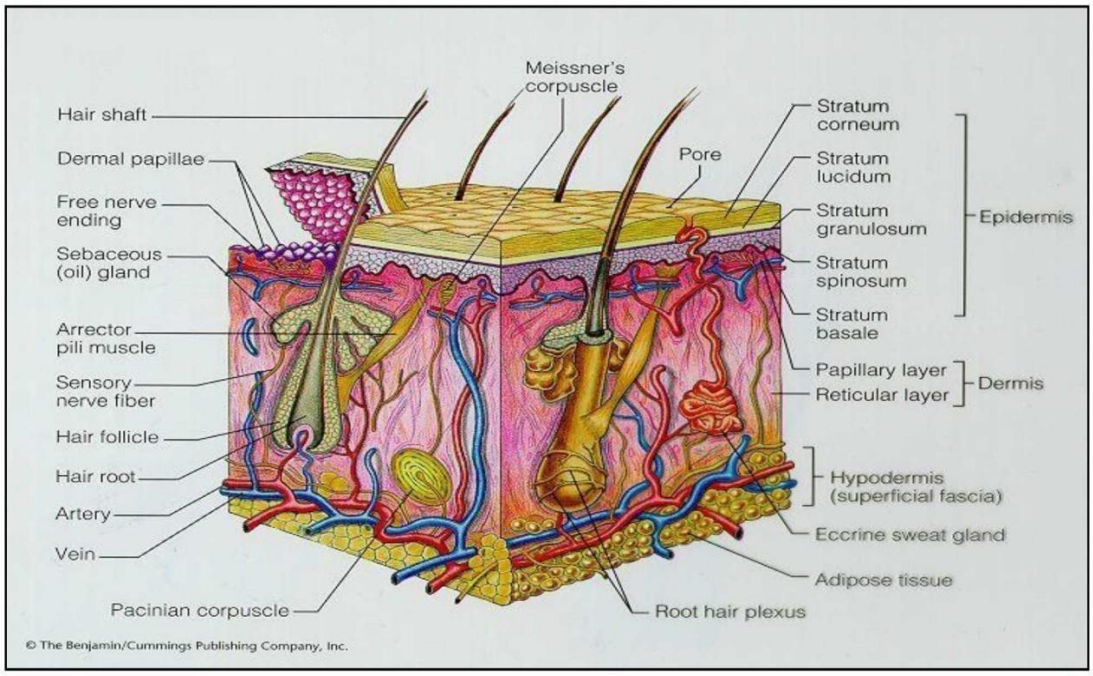
c) Hypodermis

a) Epidermis:

The epidermis is a stratified, squamous, keratinizing epithelium. The keratinocytescomprise the major cellular component (> 90%) and the responsible for the evolution of barrier function. Keratinocytes change their shape, size and physical properties when migrating to the skin surface. Other cells present which are present inthis layer include melanocytes, Langerhans cells and Markel cells, none of which appears to contribute to the physical aspects of the barrier. Microscopically, theepidermis further divided into five anatomical layers with stratum corneum forming theouter most layer of the epidermis, exposing to the external environment. Stratum corneum is the outermost layer of epidermis approximately 100-150 micrometers thick,has no blood flow. This is the most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughoutthe body. If the drug is able to penetrate the stratum corneum, then it can enter the bloodstream. A process known as passive diffusion, which occurs too slowly,is the only means to transfer normal drug across the layer.[3]

b) Dermis: The dermis is the inner and larger (90%) skin layer, comprises primarily of connectivetissue and provides supports to the epidermis layer of the skin. The boundary between dermis and epidermis layer is called dermal-epidermal junction which provides a physical barrier for the large molecules of drug and cells. The dermis incorporates bloodand lymphatic vesicles and nerve ending. Drugs absorbed through the epidermis are reabsorbed at the vast microvasculature network located in the dermis. Papillary dermisand reticular dermis are two anatomical regions that make up the dermis. The dermis' thinnest outer layer is called papillary. In the papillary region, collagen and elastin fibres are typically vertically orientated and joined at the dermal-epidermal junction. The fibres in the reticular dermis are aligned horizontally. As skin is major factor for the determination of various drug delivery aspects like permeation and absorption of drug across the dermis. [4]

Figure: 1.1 Structure of Skin



c) Hypodermis:

The hypodermis is the adipose tissue layer which is found in between of dermis and aponeurosis and fasciae of the muscles. The subcutaneous adipose tissue is structurallyand functionally is well integrated with the dermis trough the nerve and vascular network.

The hypodermis layer is composed of loose connective tissue and its thickness variesaccording to the surface of body [3]

The common fungal skin infections

i. Athlete'sfoot.

ii. Yeastinfection.

iii. Ringworm.

iv. Nailfungus.

v. Oralthrush

vi. Diaperrash.

Causes of skin disease

Skin diseases might occur as a result of certain lifestyle choices. Your skin may beimpacted by underlying medical issues. Typical causes of skin conditions include:

i. Bacteria trapped in your pores or hairfollicles.

ii. Conditions that affect your thyroid, kidneys or immunesystem.

iii. Contact with environmental triggers, such as allergens or another person'sskin.

iv. Genetics

v. Fungusor parasites living on yourskin.

vi. Medications, such as the ones that treat inflammatory bowel disease(IBD).

vii. Viruses.

2. Topical Drug Delivery

Localized drug distribution through the skin, vagina, rectal, and ocular cavities is known as topical drug administration. The primary route of topical medication deliveryis through the skin, one of the most easily accessible organs on the human body for topical administration. The logical approach to topical formulations, topical permeationprinciples, and fundamental elements of topical drug delivery systems are all covered in detail in this review. The majority of clinical evidence points to topical gel as a secureand reliable treatment choice for usage in the treatment of skin-related diseases.

Applying topical treatments to the skin can have surface, localised, or systemic effects.Because of its medicinal qualities, such as its emollient, calming, or protecting action, the base may occasionally be used on its own. However, a lot of topical treatments havetherapeutically useful components that are disseminated or dissolved in the base. A variety of topical formulations with a wide range of medication administration and therapeutic options are possible because to the combination of active components and base. The terminologies used to categorise the bases of topical preparations that containtherapeutically active chemicals might be based on either their composition, their intended application, or their physical qualities (suspension) (hydrophilic creams). Oneof the top 15 medical diseases in terms of prevalence and healthcare cost over the pastten years is skin illness (dermatological conditions), which affects the majority of the population.

The effectiveness of topical dermatological treatments is significantly impacted by optimising the topical delivery of dermatological agents (small and large molecules) using chemical enhancers, bio-polymers (like sodium hyaluronate), liposomes, particulate carriers (microspheres and lipid nanoparticles), topical sprays and foams, occlusion (via dressing and patches), topical peels, temperature (heat), iontophoresis, and ultrasound. These delivery techniques (creams, lotions, ointments, and pastes) constitute a major improvement over existing systems whether used separately or in combination. They have the potential to increase efficacy and tolerability, boost patient compliance (including dermatology life quality), and meet additional unmet needs in the topical dermatological market. Alternative routes of administration and enhanced medication delivery to localised target sites in the body are provided by non-invasive drug delivery systems. In addition to other substantial benefits including eliminating first pass hepatic metabolism, gastric degradation, and frequent dosage, topical applieddermal and transdermal delivery methods could replace needles needed to administer many of the emerging biologics-based drugs and vaccines. However, due to the skin's rigid barrier qualities, the limited dermal and transdermal transport of many tiny and big molecules is a considerable obstacle. [4]

3. GEL

The qualities of a gel, which is a solid jelly-like substance, can range from soft and weak to rigid and durable. Gels are described as a cross-liked, significantly diluted system that, in its steady state, shows no flow. [5]

Classification of Gel

Colloidal phases, natural solvents utilised, physical makeup, and rheologicalcharacteristics can all be used to classify gels. [6]

Based on Colloidal System

- **Two Phase System(Inorganic)**

If the particle size of dispersed phase is relatively large and form the three- dimensionalstructure throughout the gel such as a system consist of floccules of small particle ratherthan layer molecule and gel structure in this system is not always stable e.g. aluminumhydroxide gel USP

- **Single Phase System(Organic)**

These consist of large organic molecule existing on the twisted stands dissolved incontinuous phase.

Based on Nature of Solvent Used

- **Hydrogel**

Here they contain water as their continuous liquid phase e.g. gelatin, cellulosederivatives and poloxamer gel

- **Organic Gel (With A Non-AqueousSolvent)**

These contain a non-aqueous solvent as continuous phase.

- **Xerogels**

Xerogels are solid gel with low solvent concentration and produced by evaporationofsolvent or freeze drying e.g., dry cellulose and polystyrene.

Based on Rheological Properties

Usually, gels exhibit non-Newtonian flow properties. They are classified into:

- Plasticgels
- Pseudo plasticgels
- Thixotropicgels

Based on Physical Nature

- Rigidgels
- Elasticgels

Pharmaceutical Gels

May be loosely categorized based upon their network microstructure according to thefollowing scheme suggested by Faucci.

A) Covalently bonded polymer network with completely disorderedstructure

B) Physically bonded polymer network predominantly discovered but containingordered loci.

C) Well-ordered lamellar, including gel mesophases formed byinorganic clays.[6]

3.1 Hydrogel

A hydrogel is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Hydro gels are highly absorbentnatural or synthetic polymeric networks. Hydro gels also possess a degree of flexibilityvery similar to natural tissue, due to their significant watercontent. With the establishment of the first synthetic hydrogel by Wichterle and Lim in 1954, the hydrogel technologies may be applied to food additives, pharmaceuticals, biomedical implants tissue engineering and regenerative medicines, diagnostics, cellular immobility, separation of biomolecules or cells and barrier materials to regulatebiological adhesions, Biosensor and Bio MEMs devices and drug carriers. Additionally,the ever-growing spectrum of functional monomers and macromeres widen its applicability. Hydro gels are hydrophilic polymeric network of three- dimensionalcross-linked structures that absorb substantial amount of water. Cross linking facilitatesinsolubility in water because of ionic interaction and hydrogen bonding. It also providesrequired mechanical strength and physical integrity to the Hydro gels. Thus, Hydro gels can imbibe water nearly 10-20- times its molecular weight and hence become swollen. Some examples of Hydro gels include contact lenses, wound dressing superabsorbent.[9]

Advantages of Hydro gels

- Entrapment of microbial cells within polyurethane Hydro gels beads with the advantage of lowtoxicity.

- Hydrogel is more elastic and stronger than available Hydro gels of similar softness. Poly (methyl acrylate-hydroxyethyl acrylate) hydrogel implant materialof strength and softness.

- Compared to conventional microvalves, Hydro gels-based microvalves have a number of benefits, including relatively simple manufacturing, no need forexternal power, no integrated electronics, large displacement (185 um), and strongforce production (22mN).

- Environmentally sensitive Hydro gels. These Hydro gels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.

- Natural hydrogel materials are being investigated for engineering; these materialsinclude agarose, methylcellulose, hyaluronan and other naturally derivedpolymers.[9]

Limitations of Hydro gels

- The main disadvantages are the high cost and the sensation felt by movementofthe maggots.
- Its disadvantage includes thrombosis at anastomosis sites and the surgicalriskassociated with the device implantation andretrieval.
- Hydro gels are non-adherent they may need to be secured by asecondarydressing.

- Disadvantages of hydrogel in contact lenses are lens deposition,hypoxia,dehydration and red eyereactions.[9]

Properties of Hydro gels Swelling Properties

All polymer chains in Hydro gels are cross linked to each other either physically or chemically and thus, considered as one molecule regardless of its size. For thisreason,there is no concept of molecular weight of Hydro gels and therefore, sometimes called infinitely large molecules or super macromolecules. A slight change in the environment may cause hydrogel to alter quickly and irreversibly. The physical textureof the hydrogel may change as a result of changes in environmental factors including pH, temperature, electric signal, the presence of an enzyme, or other ionic species. These modifications could manifest macroscopically as the production of precipitates or adjustments to the size and water content of Hydro gels. The volume change is causedby variations in the pH of the solvent and the difference in mobile ion concentration between the interior of the hydrogel and the exterior solution (osmotic pressure). Hydro gels having basic or acidic functional groups react to changes in the pH of the surrounding environment. The functional groups' degree of ionisation determines their swelling profile and, thus, their volume change. The swelling ratio of polyacrylic acid changes due to the ionisation of the carboxyl groups on the polymer chain, making it asort of pH-sensitive hydrogel.[10]

Mechanical Properties

From the perspective of pharmacological and biological applications, the mechanical properties of Hydro gels are crucial. In many biomedical applications, such as ligamentand tendon repair, wound dressing material, matrix for drug delivery, tissue engineering, and as cartilage replacement material, the evaluation of mechanical property is crucial. When therapeutic molecules are delivered through Hydro gels for theprescribed amount of time, their mechanical qualities should be such that the Hydro gelscan keep their physical texture. The required mechanical property of the hydrogel mightbe obtained by adjusting the crosslinking level. A stronger hydrogel could be made byincreasing

the degree of crosslinking because this reduces the Hydro gels' percentage ofelongation and results in a more brittle structure. Therefore, there is an ideal level of crosslinking to produce a hydrogel that is both moderately robust and elastic. Many researchers have used hydrogen bonding within the hydrogel to produce desiredmechanical properties by copolymerization with co-monomers. Grassi et al. most recently identified the mechanical characteristics of calcium alginate hydrogel. [11]

Biocompatible Properties

In order for Hydro gels to be used in the biomedical industry, they must be both non- toxic and biocompatible. cytotoxicity and in-vivo toxicity tests must be passed by the majority of polymers utilised for this purpose. The capacity of a substance to function with a suitable host response in a particular application is known as biocompatibility. The two main components of biocompatibility are a) bio-safety, which refers to a suitable host reaction that is not only systemic but also local (the surrounding tissue), and b) bio-functionality, which refers to a material's capacity to carry out the particularpurpose for which it is designed. [12]

4. MATERIALS AND METHODS

Preformulation Study

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation studies are the first step in the rationale development of dosage form of drug substance. The objectives of the Preformulation studies are to develop information about the drug substance, so that this information is useful to develop formulation. Preformulation investigations are designed to identify the physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic- biopharmaceutical properties of the resulting product. The goal of thestudy is as:

1. To establish the necessary physicochemical characteristics of a new drug substance.
2. To determine kinetic release rate profile.
3. To establish its compatibility with different excipients. Hence, the Preformulation study on the obtained sample of the drug includes physicaltest determination and compatibility studies. [13]

Characterization of Terbinafine HCl Organoleptic Properties

The drug powder was analyzed for colour, odour, and taste.

Description

The drug powder of Terbinafine HCl was analyzed for physical appearance andpowder nature.

Melting Point

Melting point determination of Terbinafine HCl was done by capillary tube method. Pushed the open end of capillary tube into the powdered Terbinafine Move the powderto the closed end of the tube by tapping it on table. It was repeated until the powdered Terbinafine occupies 1-2 mm of the capillary tube. The filled capillary tube was attached firmly with the rubber bands on the thermometer and deeper into the thiel‘s tube containing liquid paraffin. It was heated and observed for the melting of the drug.The temperature was noted at which Terbinafine melted. The melting point is reportedin result and discussion section.

Solubility Analysis

Saturation solubility of Terbinafine HCl was determined in pH 5.5 Phosphate Buffer, Ethanol water (1:1), Methanol. Excess amount of drug was added to 100ml of pH 5.5 Phosphate Buffer; solution was shaking in shaker for 48 hr, to dissolve the drug. The content was then filtered through Whatman filter paper. Filtrate was suitably diluted with pH 5.5 phosphate buffer and analyzed spectrophotometrically. The same procedure was used for other solvents under study.

Spectroscopic Studies Determination of Lambda Max

Stock (100µg/ml) of Terbinafine HCl was prepared in Phosphate buffer pH 5.5. The solution was kept in Quartz cuvette having thickness 10mm. the UV spectrum was recorded in the range of 200-400nm Shimadzu UV- visible spectrophotometer (UV- 1800) at 1cm, slit width. It showed lambda max at 283nm using spectrophotometer. The procedure was repeated for accuracy at least three times.

Preparation of pH 5.5 Phosphate Buffer

Solution I: Dissolve 13.61 gm of potassium Dihydrogen phosphate in sufficient water and make up the volume upto 1000 ml with water.

Solution II: Dissolve 35.81gm of Disodium hydrogen phosphate in distilled water and make up the volume upto 1000 ml.

Mix the 96.4 ml of solution I with3.6 ml of solution II and check the pH.

Standard Calibration Curve of Terbinafine HCl in pH 5.5 Phosphate Buffer

100mg was dissolved in a 10ml of pH 5.5 buffer and the volume was made up to 100mlusing buffer pH 5.5. From this solution 10ml was withdrawn and diluted to 100ml withphosphate buffer pH 5.5. From this stock solution 20ml was withdrawing and diluted to 100ml with phosphate buffer pH 5.5. Serial dilutions were made by withdrawn 1, 2,3,4,5,6,7,8,9 and 10 ml and diluted to 10 ml with phosphate buffer pH

5.5 to obtain the solutions in concentrations of 2,4,6,8,10,12,14,16.18 and 20µg/ml. Theabsorbance was measured at 283nm using UV spectrophotometer.

IR Spectroscopy

The spectrum was recorded in the wavelength region of 4000 to 400cm-1. A disc sample of the drug and polymer were mixed uniformly and filled into the die cavity andthe sample holder and an IR spectrum was recorded using diffuse reflectance FTIR spectrophotometer**.**

Compatibility Studies of Terbinafine HCl and Formulation Excipients

The compatibility of drug and polymer under experimental conditions is important prerequite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental conditions and not affecting the shelf life of the product or any unwanted effect on the formulation.

Screening of Polymers

Preformulation studies were carried out using polymers like HPMC K4M, Carboxymethylcellulose (CMC), Carbopol 934 and Guar Gum. [14]

Formulation of Different Concentrations of Hydrogel Preparation of HPMC K4MHydrogel

Weighed 0.1gm of HPMC k4M and dispersed in 10ml water and it was stirred using magnetic stirring for 12hr. 2-3 drops of Triethanolamine was then added for neutralization and to allow gel formulation. After that, the gel was stored at room temperature for 24hr in the prepared formulation Hydrogel other ingredients were added. The composition is shown in the table no:5 same procedure was used for batchesHI- H5.

Table: 1 Preparation of HPMC Hydrogel

Name of Ingredients	Formulation Code with their Concentrations.				
	H1	H2	H3	H4	H5
Terbinafine HCl (mg)	1	1	1	1	1
HPMC K4M (%)	1	2	3	4	5
Glycerine(ml)	1	1	1	1	1
Methyl paraben (%)	0.1	0.1	0.1	0.1	0.1
Propyl paraben (%)	0.05	0.05	0.05	0.05	0.05
Water up to(ml)	10	10	10	10	10

All prepared formulation was evaluated as per procedure described in section5.7andresults are shown in table no: 13and 14.

Preparation of CMC Hydrogel

Weighed 0.1gm of CMC and dispersed in 10ml water and it was stirred using magneticstirring for 12hr. 2-3 drops of Triethanolamine was then added for neutralization and toallow gel formulation. After that, the gel was stored at room temperature for 24hr in theprepared formulation Hydrogel other ingredients were added. The composition is shown in the Table No: 6 same procedures were used for batchesCMC1-CMC5.

Table: 2 Preparation of CMC Hydrogel:

Name of Ingredients	Formulation Code with their Concentrations.				
	CM1	CM2	CM3	CM4	CM5
Terbinafine HCl (mg)	1	1	1	1	1
CMC (%)	1	2	3	4	5
Glycerine(ml)	1	1	1	1	1
Methyl paraben (%)	0.1	0.1	0.1	0.1	0.1
Propyl paraben (%)	0.05	0.05	0.05	0.05	0.05
Water up to(ml)	10	10	10	10	10

All prepared formulation was evaluated as per procedure described in section 5.7 andresults are shown in table no: 13, 14, and 16.

Table: 3 Preparation Carbopol-934 of Hydrogel:

Name of Ingredients	Formulation Code with their Concentrations.				
	CA1	CA2	CA3	CA4	CA5
Terbinafine HCl (mg)	1	1	1	1	1
Carbopol-934(%)	1	2	3	4	5
Glycerine(ml)	1	1	1	1	1
Methyl paraben (%)	0.1	0.1	0.1	0.1	0.1
Propyl paraben (%)	0.05	0.05	0.05	0.05	0.05
Water up to(ml)	10	10	10	10	10

All prepared formulation was evaluated as per procedure described in section 5.7 andresults are shown in Table No: 13, 14, and 17.

Table: 4 Preparation of Guar Gum Hydrogel:

Name of Ingredients	Formulation Code with their Concentrations.				
	GG1	GG2	GG3	GG4	GG5
Terbinafine HCl (mg)	1	1	1	1	1
Guar Gum (%)	1	2	3	4	5
Glycerine(ml)	1	1	1	1	1
Methyl paraben (%)	0.1	0.1	0.1	0.1	0.1
Propyl paraben (%)	0.05	0.05	0.05	0.05	0.05
Water up to(ml)	10	10	10	10	10

All prepared formulation was evaluated as per procedure described in section 5.7 and results are shown in table no: 13, 14, and 18

Evaluation of Prepared Hydrogel using different Gelling Agent under StudyAppearance

The hydrogel formulated were observed or their visual appearance, colour, texture,and feel upon application such as grittiness, grassiness, smoothness, stuffiness and tackiness.

Spreadability

Spreadability is measured by the amount of time it takes two slides to separate from geland move into proximity to one another under the influence of a specific load. The shorter the time, the better the spread ability.

pH

The pH was measured in each gel, using a pH meter, which was calibrated before eachuse with standard buffer solutions at pH 4, 7, 9. The electrode was inserted in to the sample 10 min priors to taking the reading at room temperature.

Viscosity

The viscosity of formulated hydrogel was determined using Brook-field viscometer (spindle number 7) Mounted the guard leg. Attached the spindle (left hand thread) to the viscometer lower shift by lifting the coupling screw slightly. It washed firmly withone hand while screwing the spindle on with the other (note left hand thread). Avoid spindle, do the following before attaching the spindle. Begin by immersing the spindlein a diagonal path, slowly drag the spindle across the fluid surface, and bring the spindleto an upright position and thead on to screw.Lower and centre spindle in the test material until the—meniscus of the fluid is at the centre of the immersion groove on the spindle shaft. To make a viscosity measurement, turn the motors witch—ON. Thisenergizes the viscometer drive motor. Allow time for the indicated reading to stabilize.The required for stabilization will depends on the speed at which the viscometer was running and the characteristics of the sample fluid. When making a viscosity measurement, the reading should be noted.

Drug Content Studies (Assay)

The gel was sampled from several points in the mixer to verify homogeneous gel formulation, and the drug content was then measured. The drug content of the gels wascalculated by dissolving a precisely weighed amount of gel (about 1 gm) in a buffer solution with a pH of 5.5 that contains phosphate. The same buffer solution was used to make the necessary dilutions after these solutions were quantitatively transferred to volumetric flasks. The resultant solutions were then filtered using 0.45 mm membranefilters before being tested for terbinafine HCl using a spectrophotometer at 283 nm. From Terbinafine HCl's standard curve, drug content was calculated.

In-Vitro Release

Franz-diffusion cells equipment from various formulations were used for the in vitro release investigations. On a membrane with a free region for diffusion, precisely one formulation (1.0 g) was dispersed. This membrane was positioned between the donor and receptor chambers. During the studies, the receptor compartment was kept at 37.2°C with phosphate buffer 5.5 and was continually agitated with a tiny magnetic barat a speed of 50 rpm to guarantee homogeneity. At various time intervals, the sampleswere taken out and replaced with the same volume of PBS. All of the sink requirementswere fulfilled. At 283 nm, the samples underwent spectrophotometrically analysis.

Kinetics of Drug Release

In vitro dissolution has been recognized as an important element in drug development.To analysis the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into Zero order, Firstorder, Higuchimatrix, Korsmeyer-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected. [15]

Stability Study

For the evaluation of stability study, maintaining the formulations at an ambient condition over a period of three months. The drug content was determined periodicallyafter the 0, 15, 30 and 45 days after topical gel preparations.

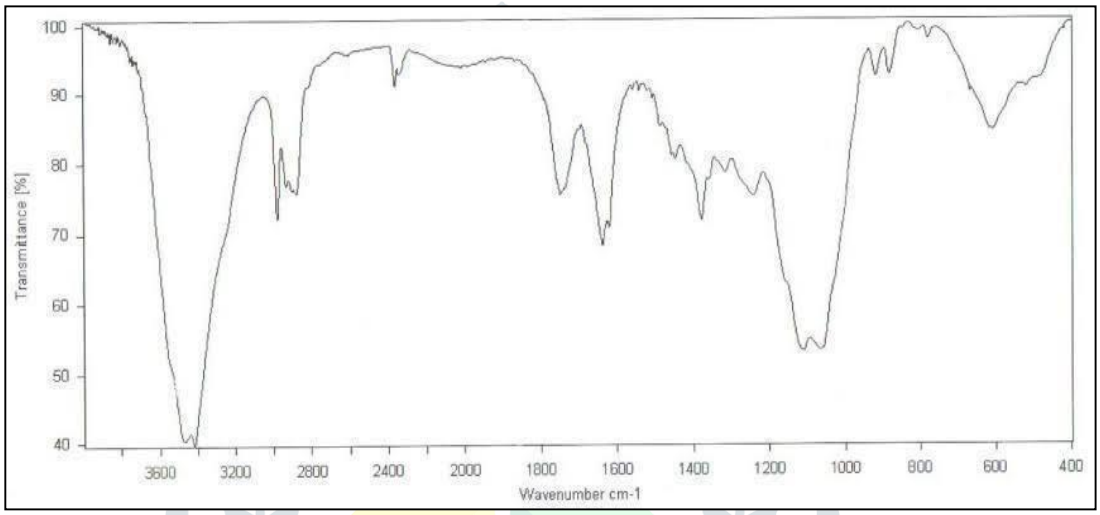
5. RESULT AND DISCUSSION:

Physical Characterization of Terbinafine HCl

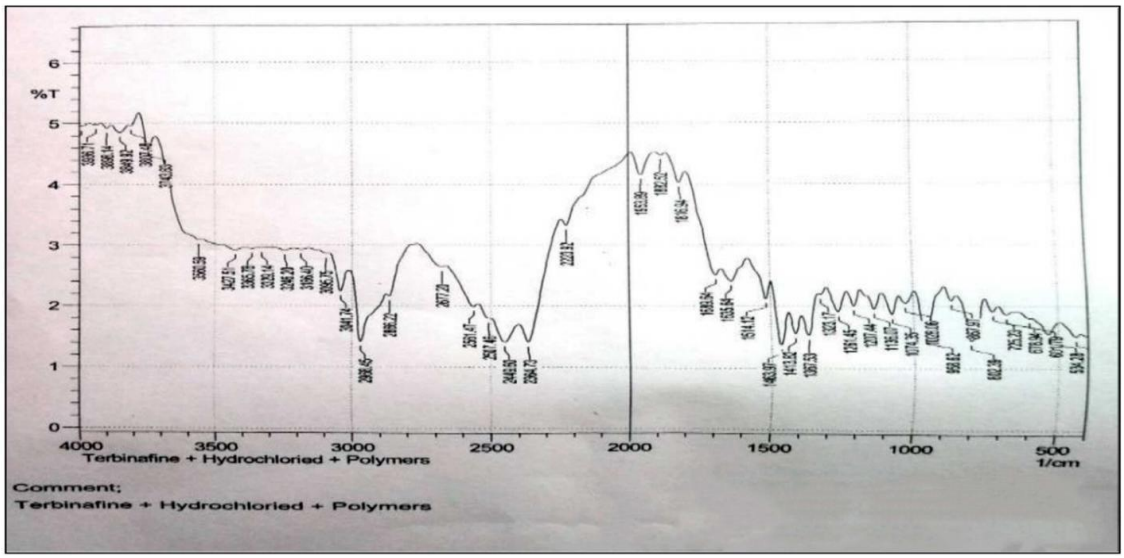
a. Colour: White
b. Odour: odourless
c. Nature: Crystalline powder
d. Taste: Slight bitter and sour
e. Melting point:195-205°C
f. Molecular weight: 291.4g/mol

FTIR Spectroscopy

Drug characterization study by FTIR was carried out as per standard procedure. FTIR spectra of Terbinafine HCl are shown in graph No. 1. It was observed that principal peak of Drug was found in FTIR spectra of a drug. It was suggested that there was no physical and chemical change of pure drug. The results are shown in Graph No. 1



Graph: 1 FTIR Spectrum of Terbinafine HCl



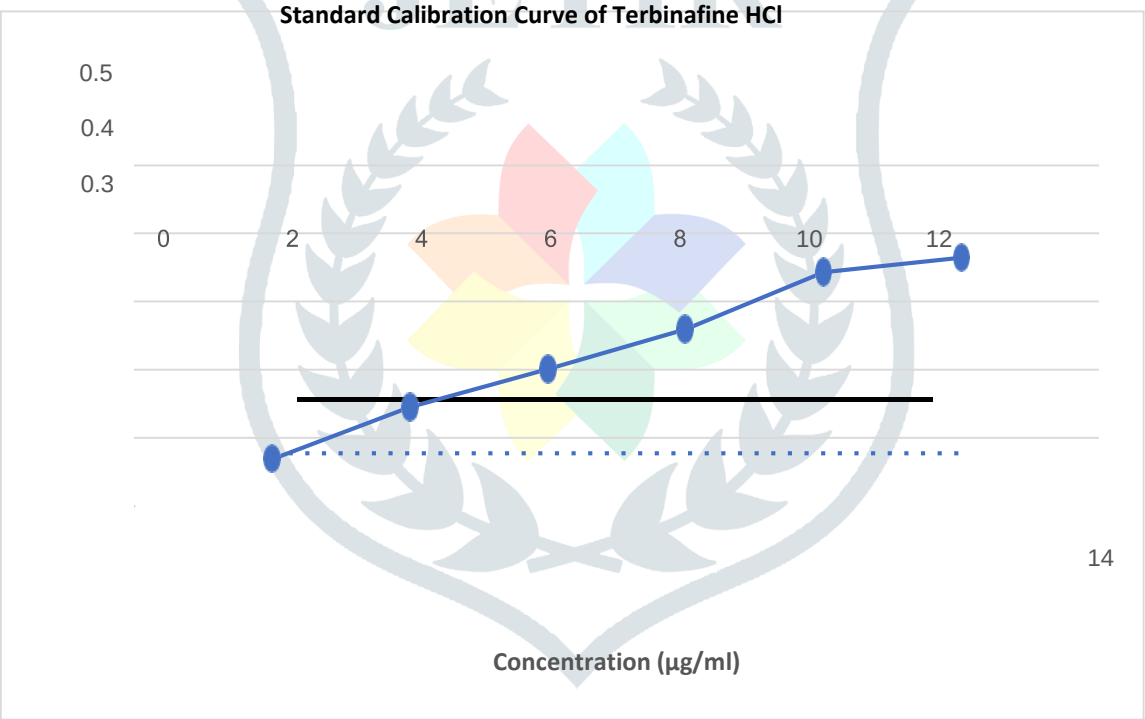
Graph: 2 FTIR Spectrum of Terbinafine HCl and polymers

Drug Polymers Interaction Study:

Drug characterization study by FTIR was carried out as per standard procedure. FTIR spectra of Terbinafine HCl and polymer mixture are shown in graph No. 2. It was observed that principle peak of Drug was found in FTIR spectra of a drug. It was suggested that there was no physical and chemical interaction is observed. The results are shown in GraphNo.2

Table: 5 Standard Calibration Curve of Terbinafine HCl in Phosphate BufferpH 5.5 At283

Sr.No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.069 ±0.0012
3	4	0.145±0.0008
4	6	0.201±0.0027
5	8	0.260±0.0014
6	10	0.343±0.0015
7	12	0.365±0.0030



Graph: 3 Standard Clibration Curve of TerbinafineHCl

From the standard curve, it was observed that the drug obeys Beer's law in concentration range of 2.0-1.5 µg/ml in phosphate buffer pH 5.5. Drug shown good linearity with regression of coefficient (**r^2 = 0.9866**) and equation for this line obtainedwas found to be **y = 0.0305±0.0015** which is used for the calculation of amount of drugand dissolutionstudy.

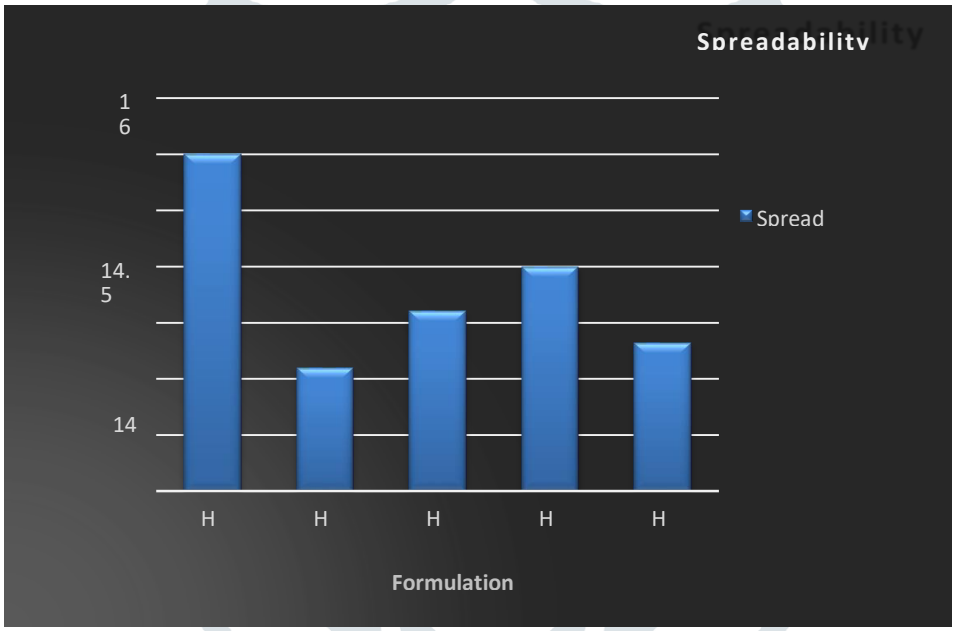
Evaluation of Prepared Hydrogel:

1) Evaluation of HPMC Hydrogel

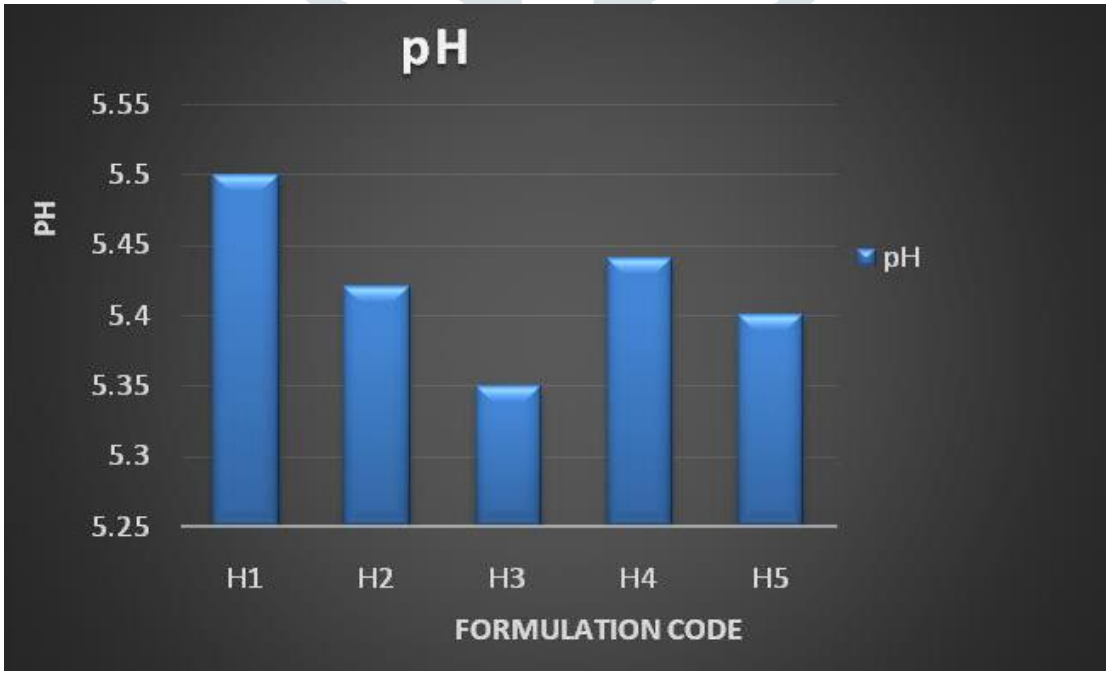
A prepared Terbinafine HCl Hydrogel was inspected visually for colour, Homogeneity,consistency and for Spreadability, pH, Viscosity and Assay (Drug content). All formulations showed yellowish color, white buff, gray appearance therefore showed suitable Homogeneity and consistency. And the observations are mentioned in Table No. 5.

Table 6: Evaluation of HPMC Hydrogel Formulations

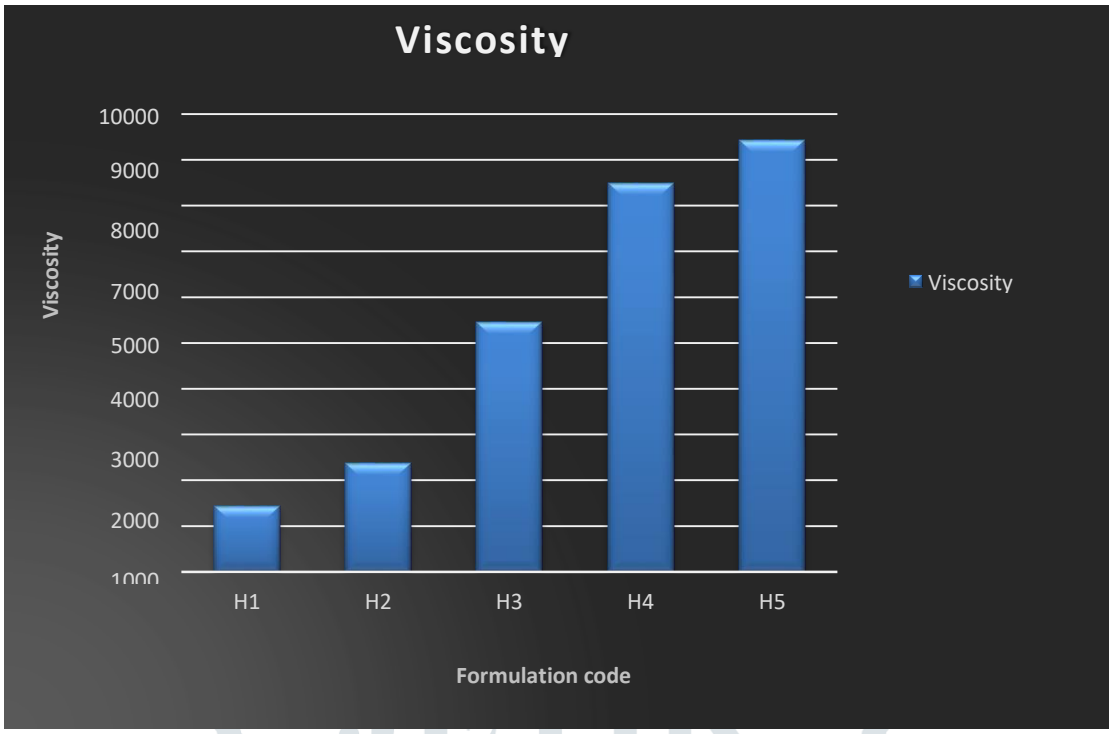
Sr no.	Formulation code	Appearance	Feel on application	Spread ability	pH	Viscosity	Assay
1	H1	White	Smooth	15.5	5.5	1442	99.65
2	H2	White	Smooth	13.6	5.42	2362	97.88
3	H3	White	Smooth	14.1	5.35	5449	97.06
4	H4	White	Smooth	14.5	5.44	8495	96.55
5	H5	White	Smooth	13.82	5.4	9433	96.31



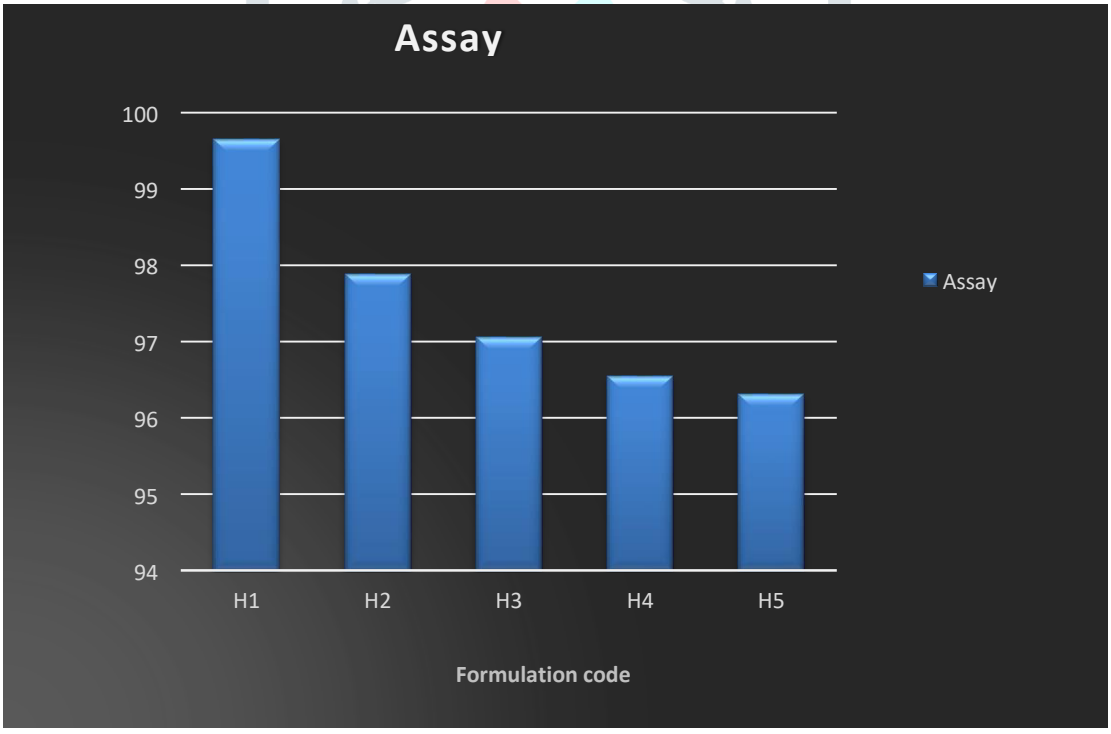
Graph: 4 Spreadability of HPMC Hydrogel Formulation



Graph: 5 pH of HPMC Hydrogel Formulation



Graph: 6 Viscocity of HPMC Hydrogel Formulation



Graph: 7 Assay of HPMC Hydrogel Formulation

Discussion:

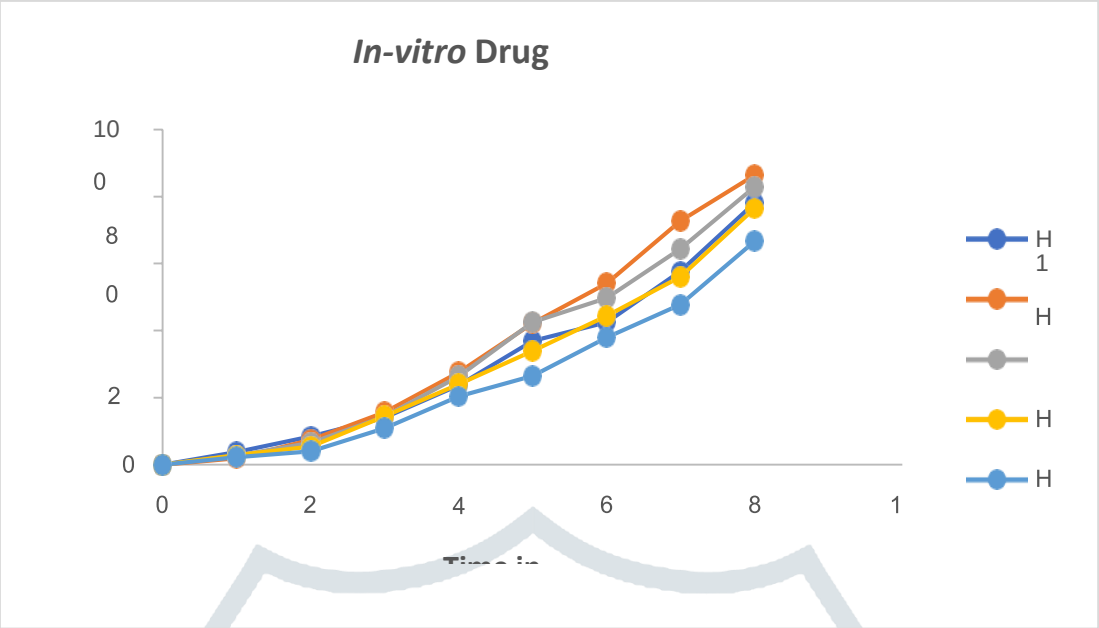
On the Basis of above results and Graphs, the results of HPMC Hydrogel formulations(H1 to H5) were found satisfactory and within limits.And it is considered that Formulation H1 is better than other as its result of Spread ability and assay found betterthan H2, H3, H5 & H5.

***In-Vitro* Drug Release:**

The *In-vitro* release of Terbinafine HCl from different hydrogel formulation was carriedout in phosphate buffer pH 5.5 for 10 hour at 37 ±0.5^{0}C was investigated and results are represented in Table No. 15-18 respectively. The plot of % drug release verses timewere plotted % drug release from batches H1 to H5. The plot % drug release verses times were plotted % drug release from batches CM1-CM5. The plotof % drug releaseverses time were plotted % drug release from batches. It was noticed that the release ofTerbinafine HCl from its Hydrogel can be ranked in the following descending order.

Table: 7 In-Vitro Drug Release of Batch H1 – H5:

Time (Hr)	**H1**	**H2**	**H3**	**H4**	**H5**
0	00	00	00	00	00
1	3.767±0.036	1.912±0.034	2.722±0.042	2.825±0.034	2.210±0.032
2	8.579±0.086	7.468±0.092	6.517±0.078	5.415±0.082	4.068±0.076
3	14.182±0.164	15.576±0.168	14.352±0.122	14.474±0.126	10.965±0.146
4	23.703±0.242	27.667±0.262	26.377±0.178	24.117±0.192	20.394±0.202
5	36.953±0.322	42.339±0.312	42.669±0.288	34.099±0.276	26.518±0.304
6	42.56±0.42	54.22±0.40	49.73±0.338	44.56±0.384	38.00±0.394
7	57.88±0.562	72.8±0.546	64.42±0.400	56.12±0.46	47.84±0.483
8	78.23±0.66	86.5±0.644	82.95±0.48	76.63±0.52	66.74±0.56



Graph: 8 Comparison of % Drug Release of Batches H1 to H5

Discussion:

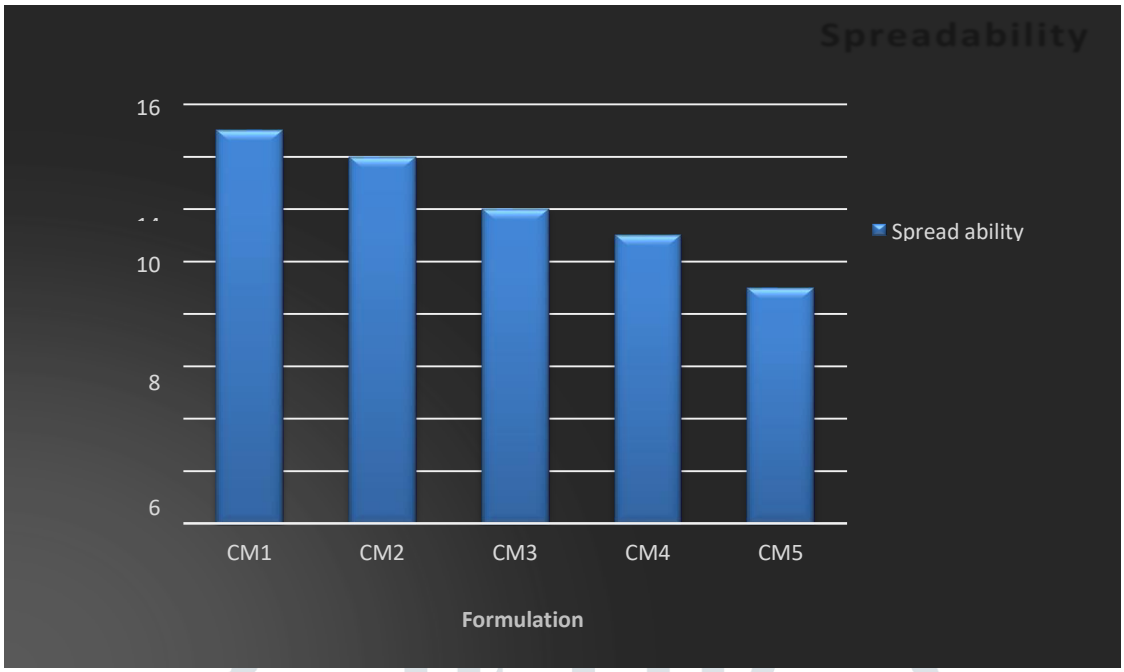
Cumulative % Drug Release of topical Hydrogel (H1 to H5) was found to be range **74.36±0.54** (8hours) to **86.48±0.50** (8 hours). It was observed that Cumulative % DrugRelease of Hydrogel depends on concentration of HPMC. Here, as concentration of HPMC increases % Drug release time of formulation also decreases. Maximum Cumulative % Drug Release i.e., **86.48±0.50** (8 hours) was found to be for H2, and prolong Cumulative % Drug Release was **74.36±0.54** (8hours) Found to before H5. Here, shows concentration dependence release behavior for these formulations.

2) Evaluation of CMC Hydrogel

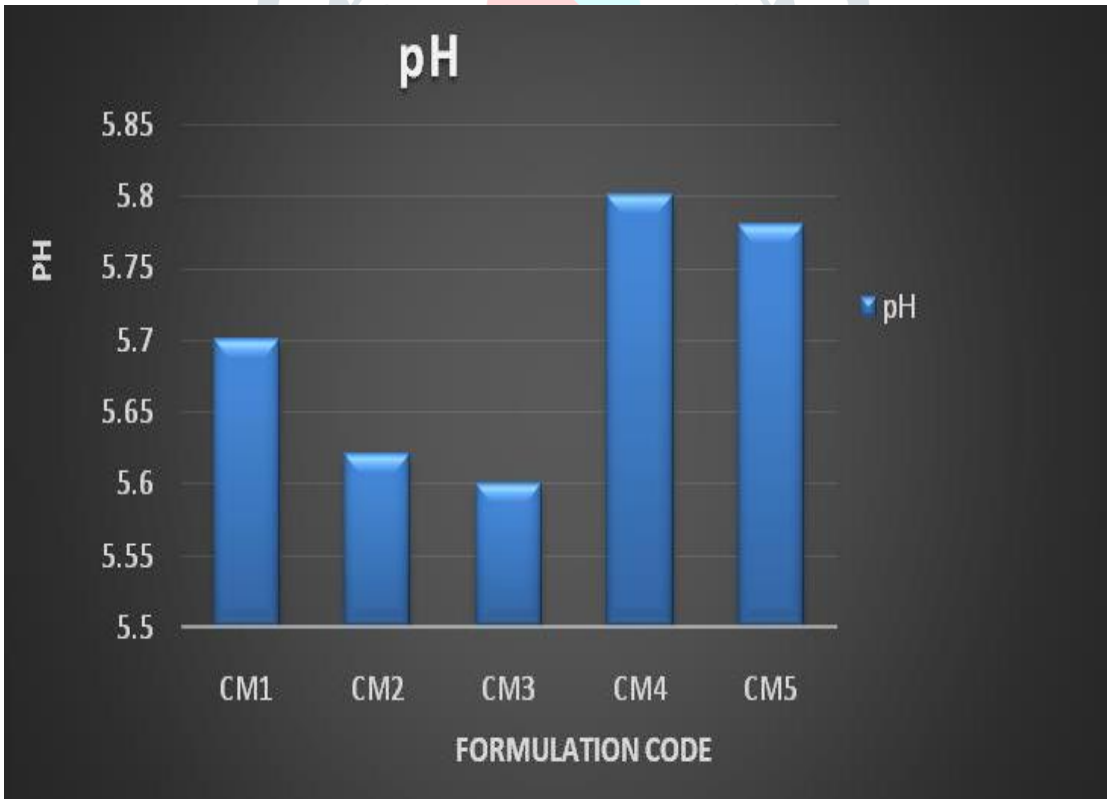
A prepared Terbinafine HCl Hydrogel was inspected visually for colour, Homogeneity,consistency and for Spreadability, pH, Viscosity and Assay (Drug content). All formulations showed yellowish color, white buff, gray appearance therefore showed suitable Homogeneity and consistency. And the observations are mentioned in Table No. 15.

Table: 8 Evaluation of CMC Hydrogel Formulations

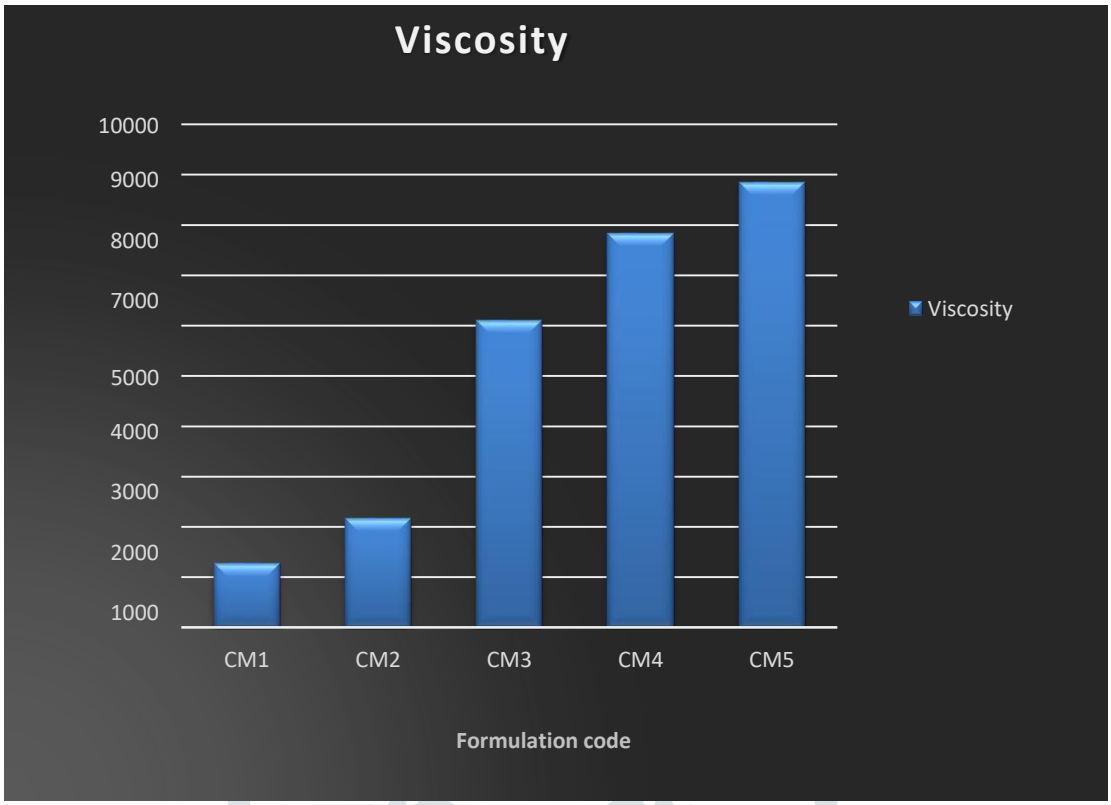
Sr no.	Formulation code	Appearance	Feel on application	Spread ability	pH	Viscosity	Assay
1	CM1	White	Smooth	15	5.7	1270	97.68
2	CM2	White	Smooth	14	5.62	2170	96.45
3	CM3	White	Smooth	12	5.6	6110	98.6
4	CM4	White	Smooth	11	5.8	7830	96.54
5	CM5	White	Smooth	9	5.78	8840	96.8



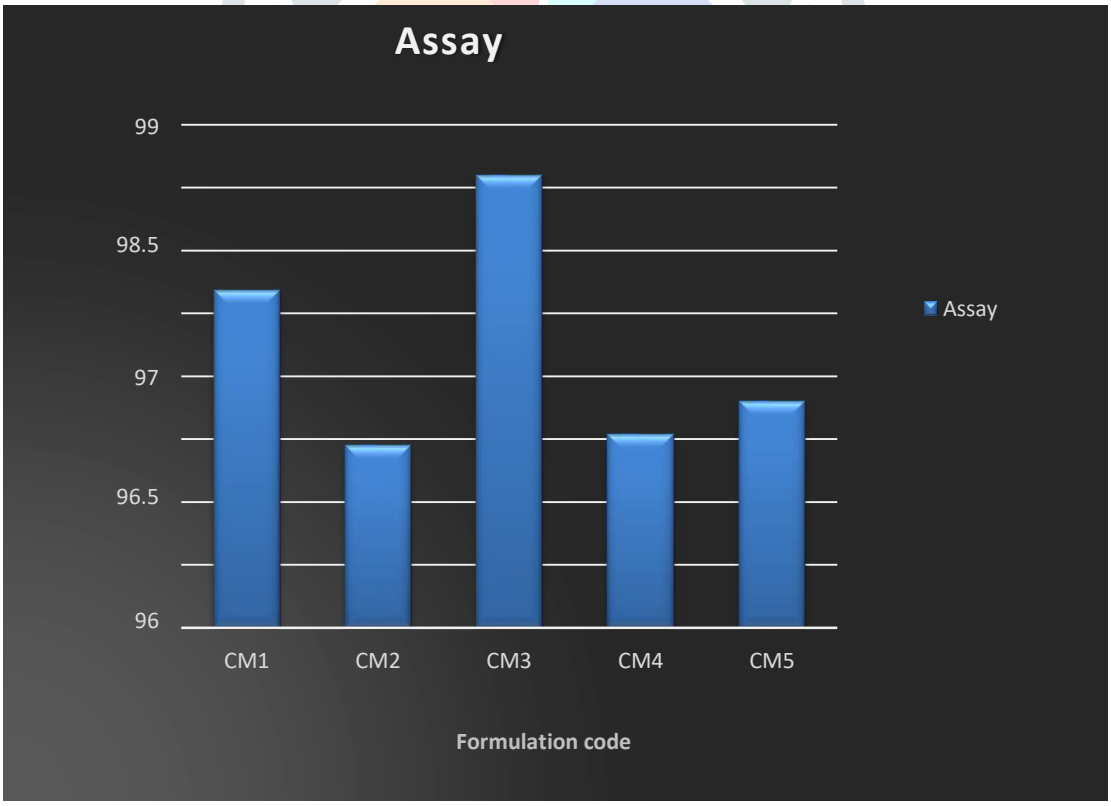
Graph: 9 Spreadability of CMC Hydrogel Formulation



Graph: 10 pH of CMC Hydrogel Formulation



Graph: 11 Viscocity of CMC Hydrogel Formulation



Graph: 12 Assay of CMC Hydrogel Formulation

Discussion:

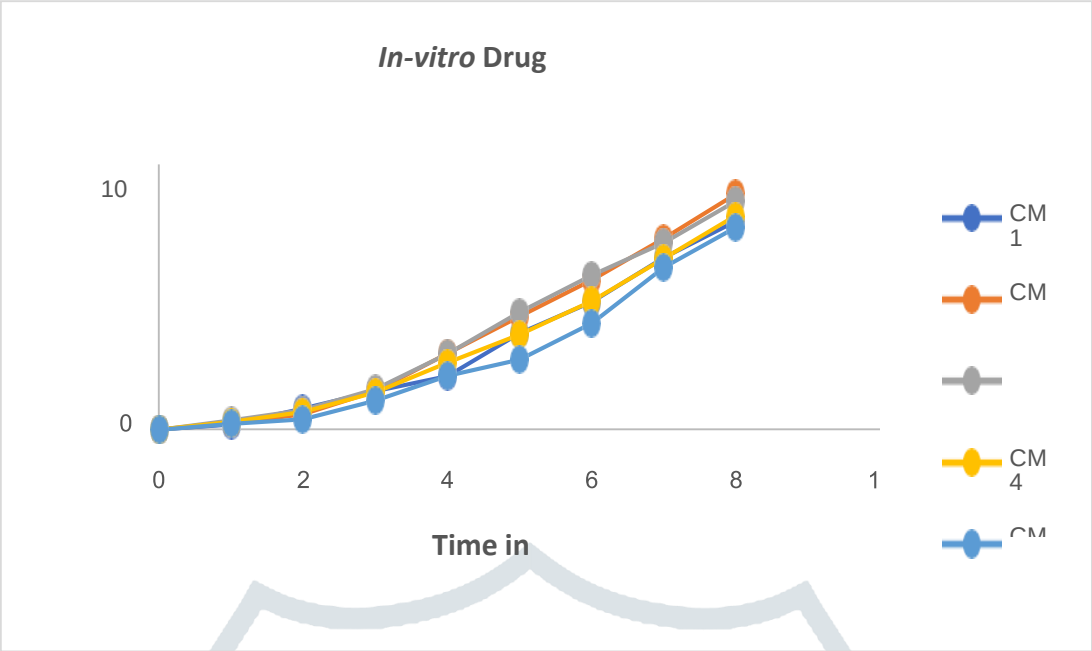
On the Basis of above results and Graphs, the results of CMC Hydrogel formulations (CM1 to CM5) were found satisfactory and within limits. And it is considered that Formulation CM3 is better than other as its result of assay found better than CM1,CM2,CM4, &CM5.

***In-Vitro* Drug Release:**

The *In-vitro* release of Terbinafine HCl from CMC hydrogel formulation was carried out in phosphate buffer pH 5.5 for 10 hours at 37 $\pm 0.5^0$C was investigated and results are represented in Table No. 16 respectively. The plot % drug release verses times wereplotted % drug release from batches CM1-CM5.

Table: 9 In-Vitro Drug Release of Batch CM1 –CM5:

Time (Hr)	CM1	CM2	CM3	CM4	CM5
0	00	00	00	00	00
1	1.780±0.036	2.364±0.028	3.522±0.025	2.835±0.033	2.210±0.034
2	7.826±0.056	5.735±0.044	7.430±0.040	6.592±0.056	4.068±0.76
3	14.549±0.12	14.427±0.102	15.453±0.094	14.154±0.093	10.965±0.128
4	20.030±0.26	28.760±0.235	28.609±0.164	25.275±0.192	20.394±0.214
5	36.284±0.32	42.744±0.28	44.373±0.31	35.888±0.320	26.518±0.334
6	48.02±0.386	56.44±0.38	58.34±0.362	48.62±0.40	40.28±0.392
7	64.80±0.442	72.08±0.423	70.64±0.406	64.54±0.448	61.62±0.45
8	78.66±0.521	88.92±0.48	86.24±0.486	80.72±0.512	76.34±0.516



Graph: 13 Comparison of % Drug Release of Batches CM1 to CM5

Discussion:

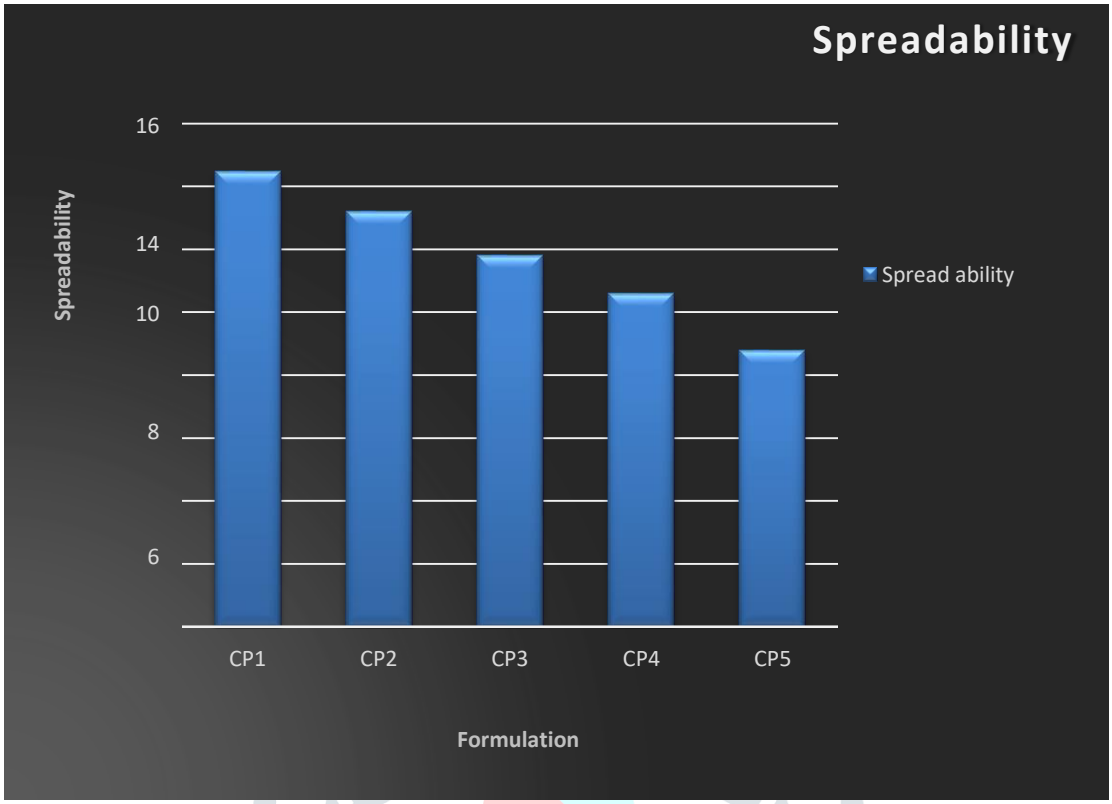
Cumulative % Drug Release of Topical Hydrogel (CM1 to CM5) was found to be range**76.34±0.51** (8hours) to **88.92±0.48** (8 hours). It was observed that Cumulative% DrugRelease of Hydrogel depends on concentration of CMC. Here, as concentration of CMCincreases % Drug release time of formulation also decreases.Maximum Cumulative %Drug Release i.e, **88.92±0.48** (8 hours) was found to be for CM2, and prolong Cumulative % Drug Release was **76.34±0.51** (8hours) Found to before CM5. Here, CMCshow concentration dependence release behavior for these formulations.

3) Evaluation of Carbopol Hydrogel

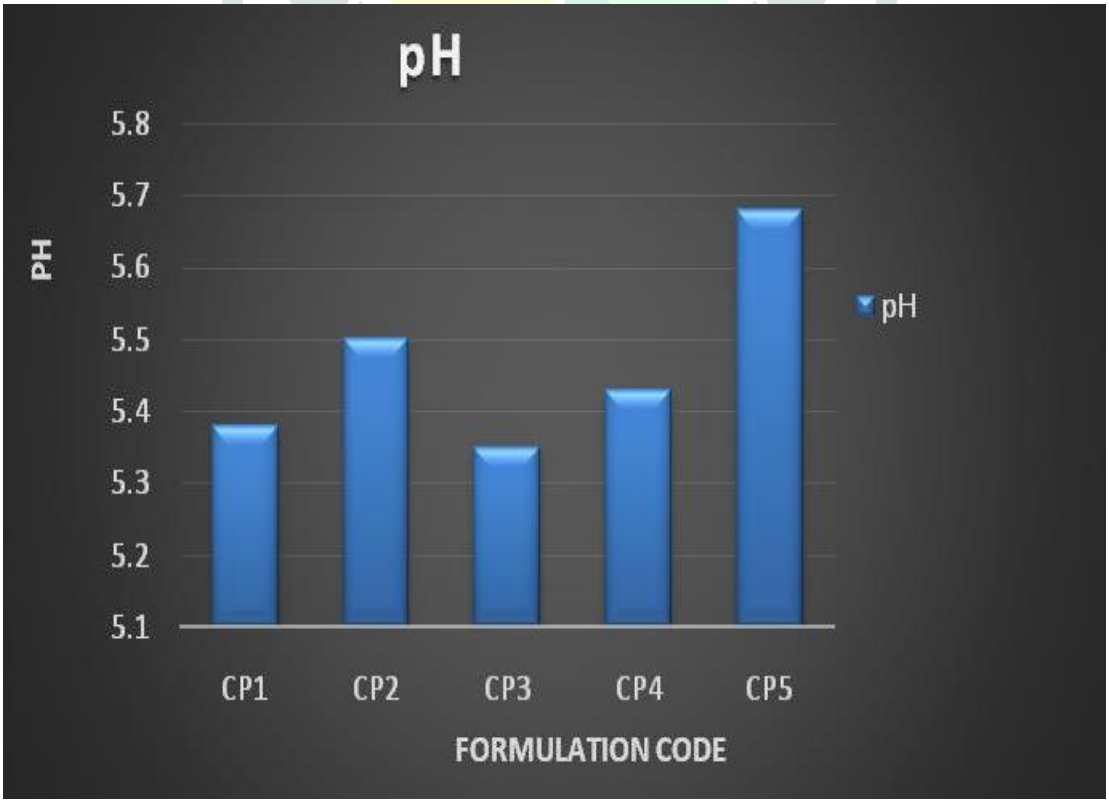
A prepared Terbinafine HCl Hydrogel was inspected visually for colour, Homogeneity,consistency and for Spreadability, pH, Viscosity and Assay (Drug content). All formulations showed white buff appearance therefore showed suitable Homogeneity and consistency. And the observations are mentioned in Table No. 10

Table: 10 Evaluation of Carbopol Hydrogel Formulations

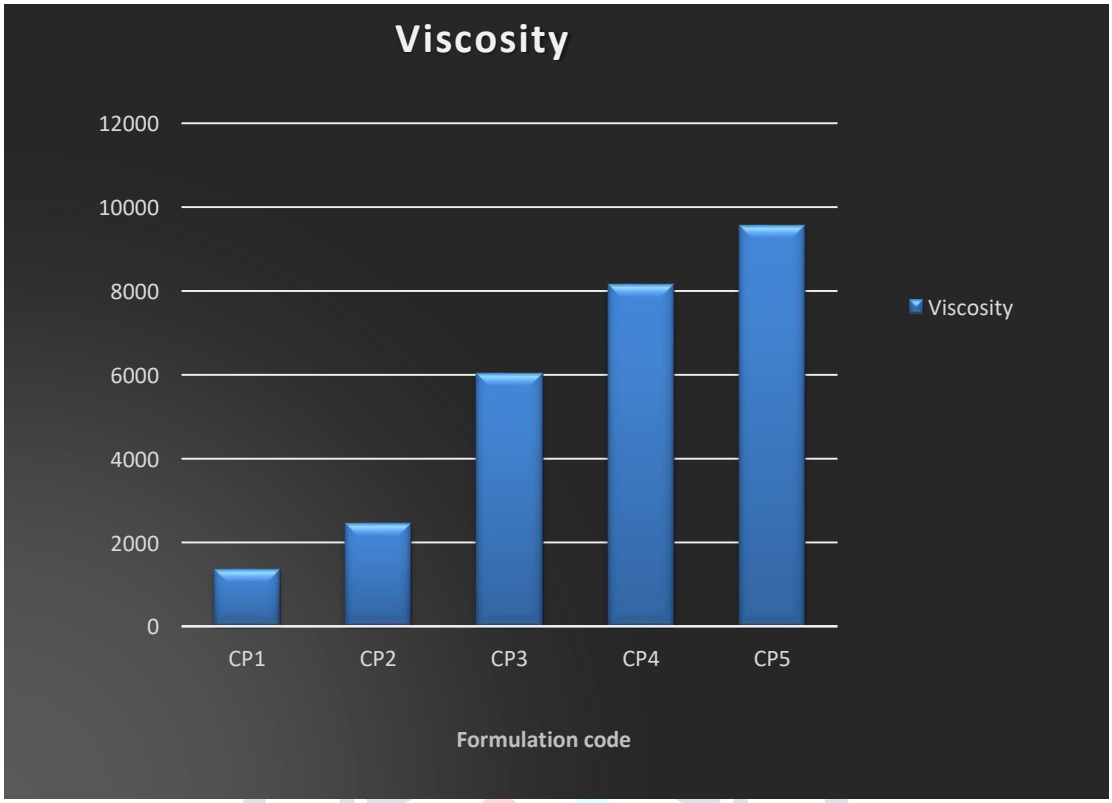
Sr no.	Formulation code	Appearance	Feel on application	Spread ability	pH	Viscosity	Assay
1	CP1	White Buff	Smooth	14.5	5.38	1355	97.1
2	CP2	White Buff	Smooth	13.2	5.5	2449	96.18
3	CP3	White Buff	Smooth	11.8	5.35	6042	98.32
4	CP4	White Buff	Smooth	10.6	5.43	8154	96.65
5	CP5	White Buff	Smooth	8.8	5.68	9572	95.78



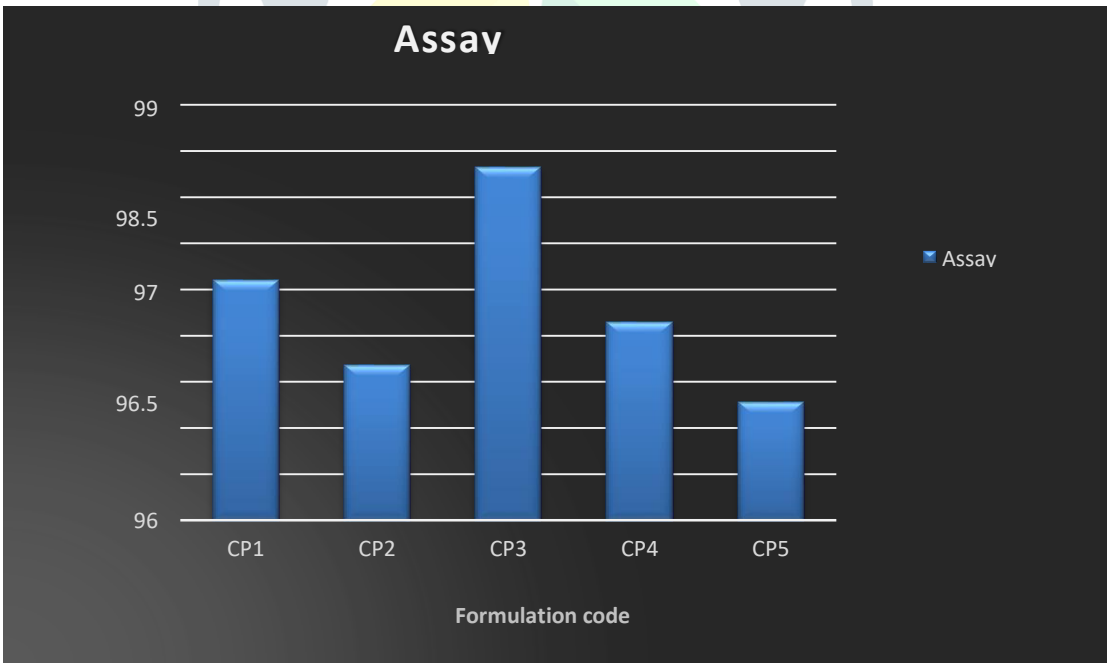
Graph: 14 Spreadability of Carbopol Hydrogel Formulation



Graph: 15 pH of Carbopol Hydrogel Formulation



Graph: 6.16 Viscocity of Carbopol Hydrogel Formulation



Graph: 17 Assay of Carbopol Hydrogel Formulation

Discussion:

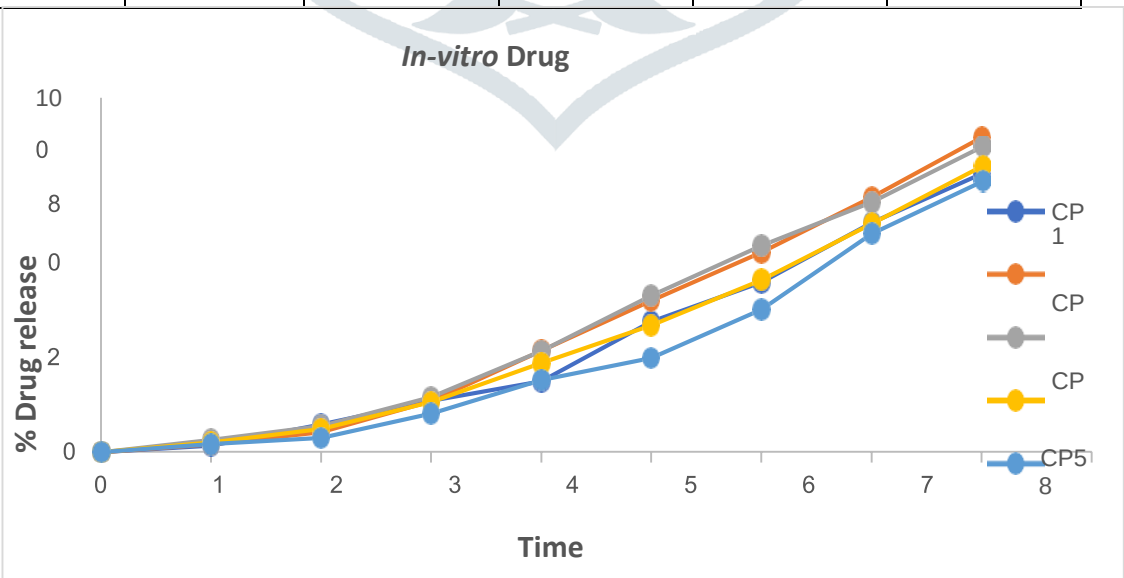
On the Basis of above results and Graphs, the results of Carbopol Hydrogel formulations (CP1 to CP5) were found satisfactory and within limits. And it is considered that Formulation CP3 is better than other as its result of assay found better than CP1, CP2, CP4&CP5.

***In-Vitro* Drug Release:**

The *In-vitro* release of Terbinafine HCl from Carbopol hydrogel formulation was carried out in phosphate buffer pH 5.5 for 10 hour at 37 ±0.5^{0}C was investigated and results are represented in Table No. 17 respectively. The plot of % drug release versestime were plotted % drug release from batches CP1 to CP5.

Table: 11 In-Vitro Drug Release of Batch CP1 – CP5:

Time (Hr)	CP1	CP2	CP3	CP4	CP5
0	00	00	00	00	00
1	1.780±0.036	2.364±0.028	3.522±0.025	2.835±0.033	2.210±0.034
2	7.826±0.056	5.735±0.044	7.430±0.040	6.592±0.056	4.068±0.76
3	14.549±0.12	14.427±0.102	15.453±0.094	14.154±0.093	10.965±0.128
4	20.030±0.26	28.760±0.235	28.609±0.164	25.275±0.192	20.394±0.214
5	36.284±0.32	42.744±0.28	44.373±0.31	35.888±0.320	26.518±0.334
6	48.02±0.386	56.44±0.38	58.34±0.362	48.62±0.40	40.28±0.392
7	64.80±0.442	72.08±0.423	70.64±0.406	64.54±0.448	61.62±0.45
8	78.66±0.521	88.92±0.48	86.24±0.486	80.72±0.512	76.34±0.516



Graph: 18 Comparison of % Drug Release of Batches CP1to CP5

Discussion:

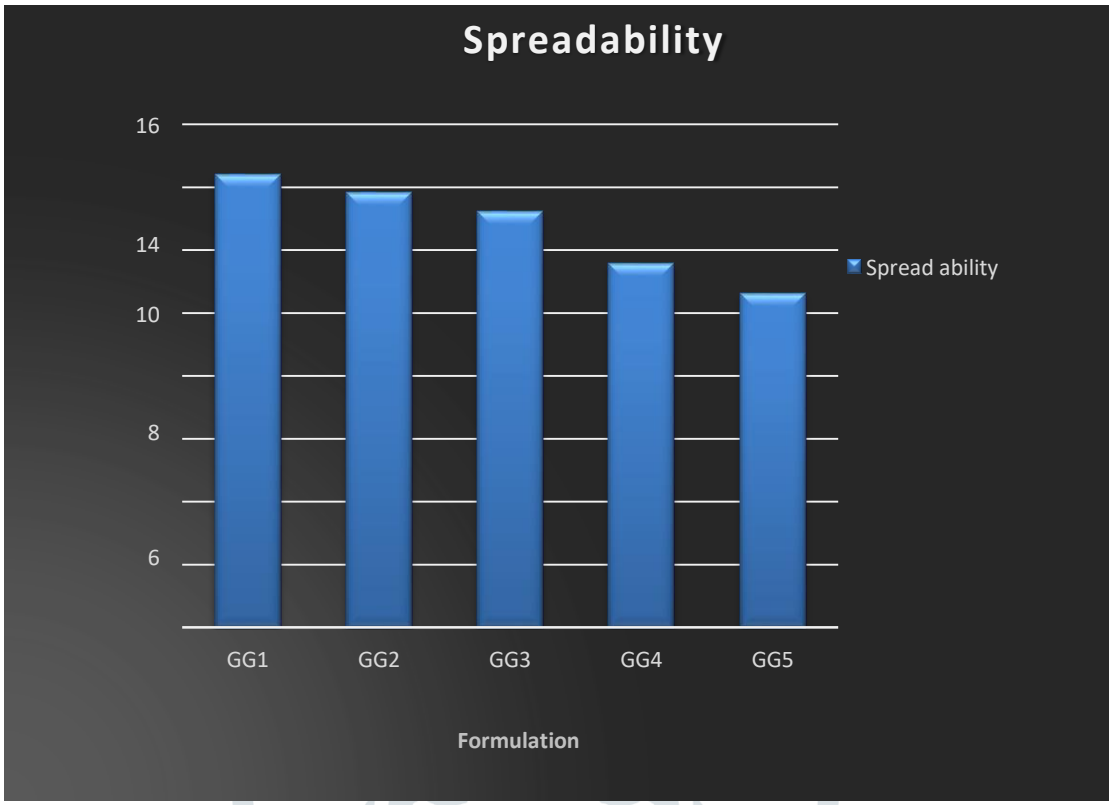
Cumulative % Drug Release of Topical Hydrogel (CP1 to CP5) was found to be range**76.34±0.516** (8hours) to **88.92±0.48** (8 hours). It was observed that Cumulative % Drug Release of Hydrogel depends on concentration of Carbopol 934. Here, as concentration of Carbopol increases % Drug release time of formulation also decreases.Maximum Cumulative % Drug Release i.e., **88.92±0.48** (8 hours) was found to be for CP2, and prolong Cumulative % Drug Release was **76.34±0.516** (8hours) Found to befor CP5. Here, Carbopol show concentration dependence release behavior for these formulations.

Evaluation of Guar Gum Hydrogel

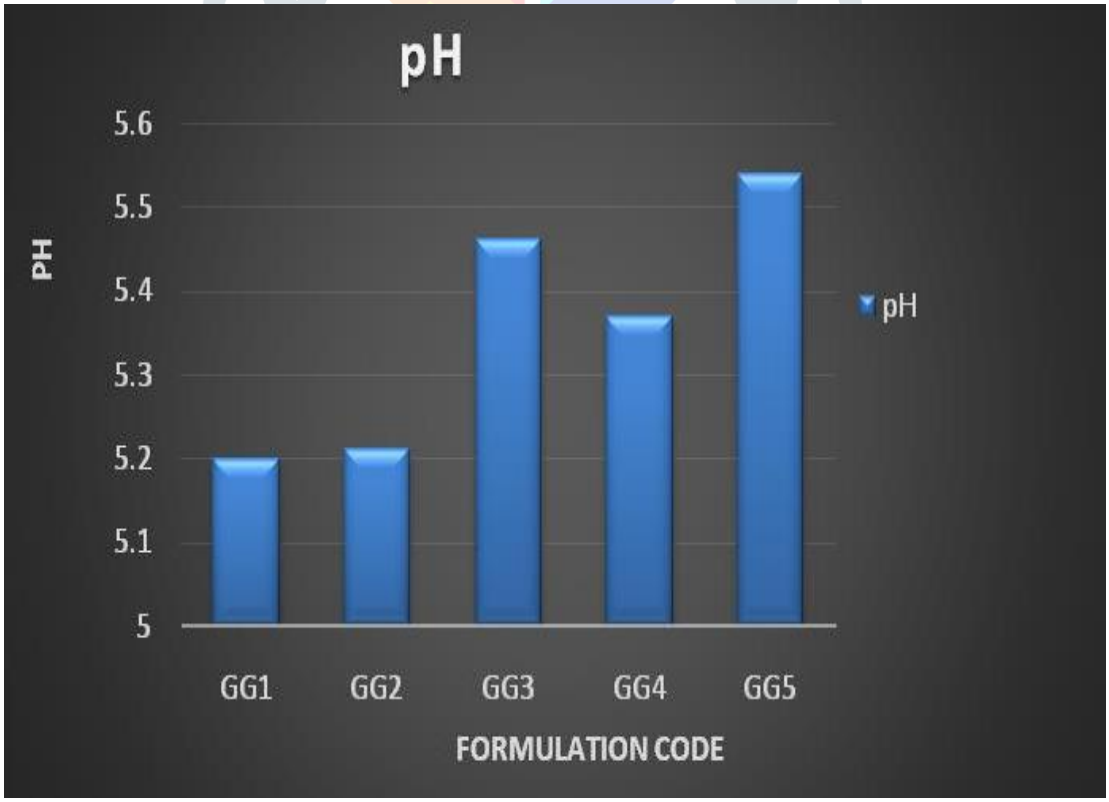
A prepared Terbinafine HCl Hydrogel was inspected visually for colour, Homogeneity,consistency and for Spreadability, pH, Viscosity and Assay (Drug content). All formulations showed yellowish color therefore showed suitable Homogeneity and consistency. And the observations are mentioned in Table No. 17.

Table: 12 Evaluation of Guar Gum Hydrogel Formulations

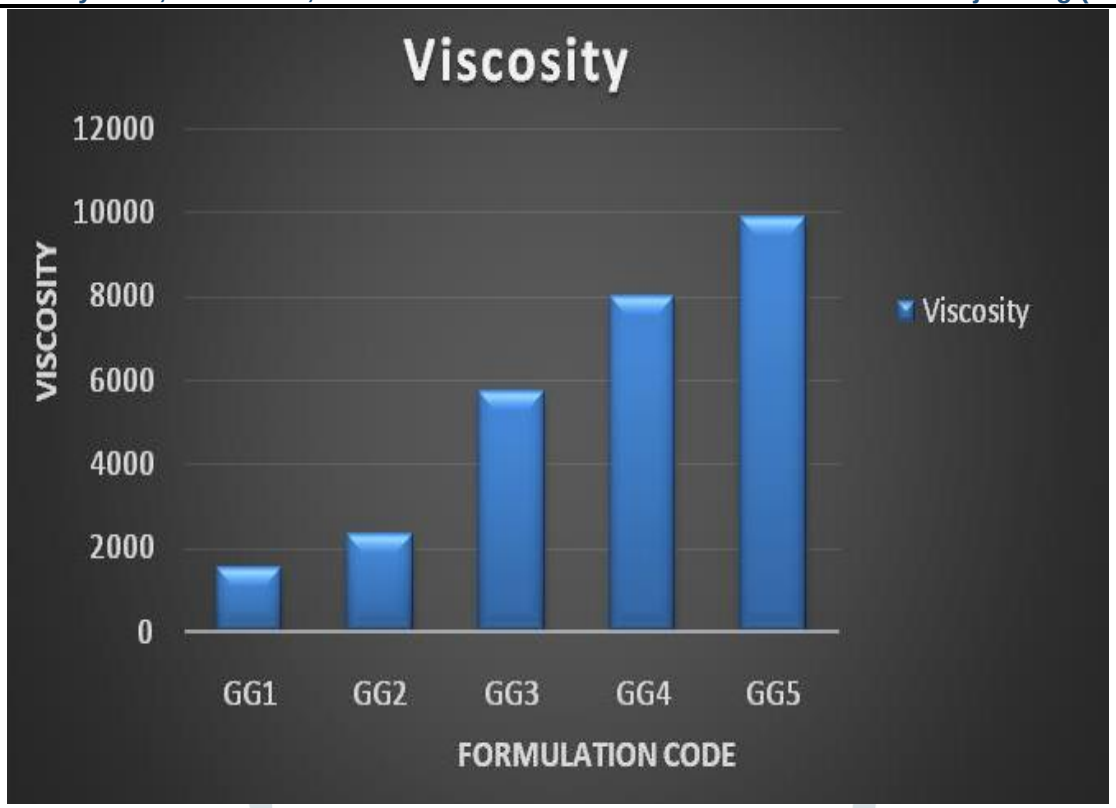
Sr no.	Formulation code	Appearance	Feel on application	Spread ability	pH	Viscosity	Assay
1	GG1	Yellowish	Smooth	14.42	5.2	1534	96.22
2	GG2	Yellowish	Smooth	13.85	5.21	2308	97.12
3	GG3	Yellowish	Smooth	13.23	5.46	5735	96.37
4	GG4	Yellowish	Smooth	11.58	5.37	7986	96.44
5	GG5	Yellowish	Smooth	10.62	5.54	9868	97.62



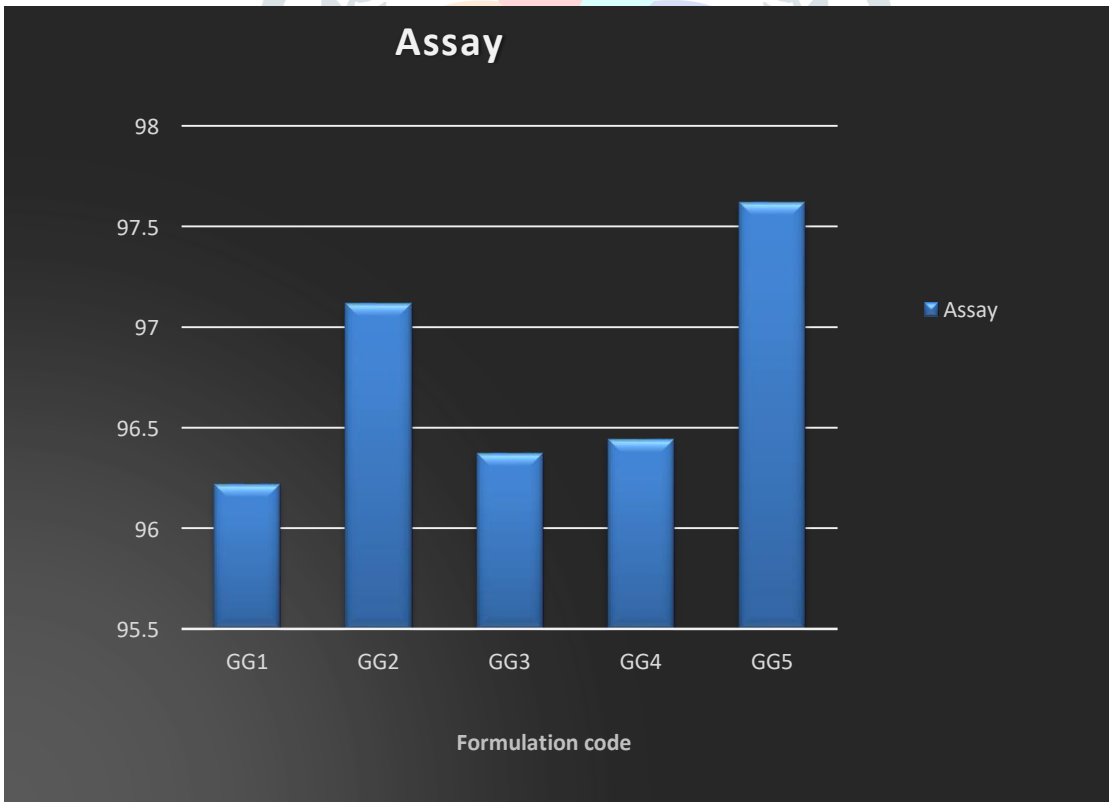
Graph: 19 Spreadability of Guar Gum Hydrogel Formulation



Graph: 20 pH of Guar Gum Hydrogel Formulation



Graph: 21 Viscocity of Guar Gum Hydrogel Formulation



Graph: 22 Assay of Guar Gum Hydrogel Formulation

Discussion:

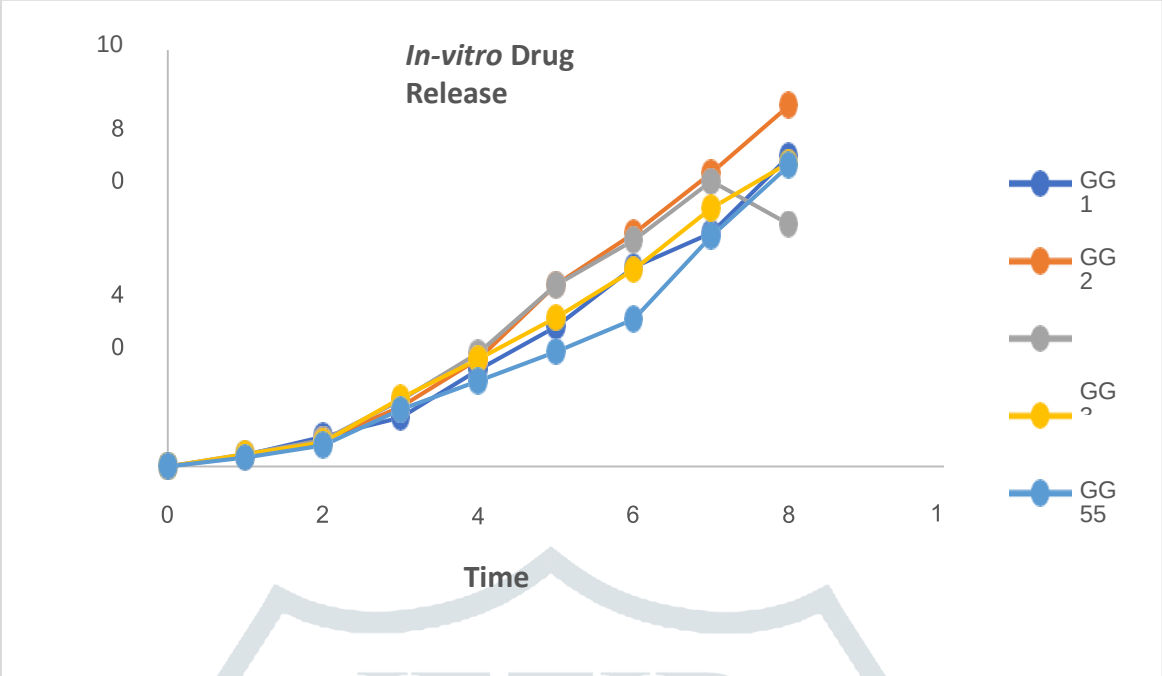
On the Basis of above results and Graphs, the results of Guar Gum Hydrogel formulations (GG1 to GG5) were found satisfactory and within limits. And it is considered that Formulation GG5 is better than other as its result of assay found betterthan GG1,GG2, GG3 &GG4.

***In-Vitro* Drug Release:**

The *In-vitro* release of Terbinafine HCl from Guar Gum hydrogel formulation was carried out in phosphate buffer pH 5.5 for 10 hour at 37 $\pm 0.5^0$C was investigated and results are represented in Table No.18 respectively. The plot of % drug release verses time were plotted % drug release from batches GG1 to GG5.

Table: 12 In-Vitro Drug Release of Batch GG1 –GG5:

Time (Hr)	GG1	GG2	GG3	GG4	GG5
0	00	00	00	00	00
1	2.872±0.045	2.411±0.038	2.929±0.024	2.985±0.032	2.113±0.032
2	7.289±0.0145	6.470±0.128	6.422±0.064	5.820±0.078	5.007±0.086
3	11.837±0.18	14.380±0.18	15.199±0.142	16.47±0.161	13.605±0.18
4	23.364±0.246	25.963±0.2	27.300±0.264	25.888±0.28	20.539±0.28
5	33.628±0.30	43.799±0.40	43.695±0.42	35.757±0.32	27.642±0.28
6	48.02±0.386	56.00±0.454	54.34±0.462	47.36±0.386	35.46±0.36
7	56.24±0.421	70.64±0.512	68.58±0.516	62.16±0.442	55.36±0.428
8	74.6±0.502	86.82±0.526	85.20±0.54	73.08±0.496	72.48±0.46



Graph: 23 Comparison of % Drug Release of Batches GG1 to GG5Discussion:

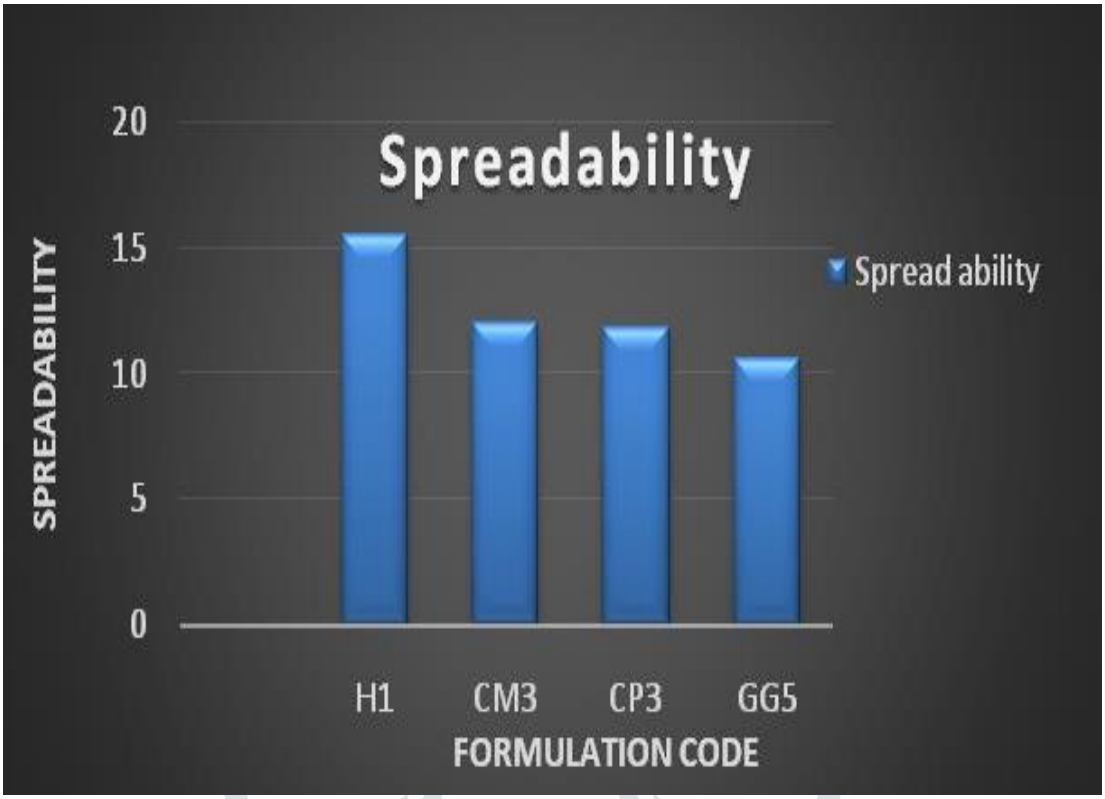
Cumulative % Drug Release of Topical Hydrogel (GG1 to GG5) was found to be range **72.48±0.46** (8hours) to **86.82±0.526** (8 hours). It was observed that Cumulative % Drug Release of Hydrogel depends on concentration of Guar Gum. Here, as concentration of Guar Gum increases % Drug release time of formulation also decreases. Maximum Cumulative % Drug Release i.e.**, 88.92±0.48** (8 hours) was foundto be for GG2, and prolong Cumulative % Drug Release was **76.34±0.516** (8hours) Found to be for GG5. Here, Guar Gum shows concentration dependence release behavior for these formulations**.**

Selection of Optimized Batch

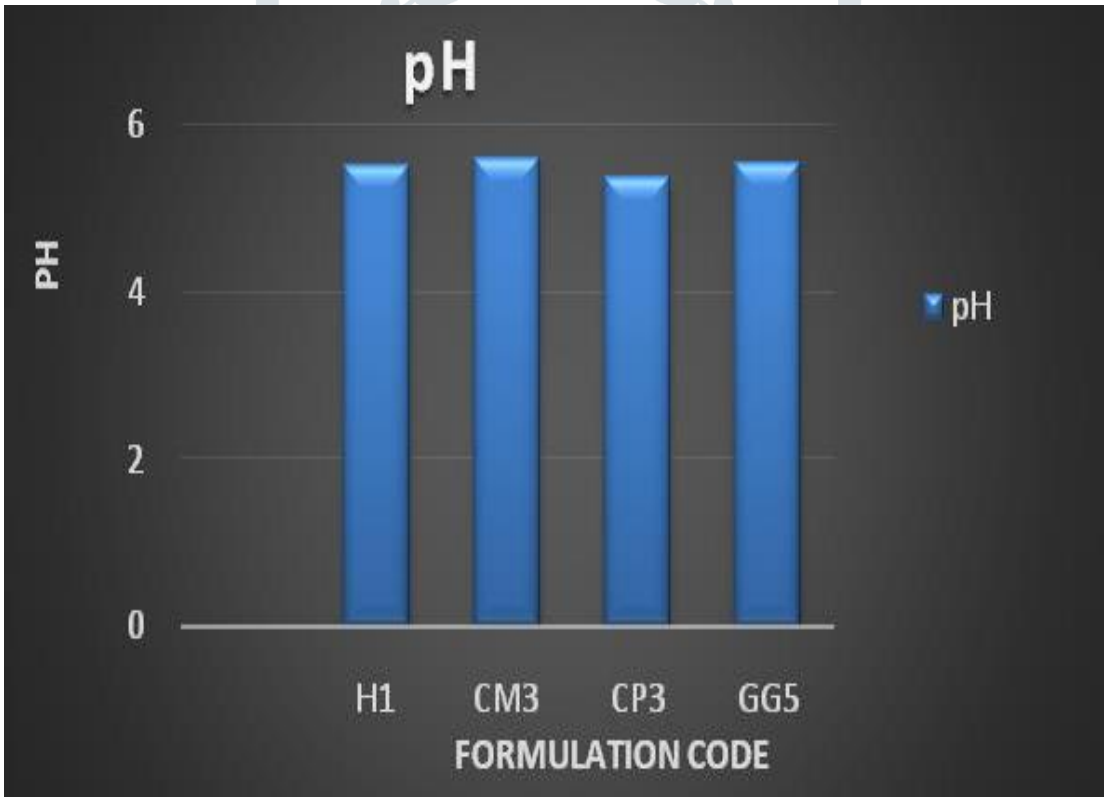
From the above data of evaluation of different formulation batches, optimized batch isselected from each of four formulations as follows:

Table: 13 Evaluation data of Selected Formulations

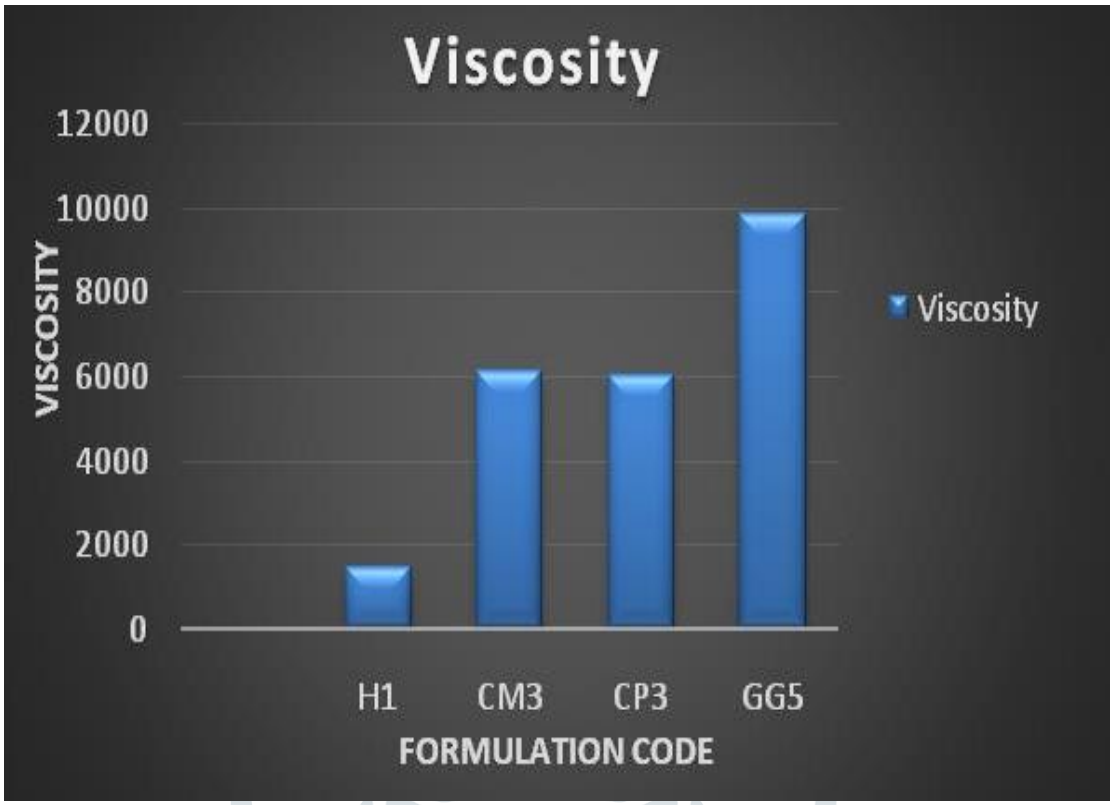
Srno.	Formulationcode	Appearance	Feel on application	Spread ability	pH	Viscosity	Assay
1	H1	White	Smooth	15.5	5.5	1442	99.65
3	CM3	White	Smooth	12	5.6	6110	98.6
3	CP3	White Buff	Smooth	11.8	5.35	6042	98.32
5	GG5	Yellowish	Smooth	10.62	5.54	9868	97.62



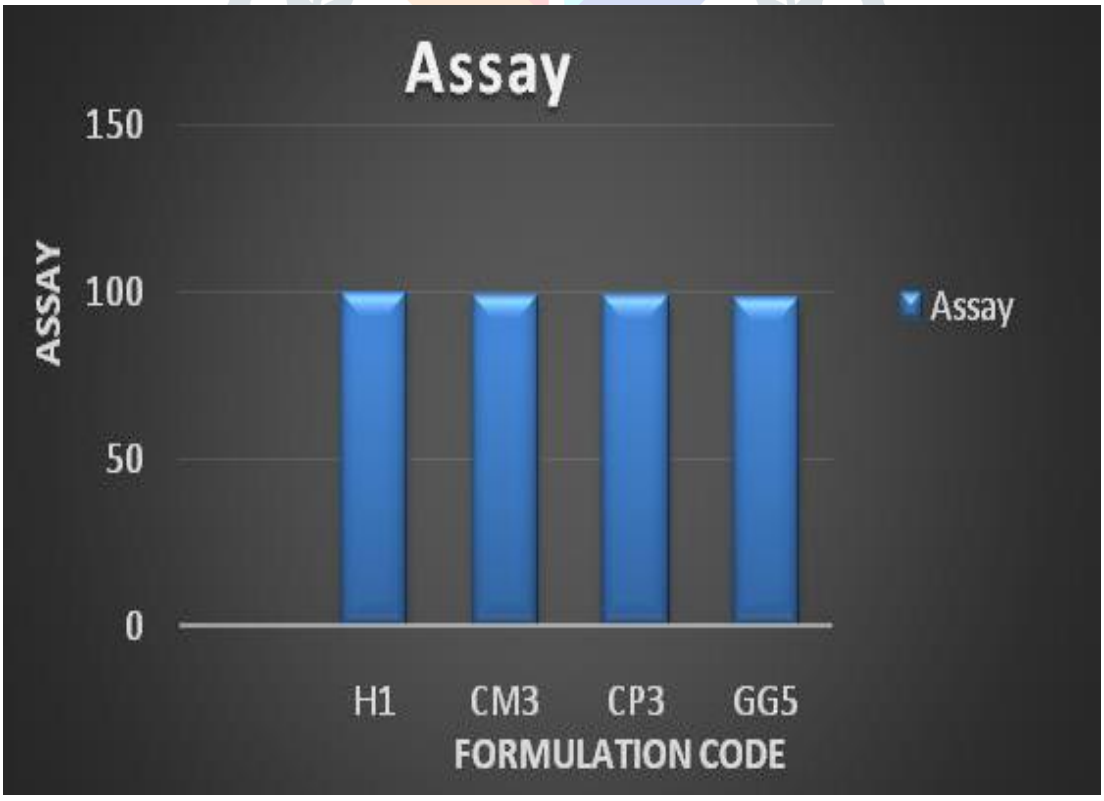
Graph: 24 Spreadability of selected Hydrogel Formulation



Graph: 25 pH of selected Hydrogel Formulation



Graph: 26 Viscocity of selected Hydrogel Formulation



Graph: 27 Assay of selected Hydrogel Formulation

Discussion:

On the Basis of above results and Graphs, the H1 Hydrogel formulation was found optimized and were found satisfactory and within limits. Formulation was selected on the basis of Spreadability test and Assay content (Drug content) .Selected formulation were further study for stability.

Table: 14 Stability Study for Batch H1 at Temp.25ºC atRelative Humidity 65±5%

Duration Time	Drug Content (%)	% Drug Release	pH of Formulations
0 Days	99.78±0.6	86.60±.35	5.8±0.038
15 days	99.55±0.52	86.40±0.36	5.6±0.08
30 days	99.40±0.42	85.72±0.54	5.4±0.035
45 days	99.29±0.56	85.30±0.50	5.2±0.028

Discussion:

The stability study of optimum batch (H1) revealed that there is slightly reduction in drug content was observed over period of 45 days. No significant change was observed in % drug content. The release condition depends upon the temperature and duration of period.Drug release (after 8 Hrs) at various storing condition 2-8 ºC,25 ºC and 40ºC Hence formulation was found to be stable for 45 days.

6. SUMMARY AND CONCLUSION

In the present study an attempt has been made to formulate the topical drug delivery system of Terbinafine HCl in the form of hydrogel. Terbinafine HCl is widely used antifungal agent mostly used to treat fungal infection. Preformulation studies were carried out using polymer like HPMC, CMC, Carbapol and Guar gum. The literature survey indicates that Carbapol and HPMC an excellent gelling agent during the formulation of Hydrogel preparation. As Carbapol and HPMC is chief, easily availableand have a wide regulatory acceptance, it was chosen as a gelling agent in thepresent study. Further it was found that Terbinafine HCl was hydrophobic drug. Due to the above factit was selected for present work. The sample Terbinafine HCl was firstly characterizedfor its identification by using characterization test like melting point UV-Absorption inphosphate buffer pH 6.8, FTIR. The result of these entire tests was found to be within the standard limit. Hydrogels were develop using Carbopol -934 shows shiny white in colour whereas hydrogel developed using Carbopol -934 and Guar gum, CMC, and HPMC shows white, yellowish and white-off colour rept. Drug content was found in the range of 96 to 99 %, Spredability in the range of 8 to 15 g.cm/sec. This combinally increases the viscosity of hydrogel and its ultimately effects on thedrugrelease from gel. It was found that pH of all formulation is in the range of 6.2 to 6.8 thatsuitable the skin pH indicating skin compatibility.While optimized batch showed pH of this is the primary requirement for good Topical formulation. It was found % drugrelease of all formulation is the range of the plot of % drug release verses time were plotted % drug release from batches HPMC, CMC, CP and GG respectively. Carbopol-934 and HPMC based Hydrogel gave the highest drug release. A stability study on developed Terbinafine HCl Hydrogel formulation shows no significant change for colour, pH, Spredability. From the above result it was concluded that Terbinafine HCl hydrogel formulation prepared by using different gelling agent HPMC, Carbopol-934 possesses and edge in terms of Spredability pH, viscosity, drug content, drug release shows acceptable physical properties. Formulated Hydrogel can be used extensively to impart better patient compliance and loading for hydrophilic and hydrophobic drug in a water-solubleHydrogel bases more over this formulation can be used despite of various advantages Hydrogel face problem of bubble formation during its formulation and stratum corneum is permeable to small molecule so concerning these facts, we can incorporate micro sponge that are highly porous micro sized particles withunique ability to entrap pharmaceutical ingredients into a Hydrogel base. Characterization such as better loading capacity than other vesicular system, less stickynature and Spredability of Hydrogel formulation promise them as a better available option for dermatological use. Various herbal oil with medicinal properties can also beincorporated into the Hydrogel formulation that may act as synergistic approach for treating a disease. The side effect associated with oral therapy of terbinafine HCl tabletscan be avoided by using the topical drug.

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