MedCrave
Step into the World of Research

Pharmacy & Pharmacology International Journal

Research Article

Open Access

CrossMark

Formulation and evaluation of topical hydrogel containing antifungal drug

Abstract

Terbinafine hydrochloride is an antifungal drug used in the treatment of fungal infections. The oral use of Terbinafine hydrochloride is not recommended as it has many potential side effects and undergoes hepatic first pass metabolism. This study was conducted to formulate and evaluate Terbinafine hydrochloride topical hydrogel for treatment of fungal infection of skin. The gel was formulated by using different gelling agents like HPMC, Sodium CMC and Polaxomer in three different concentrations. The prepared hydrogel formulations were evaluated for physico chemical parameters like physical appearance, pH, skin irritation, drug release, drug content and rheological parameters like spredability and extrudability. Antifungal activity of the prepared gels was evaluated using Candida as model fungus. The in vitro drug release from gels was evaluated using Franz diffusion cell containing cellophane membrane with phosphate buffer pH 5.8 as the receptor medium. Drug-excipients compatibility studies were performed by DSC and FT-IR analysis. All gel formulations showed acceptable physico chemical and rheological properties and results were found to be within the limits. The drug release was found to decrease with increase in polymer concentration. Among all the gel formulations Polaxomer showed superior drug release than followed by HPMC and sodium CMC. Formulation F4 shows the highest antifungal activity. Drug-excipients compatibility studies showed that there no interaction between the drug ad selected excipients.

Keywords: fungal infections, hydro gels, HPMC, polaxomer, Sodium CMC, Terbinafine hydrochloride

Volume 8 Issue 4 - 2020

T Praveen Kumar,[1] M Chinna Eswaraiah[2]
[1]Department of Pharmaceutics, Anurag Pharmacy College, India
[2]Department of Pharmacognosy, Anurag Pharmacy College, India

Correspondence: T Praveen Kumar, Department of Pharmaceutics, Anurag Pharmacy College, Kodad (M), Suryapet (D), Telangana State, 508 206, India,
Email praveensuri@gmail.com

Received: July 31, 2020 | **Published:** August 26, 2020

Introduction

The topical route of drug delivery has been utilized to produce local effect for treating skin diseases and produce systemic drug effects.[1] Hydrogels are prepared both in cosmetics and in pharmaceutical preparations.[2] Gels often provide better release of drug substance independent of the water solubility of the drug when compared to creams and ointments.[3] Local application of therapeutic compounds has many advantages over oral and parenteral drug delivery systems. The advantages include ease of application to skin, ability to deliver drugs selectively to a site of local action, elimination of hepatic first-pass metabolism and better patient compliance.[4,5] Hydrogels are widely used in topical drug delivery systems due to their physical and chemical properties such as controllable and prolonged release of drug.[6,7] These formulations on contact with the skin forms a semi occlusive film over the skin and release the drug in controlled manner.[8] Lipophilic drug can cross the Stratum corneum, but rate of diffusion decreases as it enters the more aqueous lower regions of the epidermis.[9]

Fungal infections have been divided into superficial and systemic infections.[10] Antifungal drugs are classified according to their chemical structure as azoles, polyenes, allylamines, echinocandins. Terbinafine hydrochloride is an antifungal medication used in the treatment of superficial skin infections such as jock itch, athlete's foot. it is mainly effective on the dermatophyte group of fungi. It is an allylamine antifungal drug and has a broad spectrum of antimycotic activity at low concentrations. It acts by inhibiting fungal sterol biosynthesis which leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, which results in cell death of fungus. It has been reported that terbinafine does not influence the metabolism of hormones or other drugs.[11,12] The goal of our research to formulate and evaluate Terbinafine hydrochloride hydrogels and also evaluate the in-vitro antifungal activity for prepared formulations.

Methodology

Materials

Terbinafine Hydrochloride was obtained from (Mecleods pharmaceutical, Baddi), Sodium CMC was obtained from (ultratech pharmaceutical Baddi), Poloxamer was obtained from (Signet Chemicals), HPMC was obtained from (Qualikem chemicals,Delhi), Glycerin, Propylene glycol, Methyl paraben, Propyl paraben was obtained from (S.D Fine chemical, Mumbai) of analytical grade.

Preparation of gel

All the ingredients were collected according to the formula the given in table 1. Required amount of gelling agents HPMC, Polaxomer and Sodium CMC were added in water with constant stirring at 500 rpm for about 2 hours. Drug was added to the above mixture. Glycerin, propylene glycol, methyl paraben and propyl paraben was added to it. Final weight was made with water. All the samples were allowed to equilibrate for 24 h at room temperature prior to performing evaluation test.

Drug-excipients compatibility studies

A-Differential scanning calorimetry (DSC)

The DSC studies were performed for the drug and the drug-polymer physical mixtures. The samples were inserted in aluminum pan and heated in the rate of 10ºC /min, to a temperature of 200ºC using a differential scanning calorimeter (TA-501; shimadzu corporation, Japan).

Table 1 Formulation development for antifungal gel

No.	Ingredients %	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Terbinafine Hydrochloride	1	1	1	1	1	1	1	1	1
2	HPMC	4	6	8	----	----	----	----	----	----
3	Polaxomer	----	----	----	15	20	25	----	----	----
4	Sodium CMC	----	----	----	----	----	----	4	6	8
5	Glycerin	1	1	1	1	1	1	1	1	1
6	Propylene glycol	1	1	1	1	1	1	1	1	1
7	Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
8	Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
9	Water	QS	QS	QS	QS	QS	QS	QS	QS	QS

B- Fourier Transfer Infrared spectrophotometer (FTIR):

The FTIR studies were carried for the drug and the drug-polymer physical mixture, mixed separately with IR grade KBr in the ratio of (100:1). Discs were prepared by applying 5.5 metric ton of pressure in a hydraulic press using FTIR Spectrophotometer (Genesis II, Mattson, England). The disks were scanned over a wave number range (4000 - 400cm).[13]

Evaluation of gels

The formulated gels were examined for their physical properties, rheological properties and antifungal activity. Skin irritation test was carried out only on all formulations.

Homogeneity

The gels were examined for their physical properties like color, clarity and phase separation by visual inspection. They are tested for the presence of any aggregates.[14]

Grittiness

Presence of any particulate matter in the formulations was observed microscopically.

pH measurement

The pH of gel formulations were determined by using digital pH meter. 1gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated and reported.[15]

Spredability

Concentric circles of different radius were drawn on graph paper and a glass plate was fixed onto it. 5gms of gel was placed on the centre of the lower plate. Another glass plate of 100±5 gm was placed gently on the gel and the spread diameter was recorded after 1 minute of each addition.

Extrudability

The gel formulations were filled in collapsible tubes. After being set in the containers, the extrudability of gel formulations was determined in terms of weight required in grams to extrude 0.5 cm. ribbon of gel in 10 sec.[16]

Drug content

1 g gel was dissolved in 100 ml of phosphate buffer pH5.8. Suitable dilutions were made using phosphate buffer pH5.8. Absorbance was measured at 282 λmax nm using UV spectrophotometer.[17]

In-vitro drug diffusion study

In-vitro drug release studies were carried out using Franz diffusion cell. 0.5 g of gel was applied on cellophane membrane as donor compartment. Phosphate buffer pH 5.8 was placed in the receptor compartment as the dissolution medium. The whole assembly was place on magnetic stirrer with thermostat maintained at 37°c. samples were collected regular time interval and sink conditions were maintained by replacing with new buffer solution. Collected samples are analyzed at 282 λmax nm using UV spectrophotometer.[18]

Skin irritation test

Skin irritation test was conducted on ten healthy male and female volunteers. 100 mg of gel was applied on area of 2 cm and observed for any lesions or irritation/redness.[19]

Antifungal study

Antifungal activity of prepared gels was determined using nutrient agar cup method against Candida albicans strain. Nutrient agar Cups were made aseptically and inoculated with tested fungal suspension strain by spreading on the agar surface. Wells were made in the cups using sterile borer and were filled with each prepared gels by sterile syringe. The zone of inhibition of each cup was observed and radius of the zone of inhibition was calculated and compared to the control using antibiotic zone reader.

Results and discussion

Visual examination

The prepared formulations were inspected visually for their color, homogenity and grittiness. It was observed that all the preparations were clear and white. All the formulations showed good homogeneity with absence of lumps and grittiness.

Citation: Kumar TP, Eswaraiah MC. Formulation and evaluation of topical hydrogel containing antifungal drug. *Pharm Pharmacol Int J.* 2020;8(4):249–254. DOI: 10.15406/ppij.2020.08.00302

Spredability

The diameters of the spredability in circles ranged from 13.86 cm to 21.27 cms. Highest spredability is seen in Polaxomer gel and least spredability is seen in sodium CMC gel. The results revealed that as the concentration of gelling agent is increased, spredability of the gel decreased which was expressed by the lower diameter of the spreaded circle.

Extrudability

All the formulations were tested for extrudability. Formulations prepared with Polaxomer showed excellent extrudability. Formulations prepared with HPMC and Sodium CMC showed good extrudability. It was observed that as the polymer concentration is increased the extrudability gets decreased. Results are shown in table 2.

Table 2 Rheological parameters for topical antifungal hydrogel

Formulation Code	Physical appearance	Extrudability	Spredability (cms)
F1	White, smooth, homogenous	Excellent	15.7
F2	White, smooth, homogenous	Excellent	15.07
F3	White, smooth, homogenous	Good	14.7
F4	White, smooth, homogenous	Excellent	21.27
F5	White, smooth, homogenous	Excellent	16.38
F6	White, smooth, homogenous	Excellent	16.01
F7	White, smooth, homogenous	Good	14.4
F8	White, smooth, homogenous	Good	14.13
F9	White, smooth, homogenous	Good	13.86

Skin irritation

All the formulations passed skin irritation test when applied to the volunteers.

pH determination

The pH values of all formulations were in the range of 5.6 to 6.3 which is considered as acceptable to avoid the risk of irritation upon application to the skin.

Drug content determination

Percentage drug content of all formulations was in the range of 95 to 99. The drug content results confirmed that the drug was uniformly distributed throughout the gel.

Zone of inhibition

The antifungal activity of Terbinafine hydrochloride from its different gel formulations were given in table 3. the antifungal activity was determined by measuring the zone of inhibition. The results from all the formulations were satisfactory and the greatest activity was observed in formulation F3 where the inhibition zone reached 24mm, while the lowest activity was found in the formulation F2 where the inhibition zone was 11 mm. Results are shown in table 3.

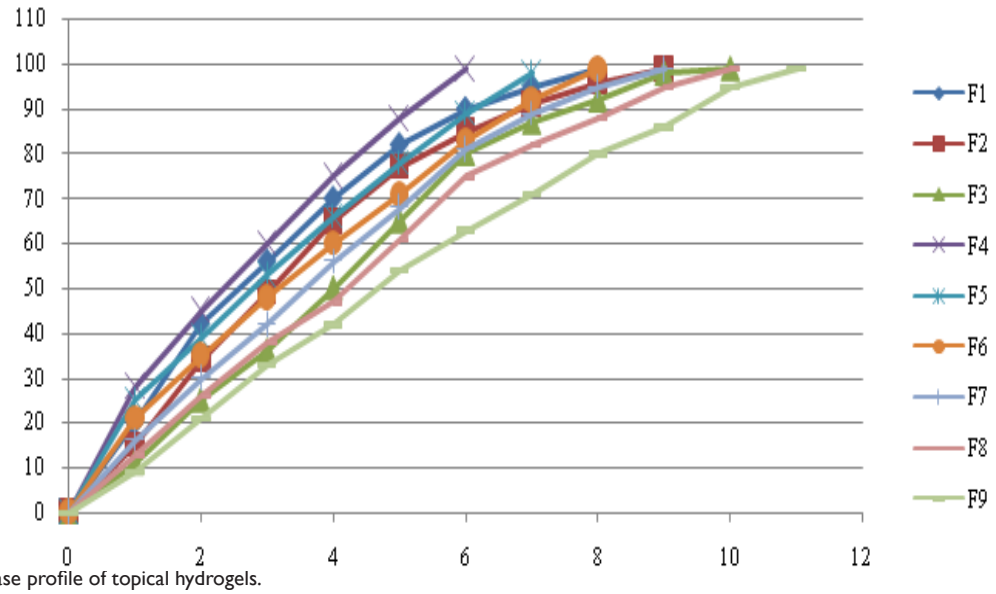

Figure 1 Drug release profile of topical hydrogels.

Citation: Kumar TP, Eswaraiah MC. Formulation and evaluation of topical hydrogel containing antifungal drug. *Pharm Pharmacol Int J.* 2020;8(4):249–254. DOI: 10.15406/ppij.2020.08.00302

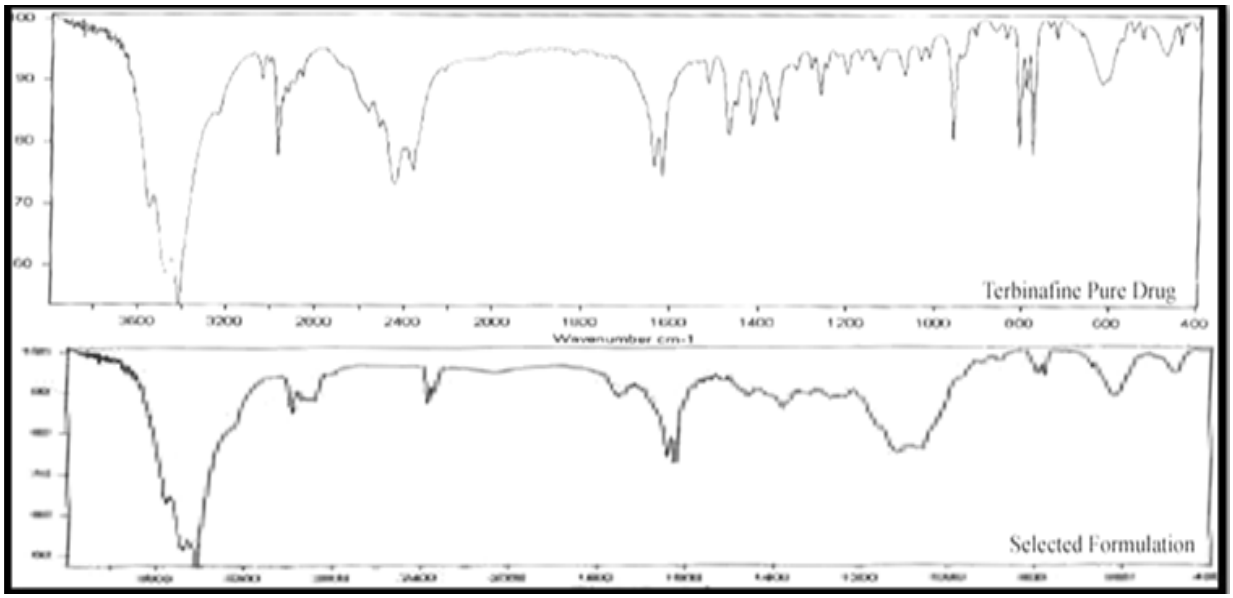

Figure 2 FTIR spectra of pure drug and selected formulation.

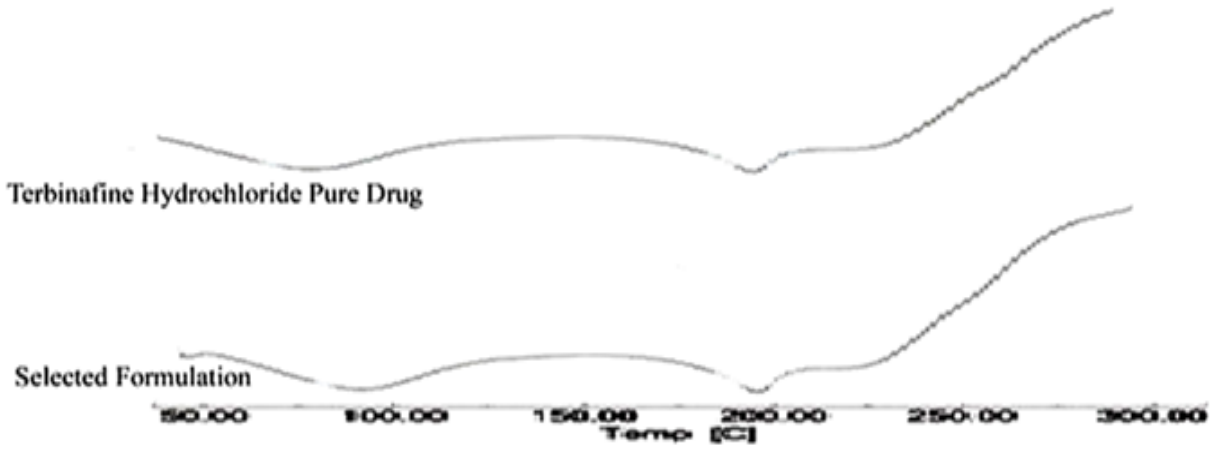

Figure 3 DSC curves of pure drug and selected formulation.

Table 3 Evaluation parameters for topical antifungal hydrogel

Formulation Code	Skin irritation	pH	Drug content	Zone of inhibition (mm)
F1	Pass	6.1	95	18
F2	Pass	6.04	98	17
F3	Pass	6.3	99	14
F4	Pass	6	96	24
F5	Pass	5.6	95	22
F6	Pass	6.1	98	20
F7	Pass	6.22	99	14
F8	Pass	6.5	97	13
F9	Pass	6.8	96	11

Citation: Kumar TP, Eswaraiah MC. Formulation and evaluation of topical hydrogel containing antifungal drug. *Pharm Pharmacol Int J.* 2020;8(4):249–254. DOI: 10.15406/ppij.2020.08.00302

In-vitro release studies

The In-vitro drug release profile of topical gels was represented in Figure 1. It was found that the amount of drug diffused from all the formulation ranged from 28 to 9% during first hour. Formulation F4 to F6 containing Polaxomer showed complete drug release in 6 to 8hrs. The drug release from formulations F2 and F7 extended up to 9 hrs and from formulations F3 and F8, drug release extended up to 10 hrs. F9 formulation extended drug release up to 11 hrs. Highest drug release was observed in formulation F4 and lowest in formulation F9. It was observed that the drug release was influenced by the polymer type and the concentration of the polymer used. The release rate of the drug was found to decrease drastically with the increase in viscosity.

In vitro drug release kinetics of Terbinafine hydrochloride topical Hydrogels:

The drug release kinetic study revealed that drug release followed krossmeyer peppas model in all the formulations F1 to F9 which indicates that drug is diffused through the membrane. The Krosmeyer peppas graphs were plotted and the release rate constant, k, and the slope n, determined. The results showed that most of the 'n' values were between 0.711 and 0.988. Therefore it can be inferred that the drug may have followed case II transport mechanism. Results are shown in table 4.

Table 4 *In vitro* drug release kinetics of Terbinafine hydrochloride topical hydrogels

Formulation codes	R^2 values of Kinetic Models					
	Zero order	First order	Higuchi	Hixson Crowell	korsmeyer peppas	Slope (n)
F1	0.942	0.913	0.987	0.606	0.975	0.764
F2	0.935	0.923	0.984	0.607	0.97	0.855
F3	0.955	0.913	0.984	0.65	0.984	0.979
F4	0.995	0.803	0.997	0.574	0.999	0.711
F5	0.994	0.85	0.995	0.729	0.998	0.714
F6	0.992	0.815	0.996	0.531	0.999	0.757
F7	0.976	0.878	0.993	0.569	0.994	0.853
F8	0.977	0.861	0.991	0.54	0.993	0.898
F9	0.988	0.818	0.995	0.502	0.991	0.988

Drug-excipients compatibility studies

Purity of the drug and drug-excipient compatibility studies were performed using DSC and FT-IR analysis. FT-IR study revealed that there was no major change in the position of peak obtained in the drug alone and in a mixture of drug with excipients. This shows that there was no interaction between drug and excipients. The pure drug showed a sharp exothermic peak at 205°C in DSC study. Similar exothermic peaks were observed at similar temperature in the selected formulation at 207°C. The above study confirms that there was no drug and excipients interaction.

Conclusion

From above results, it was concluded that Terbinafine hydrochloride gel formulations prepared with different gelling agents HPMC, Sodium CMC, Polaxomer showed acceptable physic chemical, rheological properties and antifungal activity. All prepared gel showed acceptable physical properties concerning color, homogeneity, consistency, spredability and pH value. All the above parameters showed satisfactory results and were found to be within the prescribed limits. It can be concluded that formulation F4 produced better spredability, consistency, and homogeneity and drug release study. The prepared gels showed promising antifungal activity against C. albicans strains. Therefore, it was concluded that prepared formulation could be a promising topical alternative for the treatment of skin fungal infections. The side effects associated with oral therapy of Terbinafine hydrochloride tablets can be avoided by using the topical gels.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

References

1. Flynn GL, banker GS, Rhodes CT. *Modern Pharmaceutics*. Marcel Dekker Inc: New york, USA; 2002. 294 p.
2. Niyaz B, kalyani P, Divakar G, e al. Formulation and Evaluation of Gel Containing Fluconazole-Antifungal Agent. *International Journal of Drug Delivery and Research*. 2011;3(4):109–112.
3. Abdel-hamid SM, Abdel-hady SE, El-shamyAA, e al. Formulation of an Antispasmodic Drug as a Topical Local Anesthetic. *International Journal of Pharmaceutics*. 2006;326(1-2):107.
4. Vidya S, Sejal V. Formulation and Evaluation of Microemulsion-Based Hydrogel For Topical Delivery. *International Journal of Pharmaceutical Investigation*. 2012;2(3):140–149.
5. Pal K, Banthia AK, Majumdar DK. Polymeric Hydrogels: Characterization and Biomedical Applications–A Mini Review. *Designed Monomers and Polymers*. 2012;1:197–220.
6. Emma R, Stepan G, Ashot M, e al. New Drug Delivery System for Cancer Therapy. *International Journal of Medical, Health, Biomedical, Bioengineering and Pharmaceutical Engineering*. 2013;7(12):899–904.
7. Enas MA. Hydrogel: Preparation, Characterization and Applications: A Review. *Journal of Advanced Research*. 2013;6(2):106–121.

Citation: Kumar TP, Eswaraiah MC. Formulation and evaluation of topical hydrogel containing antifungal drug. *Pharm Pharmacol Int J.* 2020;8(4):249–254. DOI: 10.15406/ppij.2020.08.00302

8. Lackner TE, Clissold SP. Bifonazole. A Review of Its Antimicrobial Activity and Therapeutic Use In Superficial Mycoses. *Drugs*. 1989;38(2):204–225.
9. Chandra A, Sharma PK. Microemulsion: An Overview. *Pharmacological Reviews*. 2008;6:2–4.
10. Bennett JE. *Antimicrobial Agent: Antifungal Agents*. 10th ed; 2001. 1295 p.
11. Bennett PN, Brown MJ, Bennett PN. *Viral, fungal, protozoal and helminthic infections*. 10th ed; 2008. 233–238 p.
12. Ryder NS. Terbinafine: Mode of Action and Properties of The Squalene Epoxidase Inhibition. *British Journal of Dermatology*. 1992;126(39):2–7.
13. Doaa AH, Dalia Abd El-Rhman, Sally A Abdel-halim, e al. Formulation and Evaluation of Fluconazole Topical Gel. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2012;4(5):176–183.
14. Kumar TG, Kaur LP. Formulation and Evaluation of Topical Gel of Aceclofenac. *Journal of Drug Delivery & Therapeutics*. 2013;3(6):51–53.
15. Saroha K, Singh S, Aggarwal A, e al. Transdermal Gels- An Alternative Vehicle For Drug Delivery. *International Journal of Pharmaceutical, Chemical and Biological Sciences*. 2013;3(3):495–503.
16. Thorat SP, Rane SI. Formulation and In Vitro Evaluation of Lecithin (Soya And Egg) Based Aceclofenac Organogels. *Journal of Pharmaceutical Research*. 2010;3(6):1438–1441.
17. Patel HK, Dhiren PS. A Review on Micro Emulsion Based Gel: An Innovative Approach For Topical Delivery Of Hydrophobic Drug. *World Journal of Pharmaceutical Research*. 2018;7(7):344–349.
18. Doijad RC, Manvi FV, Rao SNM, e al. Sustained Ophthalmic Delivery of Gatifloxacin From In Situ Gelling System. *Indian Journal of Pharmaceutical Sciences*. 2006;68(6):814–818.
19. Singh V, Singh PK, Sharm PK, e al. Formulation and Evaluation of Topical Gel of Aceclofenac Containing Piparine. *Indo American Journal of Pharmaceutical Research*. 2013;3(7):5266–5280.

Citation: Kumar TP, Eswaraiah MC. Formulation and evaluation of topical hydrogel containing antifungal drug. *Pharm Pharmacol Int J.* 2020;8(4):249–254. DOI: 10.15406/ppij.2020.08.00302