Research Article

Formulation and Evaluation of Gel Containing Miconazole Nitrate an Antifungal Agent

Bharat Parashar, Atul Kabra, *Ajay Chandel

Department of Pharmaceutics, Manav Bharti University, Solan, HP, India.

ABSTRACT

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. There are various skin infections caused by fungus. An antifungal medication is a pharmaceutical fungicide used to treat mycoses such as athlete's foot ringworm, candidasis. Antifungal works by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effect on host. Miconazole is an imidazoles antifungal derivative and used for the treatment of local and systemic fungal infection. The oral use of miconazole is not recommended as it has many side effects. Miconazole topical gel formulation is made for better patient compliance and to reduce the dose of drug and to avoid the side effects like liver damage and kidney damage. The gel was formulated by changing the polymer ratio. FT-IR study confirmed the purity of drug and revealed no interaction between the drug and excipients. Gel formulations were characterized for drug content, pH determination, viscosity measurement, *in vitro* diffusion, antifungal activity and skin irritation. Among the five formulations, F1 was selected as the best formulation.

Keywords: Carbopol 940, gel, gel forming agents, miconazole, topical delivery.

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***Address for correspondence:**
Ajay Chandel
Department of Pharmaceutics, Manav Bharti University, Solan, HP, India.
E-mail: ajay.chandel5@gmail.com

INTRODUCTION

Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Fungal infections of skin are one of the common dermatological problems. Among the topical formulations a wide choice for the treatment from solid dosage to semisolid doses forms and to liquid dosage formulation the transparent gels have widely accepted in both cosmetics and pharmaceuticals.

A wide variety of vehicles ranging from solid to semisolids and liquid preparations are available for topical treatment of dermatological disease as well as skin care. Topical drug administration is a localised drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical route [1]. There are various medicated products that are applied to the skin. Such products are referred as topical or dermatological products. There are various Hydrophilic polymers such as carbopol 940, hydroxy propyl methyl cellulose (HPMC), Sodium alginate that are used in topical gel delivery system [2]. Based on molecular fraction these polymers are used concentration between 1-5 % in topical formulation.

Topical delivery

It is necessary to understand the anatomy, physiology and physiological properties of the skin. Microscopically skin is composed of three histological layers: epidermis, Dermis and Hypodermis (subcutaneous layer). The epidermis is 0.1 -1.5 mm thick. It is further divided into five parts: stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum, the epidermis forms the pigment melanin [1]. The squamous cell layer is the thickest layer of epidermis and helps to

move certain substances in and out of the body. The stratum corneum is made up of 10-30 thin layers of dead cells.

Beneath the epidermis the layer dermis lies which is 1.5-4 mm thick. It consists of collagen elastins, sweat and oil glands, hair follicles, nerve endings, blood and lymph vessels. Dermis contain scavengers cell from the immune system which engulf the foreign organism and destroy them. Nerve endings are responsible for the sense of touch. The hypodermis also known as subcutaneous tissue is the deepest layer of skin which acts as an insulator conserving body heat and as a shock absorber protecting internal organ from injury. It also stores fat. The blood vessels, nerves, lymph vessels and hair follicles also cross linking through these layers.

Topical route of administration:

Drug molecules contact at skin surface with cellular debris, microorganisms and other materials which effect permeation. The applied medicinal substances follow three pathways:

- Through hair follicles
- Across continuous stratum corneum
- Via sweat duct

This route of drug delivery has gained popularity because it avoids first pass metabolism, gastrointestinal irritation and metabolic degradation associated with oral administration. The pathway of drug movement through this layer is believed to be mainly transcellular. Although the paracellular pathways becomes important for small molecular weight compound. Being a diffusion barrier the stratum corneum also serves as a reservoir for compound such as corticosteroids, grisofulvin and many other drugs. Upon reaching the subcutaneous tissue there is evidence that some drugs e.g. Like thyroxin estradiol and corticosteroids remain in this layer for an extended period of time or for prolonged release of drugs.

Fungal infections are very common and can be topical as well as systemic. Treatment of fungal infection includes medicines like fluconazole, miconazole, ketoconazole, clotrimazole and grisofulvin [3].

Gel:

The term gel was introduced in late 1800 to name sum semisolid material according to pharmacology. The USP defines gel as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing an interpenetrated by liquid. The inorganic particles form a three dimensional structure. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved into the continuous phase [4].

Classification of gels: Gels can be classified depending upon colloidal phases and nature of solvent used, physical nature and rheological properties [5].

A. Based on colloidal

- **Two phase system (Inorganic) –** If the partial size of the dispersed phase is relatively large and form the three dimensional structure throughout gel such a system consists of floccules of small particles rather than layer molecules and gel structure in this system is not always stable. They must be thixotropic-forming semisolids on standing and become liquid on agitation.
- **Single phase system (organic) –** These consists of large organic molecules existing on the twisted stands dissolved in a continuous phase. These organic molecules either natural or synthetic polymer are referred as gel forms.

B. Based on nature of solvent used

- **Hydro gel (water based) –** In hydro gels water acts as a continuous liquid phase. E.g. gelatin, cellulose derivatives, poloxamer gel.
- **Organic gels (with a non aqueous solvent) –** They contain a non aqueous solvent on their continuous phase. E.g. Plastibase olag gel and dispersion of metallic state in oils.
- **Xerogels –** these are solid gels with low solvent concentration. They are formed by the evaporation of solvent leaving the gel framework behind. On contact with fresh fluid they swell and can be reformed. E.g. tragacanth ribbons, dry cellulose and polystyrene.

C. Based on rheological properties they are classified into three types.

- **Plastic gel –** Flocculated suspensions of aluminium hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of gels above which the elastic gel distorts and begins to flow.
- **Pseudo plastic gel –** For example liquid dispersion of tragacanth, sodium alginate etc exhibit pseudo plastic flow. There is a decrease in the viscosity of this type of the gel with the increasing rate of shear, the rheogram results from the shearing action on the long chain molecules of the linear polymer. As the shearing stress increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.
- **Thixotropic gel-** In this type of gel the bonds between the particles are very weak and can be broken down by shaking. The resultant solution will revert back to gel due to the particles colliding and linking together again, e.g. bentonite and agar.

D. Based on physical nature

- **Elastic gel –** Due to elastic behaviour of agar, pectin, guar gum the fibrous molecules being linked at the point of junction by relatively weak bond such as hydrogen bonds and dipole attraction. E.g. alginate and carbopol.
- **Rigid gels –** In this type of gel macromolecules in which the framework linked by primary valance bond .e.g. Silica gel [4].

Bases or gel forming polymers

Polymer is simply a compound made up of repeating units. Polymers are used to give the structural network which is essential for the preparation of gels [5].

Gel forming bases or polymers is classified as follows: -

1. Natural polymers – Natural polymers are those polymers which exist naturally and can be synthesized by living bodies, e.g. Proteins like collagen, gelatine etc and polysaccharides like agar, tragacanth, pectin and gum etc.

2. Semi synthetic polymers – These polymers are mostly derived from natural polymers by chemical modification, e.g. cellulose derivatives like carboxymethylecelulose, methylcellulose, hydroxypropyl cellulose and hydroxyethyle cellulose.

3. Synthetic polymers – The polymers which are prepared in laboratories are called synthetic polymers. These are also called man made polymers, e.g. Carbomer carbopol 940, carbopol 934, Poloxamer, Polyacrylamide, Polyvinyl alcohol and Polyethylene.

4. Inorganic substances – Aluminium hydroxide and Besitonite.

5. Surfactants – Sebrotearyle alcohol and Brij-96.

Preparation of gels:

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before processing. Gels can be prepared by following methods [4].

- Thermal changes **–** Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelation occurs (Cooling of a concentrated hot solution will produce a gel), e.g. Gelatin, agar sodium oleate, guar gum and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.
- Flocculation **–** Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g. Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation

method are thixotropic in behaviour. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to "salt out", the colloidal and gelation doesn't occur.

- Chemical reaction – In this method gel is produced by chemical inter action between the solute and solvent, e.g.: aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with Glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl isocyanine (MDI) that cross-links the polymeric chain.

Materials and methodology

Table 1: List of Materials Used

Sr. No	Materials	USE	Supplier
1	Miconazole Nitrate	Drug	Aurochem Lab.
2	Carbopol 940 LR	Gelling agent	SDFCL
3	Benzyl alcohol	Preservative	SDFCL
4	Tween 80	Penetration enhancer	SDFCL
5	Glycerine	Moistening agent	SDFCL
6	Triethanolamine	pH adjustifier	SPB Pharma

Table 2: Lists of Equipments Used

Sr. No	Equipments	Manufacturer
1	Electronic Weighing Balance	CONTECH
2	Viscometer	BROOKFIELD
3	UV- Spectrophotometer	UV- 1 800 Shimadzu
4	Digital Melting Point Apparatus	MAX
5	Magnetic Stirrer	Kapla Scientific Works
6	Mechanical Stirrer	INCO
7	Digital pH Meter	Max Electronics
8	FTIR Spectrophotometer	IR Prestige-21,Shimadzu
9	Millipore	Kapla Scientific Works

Preparation of Standard Graph in Methanol: [6, 7]

Standard Stock Solution of Miconazole nitrate: Accurately weighed 100 mg of miconazole and was dissolved in 100 ml of methanol, from this stock solution 1 ml was withdrawn and the volume was made up to 10 ml which was named as a stock solution. Form this standard stock solution, a series of dilution (10, 20, 30, 40, 50 µg/ml) were prepared using methanol. The absorbance of these solutions was measured spectrophotometrically against blank of methanol at 272 nm for miconazole (Fig 2).

FT-IR spectrum analysis of miconazole: [8]-The FT-IR infrared spectrum of pure drug was seen in between 400 to 4000 cm^{-1} Drug-excipients compatibility studies were carried out using FT-IR infrared spectrum of pure drug was seen in between 600 to 3800 cm-1. The study was carried out on individual pure drug and its physical mixture with the excipients used in the study (**Fig. 3, 4**).

Preparation of gel base:

Carbopol 940 and purified water were taken in a beaker and allowed to soak for 24 hours. To this, required amount of drug (2 gm) was dispersed in water and then carbopol 940 was than neutralized with sufficient quantity of triethanolamine (6.5). Glycerine as a moistening agent and Tween 80 as a penetration enhancer and benzyl alcohol as a preservative added slowly with continuous gently stirring until the homogenous gel was formed. Formulation of various batches is shown in (**Table 3**).

Table 3: Formulation code for gel preparation:

INGREDIENTS	F1	F2	F3	F4	F5
DRUG(gm)	1	1	1	1	1
CARBOPOL 940 (gm)	2	4	6	8	10
BENZYL ALCOHOL (ml)	2	2	2	2	2
TWEEN 80 (ml)	1	1.25	1.50	1.75	2
GLYCERINE (ml)	20	20	20	20	20
TEA(ml)	3	3	3	3	3
WATER (ml)	qs	qs	qs	qs	Qs

Preformulation Studies:

Organoleptic Characteristics:

The characteristics like taste, colour, odour etc were studied. The results for organoleptic characteristics are shown in (**Table 4**).

Table 4: Organoleptic properties of model drug

Properties	Results
Description	Crystalline Powder
Taste	Slightly unpleasant
Odor	Odourless
Colour	White

Solubility: Results for the solubility profile of the drug in various solvents is shown in (**Table 5**).

Table 5: Solubility study of Model drug

Media	Solubility
Water	Very Slightly soluble
Methanol	Freely soluble
Ethanol	Slightly Soluble
Chloroform	Slightly Soluble

Melting Point:

The observed melting point of miconazole using digital melting point apparatus was found to be 174^0C which comes near the ranges 170.5°C to 184–185°C.

U. V. Spectroscopy:

FT-IR Study:

The FT-IR spectrum of miconazole was seen in between 400 to 4000 cm^{-1}.

The FT-IR spectrum of miconazole

Compatibility study of peaks:

All the peaks observed in the FT-IR of miconazole nitrate were appeared unchanged when used with or in combination with the polymer (carbopol 940). The above interpretational data clearly states that there is no interaction between the drug and polymer. Therefore it can be concluded that the drug and polymer are compatible as shown in (**Table 6**).

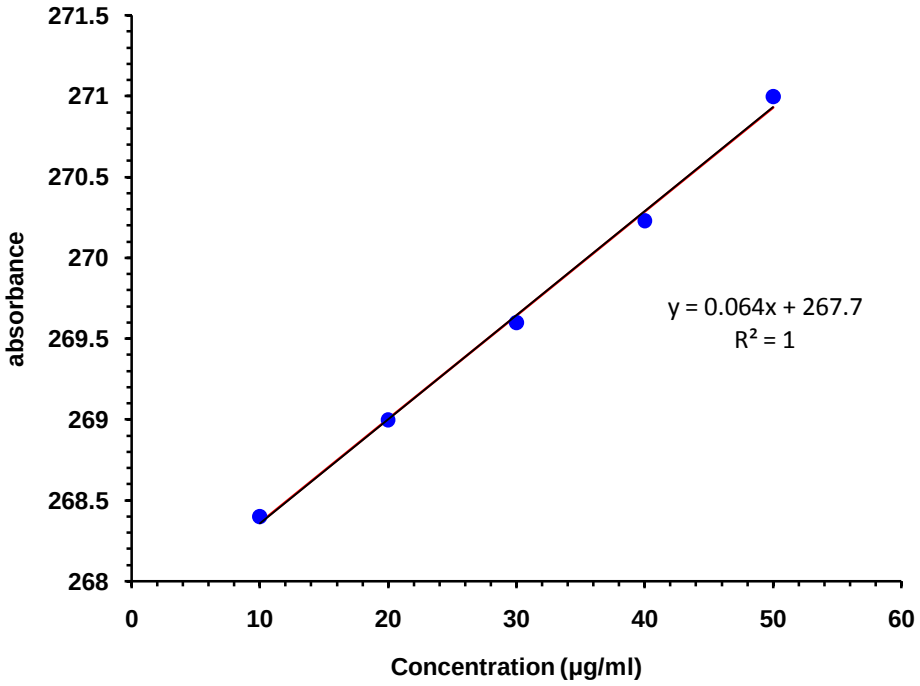

Fig.2: Calibration curve of miconazole in methanol

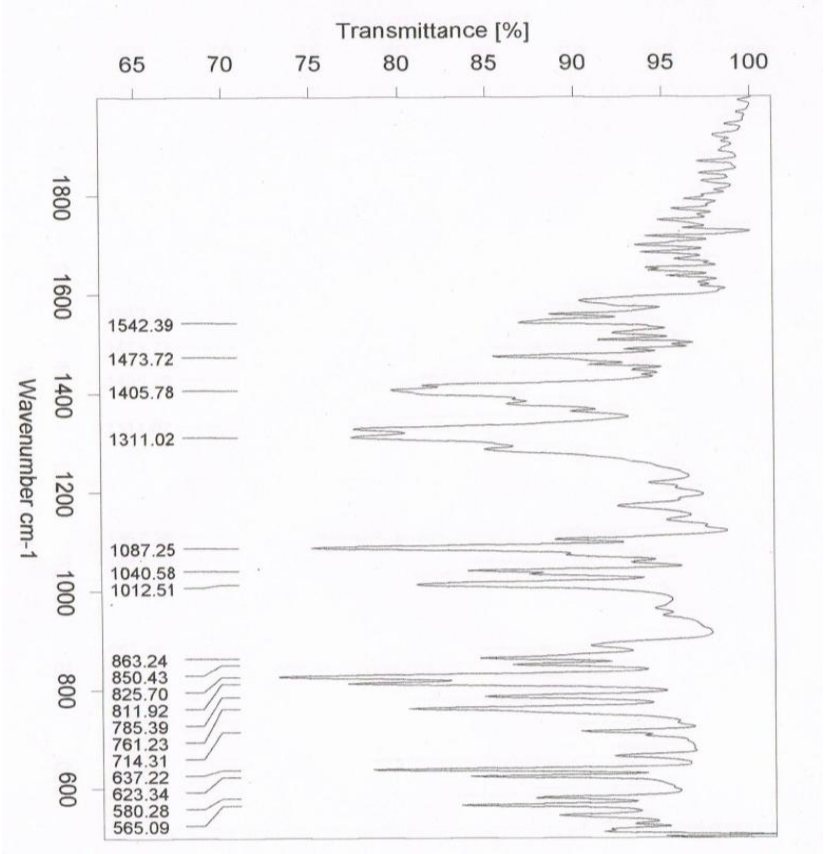

Fig. 3: FT-IR spectrum of miconazole

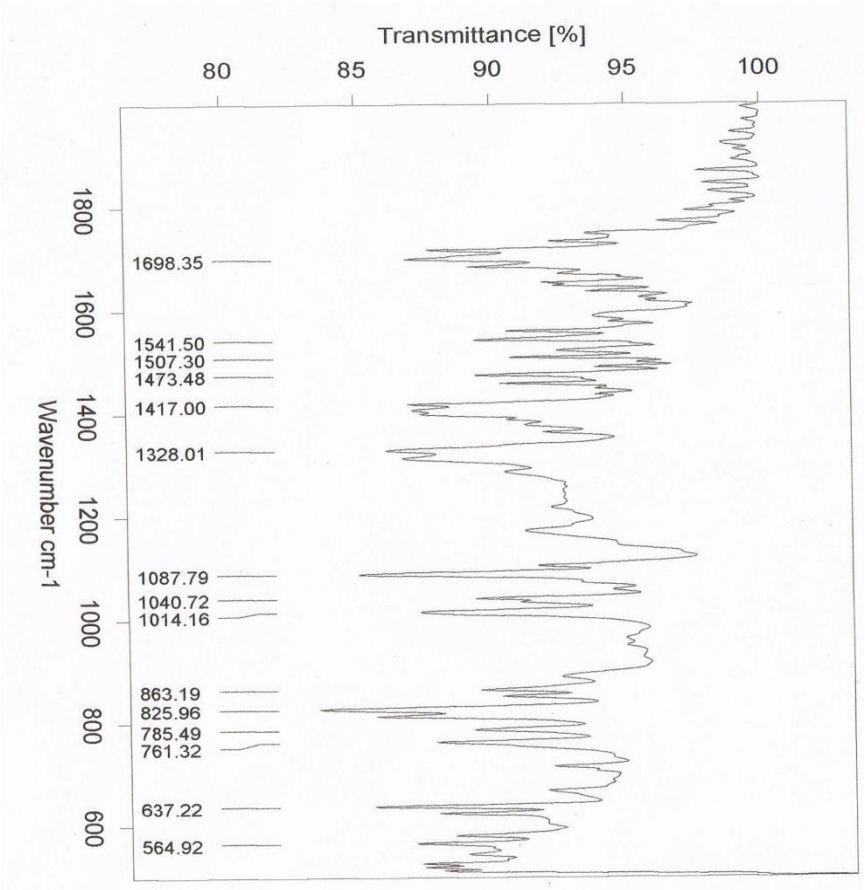

Fig. 4: FT-IR spectrum of miconazole + carbopol (mix)

Table 6: compatibility study of peaks

Description	FT-IR range of miconazole nitrate
C-cl	785-540 cm^{-1}
C=C	1600-1475 cm^{-1}
C-0	1300-1000cm^{-1}
Aromatics out of plane blend	900-690 cm^{-1}
C-N	1350-1000cm^{-1}

Evaluation Parameters:

Physical Evaluation:

Following table shows results for physical evaluation of Miconazole nitrate gels. The evaluation parameters like spreadability, washability, colour, odor etc of the formulated gels were studied shown in (**Table 7**).

Table 7: Physical evaluation of formulations

Formulation Code	Spreadability	Washability	Occlusiveness	Colour	Phase separation	Odour
F1	Easy	Washable	Yes	White transparen t	No	No
F2	Easy	Washable	No	White	No	No
F3	Easy	Washable	No	White	No	No
F4	Easy	Washable	No	White	No	No
F5	Easy	Washable	Yes	white	No	No

pH of Formulations:
Nearly the pH of all the formulations was near to 6.8. The (**Table 8**) shows the results for pH of all the formulations.

Table 8: pH of various formulations

Formulation Code	pH
F1	6.7
F2	6.2
F3	7.1
F4	6.8
F5	6.5

Viscosity:
The (**Table 9**) shows values for viscosity of various formulations. The viscosity values of Carbopol gels gave satisfactory viscosity.

Table 9: Viscosity of various formulations

Formulation Code	Spindle No.	RPM	Viscosity Centipose
F1	4	10	4900
F2	4	10	5300
F3	4	10	5670
F4	4	10	5903
F5	4	10	6115

Spreadability:
The following values were recorded for spreadability of formulated gels and it has been found that the formulations have good spreadability shown in (**Table 10**).

Table 10: Spreadability of various formulations

Formulation Code	Quantity (mg)	Diameter (cm)
F1	3	2
F2	3	1.8
F3	3	1.8
F4	3	1.5
F5	3	1.3

Homogeneity and Grittiness:
The (**Table 11**) shows results for Homogeneity and Grittiness. All the formulations were found to be homogenous except a few formulations (F3, F4, and F5). Grittiness was observed in none of the formulations

Table 11: Homogeneity and grittiness of formulations

Formulation Code	Homogeneity	Grittiness
F1	Yes	No
F2	Yes	No
F3	No	No
F4	No	No
F5	No	No

Extrudability study:

The results for Extrudability are shown in the (**Table 12**). Carbopol gave good extrudability.

Table 12: Extrudability of various formulations (++ very good, +good)

Formulation code	Extrudability
F1	+
F2	++
F3	++
F4	++
F5	++

Sensitivity test:

After investigation it was concluded that none of the formulations caused any erythema, wheel or any allergic reaction.

Drug Content:

The (**Table 13**) shows results for drug content. All the formulations gave satisfying results for the percentage drug content.

Table 13: Drug content of the formulations

Formulation Code	Drug Content
F1	95.4
F2	92.86
F3	93.4
F4	96.74
F5	95.113

In vitro diffusion study:

The (**Table 14**) show the results for *in vitro* diffusion study of the formulations. The percent of Miconazole released was calculated after uniform time interval i.e. 1, 3 and 6 hours (**Fig. 5**).

Table 14: Percentage drug released after 1, 3 and 6 hours

Formulation Code	Percentage Miconazole Released after 1 hour	Percentage Miconazole Released after 3 hours	Percentage Miconazole Released after 6 hours
F1	17.2	26.5	60.3
F2	15.1	24.3	57.5
F3	14.7	21.6	54.4
F4	12.5	22.7	51.5
F5	10.6	19.5	49.3

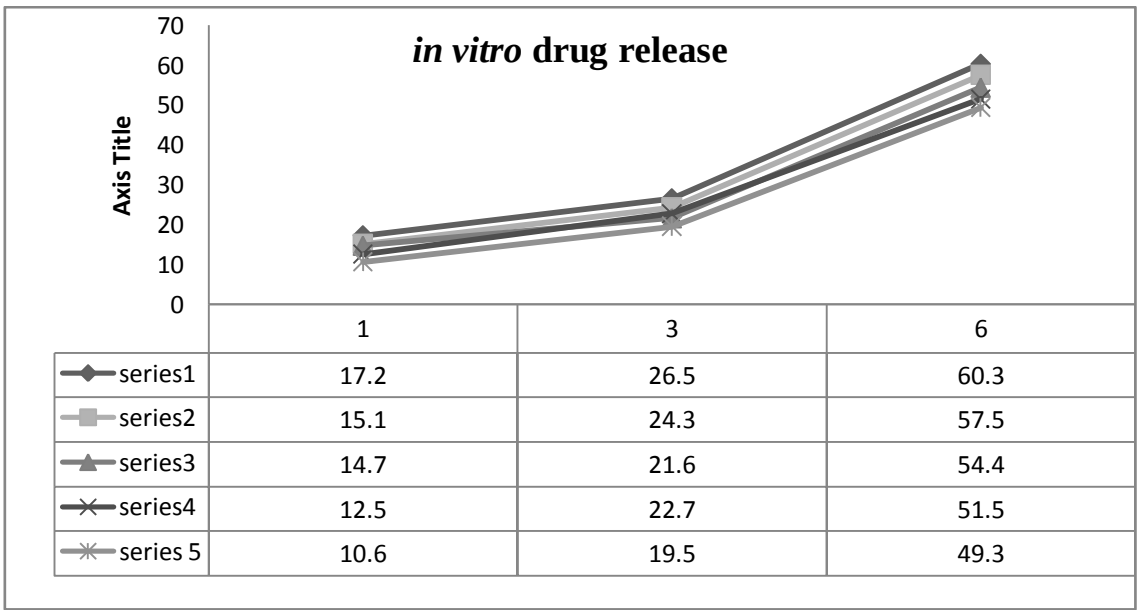

Fig. 5: Graphical presentation of release of formulations after 1,3and 6 hours

Fig. 6: Various formulations of gel

DISCUSSION

Topical and transdermal drug delivery systems offer several advantages over oral delivery systems. These delivery systems include patch, gel, cream, ointment and lotion [1, 2]. However it has been found so many side-effects were proved by the oral delivery system of Miconazole and here to over the side-effects of oral dosage form. The dosage form has been changed by formulation and evaluation of Miconazole nitrate gel.

Miconazole is an imidazoles derivative, used in the treatment of topical as well as systemic fungal infection. The bioavailability of miconazole is 90%. In the present study, an attempt was made to formulate miconazole gel for efficient delivery of drug to the skin [7].

In the present study, miconazole gel was prepared by using Carbopol 940 LR (synthetic polymer), for treatment of fungal infections [4]. Various formulations were made using penetration enhancers; Tween 80. Triethanolamine and distilled water were used. A total number of five formulations were prepared. The Preformulation study of drug was carried out by FT-IR, which showed there was no major change in the position of peak obtained in the drug [6, 8]. The data obtained from viscosity studies, drug content, spreadability test, Extrudability studies, in vitro drug diffusion, skin irritation and anti fungal studies of various formulations was compared which gave satisfactory results [3].

The physical evaluation of various formulations was successfully carried out. Most of the formulations were easily spreadable and easily washable. The colour of formulations was white transparent and few of them were white. All the formulations were odourless.

The pH of all the formulations was found near 6.8. Viscosity measurements were carried out using Brookfield viscometer. The viscosities of Carbopol gels ranged from 4900 to 6115 centipoises. It can be concluded that the viscosity readings of carbopol gels were in the acceptable limits. By increasing the concentration of any of the gelling agent there should be an increase in the viscosity (F1< F2<F3<F4<F5) and decrease in the spreadability (F1>F2>F3>F4>F5). Almost all the formulations were found to be homogeneous and none of the formulations showed grittiness. The results for extrudability showed that extrudability of Carbopol gels were in acceptable limits. The results for the drug content of all the formulations were acceptable. The *in vitro* diffusion studies of the formulations also gave acceptable results. The percentage drug released after 1 3 and 6 hours were found to be decreased with the increase in the amount of gelling agent (carbopol) (F1> F2>F3>F4>F5). Thus, the objective of the present work of formulation and evaluation of miconazole topical gel has been achieved with success [3, 5,-7].

SUMMARY

In the present study topical gel of Miconazole for efficient delivery of drug across the skin was formulated. Miconazole is an imidazoles derivative and used for the treatment of local and systemic fungal infection. The oral use of Miconazole is not much recommended as it has many side

effects, thus this formulation is made for better patient compliance and to reduce the dose of drug and to avoid the side effects like liver damage and kidney damage. Firstly preformulation studies were carried out; parameters like organoleptic characters, melting point, solubility etc were studied and the drug was spectrophotometrically analyzed using UV spectrophotometer. FT-IR study confirmed the purity of drug. Five gels were designed using Carbopol 940 LR (synthetic polymer) as the gelling agents. Penetration enhancer Tween 80 was used to enhance drug penetration from these preparations. Gel formulations were evaluated for drug content, pH determination, viscosity measurement, in vitro diffusion and skin irritation. Thus, formulation and evaluation of miconazole gel was carried out successfully.

CONCLUSION

- Miconazole is an imidazoles derivative, used for the topical as well as systemic fungal infections. The bioavailability of miconazole is 90%. In the present study, an attempt was made to formulate topical gel of miconazole for efficient delivery of drug across the skin.
- A suitable method of analysis of drug was UV spectrophotometric. Miconazole showed maximum absorption at a wavelength of 272 nm in alcohol.
- Various formulations (F1, F2…F5) were developed by using Carbopol 940 for local release of miconazole for the treatment of fungal infections by using penetration enhancer Tween 80.
- Developed formulations of miconazole were evaluated for the physiochemical parameters such as drug content, viscosity, spreadability, in vitro diffusion.
- Viscosity studies of various formulations revealed that formulation F1 is better compare to others.
- Thus, the objective of the present work of formulation and evaluating of miconazole

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