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Research Article

FORMULATION OF KETOCONAZOLE OPHTHALMIC OINTMENT USING COW GHEE AS A BASE AND PENETRATION ENHANCER

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ABSTRACT

The present work is concerned with the study of cow ghee as penetration enhancer in ketoconazole ophthalmic ointment as an ointment base with respect to conventional ointment base. Ophthalmic ointment was prepared with 1% ketoconazole, 0.01% w/v Benzalchonium chloride and butylated hyroxytoluene B.P (0.02%) with cow ghee as a base as well as petrolatum base and investigated their usefulness in the ophthalmological field by evaluating pH, acid value, freeze thaw cycle, isotonicity, corneal toxicity and in vitro transcorneal permeation study using excised goat cornea. cow ghee is an effective penetration enhancer as an ointment base. The interaction study between ketoconazole and cow ghee were found to be negative. Evaluation parameters such as pH, acid value, freeze thaw cycle, isotonicity, were carried out. Overall results suggest that cow ghee is safe for use as a penetration enhancer in ophthalmic delivery system as an ointment base.

Keywords: Ketoconazole, penetration enhancer, goat cornea

INTRODUCTION

Amongst several physiological barriers in human body such as blood brain barrier, placental barrier etc. the 'Corneal Barrier' is equally important. It protects the inner structure of our eye from external object and infection. However it creates a problem by preventing many drugs from entering inside the eye beyond cornea. This is problematic because the major microorganism invading the structure of an eye includes 'fungi' and when this occurs, the antifungal drugs are unable to penetrate cornea leaving the infection untreated [1].

According to World Health Organization, corneal diseases are the major cause of vision loss and blindness. Fungal keratitis is the major cause of blindness in Asia and *Candida albicans* is a species which is responsible for fungal keratitis [2].

Ketoconazole is a known antifungal agent which is use for their superficial action as well as to treat the infection of the internal eye. It is a potent inhibitor of ergosterol biosynthesis in *Candida albicans* both in vitro and in vivo. Ergosterol is the major sterol found in most yeasts and fungi and by interfering with this major template for mycotic biosynthesis [3].
The ability of the compound to penetrate the eye is depending upon molecular mass, route of administration, duration of contact time. But the ketoconazole have a high molecular mass exceeding 500 Dalton, resulting in their poor penetration even if it is lipophilic in nature [4,5].

So it is necessary to enhance the penetration of the drug through transcorneal barrier to give its 100% action. By using penetration enhancers which possible to penetrate the drug through the corneal barrier.

It is therefore necessary to develop a formulation containing cow ghee as a key excipient through which the drug such as antifungal could penetrate corneal barrier. The cow's ghee contains several fatty acids with varying physiochemical properties. The lipoid nature of this substance aids passage of many drugs through many physiological barriers because the nature of barrier is also lipoidal [6].

Hence, the present work based on development of ophthalmic ointment using cow ghee as an excipient through which the drug such as antifungal could penetrate the corneal barrier.

MATERIAL AND METHOD

Ketoconazole was gift sample from Alkem Pharmaceuticals, Mumbai, India. Cow ghee was purchased from Madhuban dairy products, Nagpur (MS) India. Dichloromethane R) and Potassium dihyrogen phosphate (Merks Pvt.Ltd), Disodium hydrogen phosphate and Sodium chloride (Fisher Scientific India Pvt. Ltd) and all other chemical were analytical grade.

Fractination of cow ghee

The fraction of cow ghee $\geq 40^0$C, were carried out in B.O.D incubator (Thermotech TH-102) by maintaining the respective temperature up to 24hr. fraction were collected and filtered through Whatmann filter paper (no. 41)

Evaluation of cow ghee ($\geq 40^0$C)

Acid value

10.0gm of cow ghee $\geq 40^0$C was weighed accurately and dissolved in 50 ml of equal volumes of ethanol (95%) and ether, previously neutralized with 0.1M potassium hydroxide to

phenolphthalein solution in a 250ml borosilicate conical flask. To this solution, 1.0ml of phenolphthalein solution was added and titrated against 0.1M potassium hydroxide until the solution remains faintly pink till 30secs with shaking. The acid value was calculated from the expression

Acid value= 5.61n/w

Where,
n= the number of ml of 0.1M potassium hydroxide
w= the weight, in g, of the substance [7].

Saponification value

2.0gm of cow ghee (≥40^{0}C) was weighed accurately and transferred in 200ml borosilicate round bottom flask fitted with a reflux condenser. 25ml of 0.5M ethanol potassium hydroxide and a little pumice powder were added to this, refluxed for 30 mins on a water bath. 1ml of phenolphthalein solution was added and titrated immediately against 0.5M hydrochloric acid (a ml). Blank titration was also carried out omitting the ghee under examination (b ml). Saponification value was calculated from the expression

Saponification value=28.05(b-a)/w

Where,
w= weight, in gm, of the substance [8].

Interaction study of Ketoconazole and cow ghee (≥40^{0}C)

UV/Visible spectroscopy
Different ratios of ketoconazole : cow ghee (≥40^{0}C) (1:9, 2:8, 3:7, 4:6, 7:3, 8:2, 9:1) were prepared and each mixture was diluted in DCM to make concentration 100µg/ml and screened spectrophotometrically in the range of 200- 400nm wavelength.

Thermal Analysis (DSC) for cow ghee (≥40^{0}C)
A differential scanning calorimeter model DSC Shimadzu 60 with trend line software (Shimadzu Co., Kyoto, Japan) was used [9].

Formulation of ophthalmic ointment

Formulation of FCA (using cow ghee as base)
Required amount of ketoconazole and small amount of molten base (Cow ghee ≥40^{0}C) was triturated in sterilized mortar and pestle. Then remaining amount of base, benzalkonium chloride (0.01%w/v), butylated hyroxytoluene B.P (0.02%) were transfer to this, triturated thoroughly to room temperature. The ointment was stored in the glass vials for further study.

All operation has been carried out in a laminar flow for maintaining the aseptic condition [10].

Formulation of FCB (using Petrolatum base)
The Ointment was formulated using procedure same as given in With petrolatum base, instead of Cow ghee ≥40^{0}C .

Table 1: Formulae of Ketoconazole ophthalmic ointment

Name of Ingredients	FCA	FCB
Ketoconazole	1%w/w	1%w/w
Cow ghee fraction (base)	Up to100gm	-
Petrolactum base	-	Up to100gm
Benzalkonium chloride	0.01%w/v	0.01%w/v
Butylated hyroxytoluene B.P	0.02%	0.02%

Evaluation of ophthalmic preparation

Physical parameters

pH
pH values of FCA and FCB were measured in 1.0% aqueous solution using digital pH meter (NIG-333). The pH meter was calibrated by using standard buffer solution of pH-7 and pH-4 [11].

Freeze Thaw cycle
FCA and FCB (10.0gm) were employed as a thin layer in a beaker. Initial reading i.e. creaming and cracking were noticed if any. The sample was kept in the freezer (4^{o}C) for 24 hrs, removed and allowed it to thaw at room temperature. The same sample was then kept in oven (50^{o}C) for 24 hrs. Then the sample removed and allows it to equilibrate at room temperature. At the end of each cycle readings were recorded [12].

Isotonicity studies
FCA and FCB (10.0 mg) were mixed with 1-2 drops of blood on a microscopic slide and kept it side for 15 min, observed under microscope (Motic-2.0) at 45X magnification to see the shape of blood cell (bulging or shrinkage). The observations were compared with standard marketed ophthalmic formulation (ciprofloxacin ophthalmic ointment) [13].

Drug content of Ketoconazole
1gram of ointment was weighed accurately and transferred to a 100ml volumetric flask and volume was made up to 100.0ml with DCM. This was then filtered. 1 ml of the filtrate was taken and further diluted up to 10.0ml in 10 ml volumetric flask .The content was estimated using UV/ visible spectrophotometer at 230 nm [14].

In vitro Antifungal activity
In vitro antifungal test of standard Ketoconazole solution, FCA, and FCB were performed against *Candida albicans* by Agar diffusion (cup-plate method). 100µg/mL. concentration of Ketoconazole solution.

All the operations were carried out under aseptic conditions. The sterile medium was melted on water bath and kept at 45^0 c in constant temperature water bath. In each sterile petridish 25 ml of molten medium was added and subcultured organism under study was inoculated.

The culture and agar medium were mixed and allow solidifying. Five cups of 8 mm diameter was then made with the help of sterile stainless steel cork borer for the respective samples. Two drops of test solution was added to three cup, whereas standard solution was added in one cup and one cup was kept control. Solutions was allowed to diffuse in the medium for 2 hr by keeping the petridish at room temperature and then incubated for about 24 hr at 37^{0}C [15,16].

In vitro drug release studies of Ketoconazole, FCA and FCB

The release studies were carried out using Franz diffusion cell containing donor- receiver compartment model designed using goat corneal membrane. The diffusion cell has capacity of 20ml and surface area of 3.14 cm^2. The receptor compartment was filled with saline phosphate buffer (pH=7.4) with 1% sodium lauryl sulphate. The membrane was cut to a suitable size and placed between the two half cells of the separate cells. The lower part of the membrane was facing the receptor compartment. The cells were thermo stated at 37± 1^{o}c and receptor solution stirred with magnetic stirrer at 200 rpm.

1gm of FCA, FCB and one ml solution of Ketoconazole (1%w/w) were place on membrane surface of three separate donor compartment of three separate diffusion cells. One ml sample was withdrawn from each receptor compartment at 30, 60 90,120, 150, and 180 min intervals and was replaced with equal amount (1ml) of fresh buffer solution and the absorbance was taken on the UV spectrophotometer at 230 nm. Amount of drug release across the membrane was estimated by using standard calibration curve equation Y= 0.024x + 0.088 [17].

In -vivo eye irritancy test (Drained test in rabbit)

The optimized formulation was evaluated for in vivo performance in animal model (Rabbits). The protocol is approved by college ethical committee (Ethical committee Registration number is CPCSEA/ 729/02/a/CPCSEA)

Eye irritancy potential of a substance is evaluated on the basis of its ability to cause injury to the cornea, iris, and conjunctivae, on the application to the eye.

Ocular reaction was read with the controlled eye. Reading was noted at 1,4,24, 48 and 72 hrs after exposure [18, 19].

Accelerated Stability study

The stability study was carried out as per ICH and European guidelines at 40˚C ± 2˚C at 75 ± 5% RH for 30 days. The various parameters viz. appearance, pH, and % drug content has taken into consideration for the stability study [20, 21].

RESULT AND DISCSSION

Fractionation of cow ghee

Fraction of cow ghee (≥40^{0}C**)** was isolated. The objective of fractionation of cow ghee was to isolate suitable fractions depending upon the type of dosage forms such as ophthalmic ointment . Cow ghee (≥40^{0}C) is quite stable with the changes in temperature of environment.

Evaluation of cow ghee (≥40^{0}C)

Table 2: acid value and Saponification value of cow ghee (≥40^{0}C)

Test	Result	Limit
Acid Value	4.488	Less than 5
Saponification value	194.94	Less than 220

Interaction study of ketoconazole and cow ghee (≥40^{0}C)

UV/Visible spectroscopy

The UV visible spectrogram for different ratios of ketoconazole : cow ghee (≥40^{0}C) (1:9, 2:8, 3:7, 4:6, 7:3, 8:2, 9:1) were studied to see the interaction at different ratios of concentration. An overlay spectrum of different ratio shown in Figure 1 indicates that ketoconazole and cow ghee (≥40^{0}C) are compatible with each other

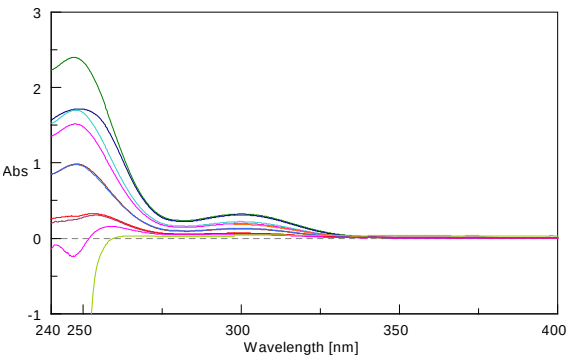


Figure 1: An overlay of mixtures of ketoconazole and cow ghee (≥40^{0}C)

From Figure 1 the absorption spectrum of different ratio does not show any significant changes as per as λmax of ketoconazole is concern. Slight changes was observed in absorption spectrum of 8:2 and 9:1 (ketoconazole and cow ghee), indicate interaction at this ratio.

Thermal analysis (DSC)

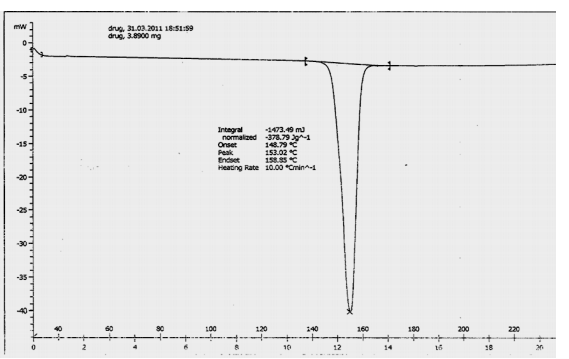


Figure 2: DSC thermogram of ketoconazole

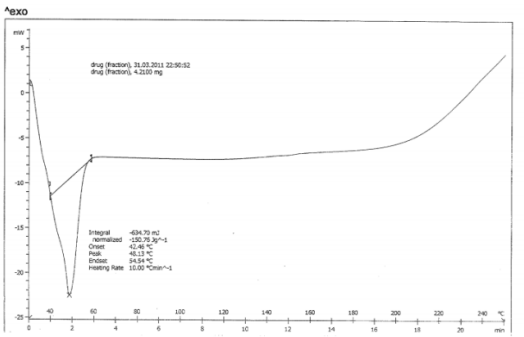


Figure 3: DSC thermogram of cow ghee (≥40^{0}C)

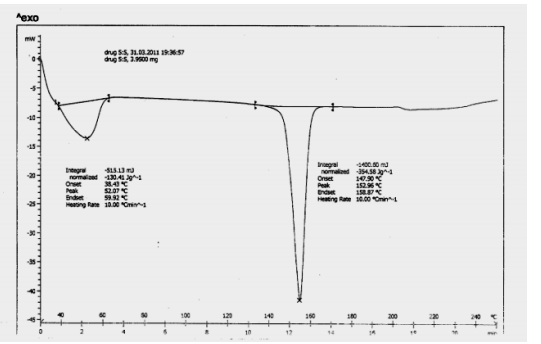


Figure 4: DSC thermogram of ketoconazole: cow ghee (≥40^{0}C)

Table 3: Result of Fusion temperature and Enthalpy of fusion of ketoconazole, cow ghee (≥40^{0}C), and ketoconazole : cow ghee (≥40^{0}C)

System	Fusion temperature (^{0}C)						Enthalpy of fusion (mJ)	
	Main peak		Onset		End set			
ketoconazole	153.02		148.79		158.85		-1473.49	
Cow ghee(≥40^{0}C)	48.13		42.46		54.54		-634	
	ketoconazole			Cow ghee (≥40^{0}C)			Ketoconazole	Cow ghee≥40^{0}C
	Main peak	Onset	End set	Main peak	Onset	End set		
Ketoconazole and cow ghee	152.96	147.90	158.87	52.07	38.43	59.52	-1400.60	-515.3

The melting point, onset temp, end set temp, and enthalpy of fusion are tabulated in Table 3, does not show any significant changes as per as the endothermic peaks of ketoconazole and cow ghee.

Evaluation of an ophthalmic ointment

Physical parameters

Table 4: Results of physical parameters

Sr. No.	Parameter	FCA	FCB
1	Color	Yellow	Yellow
2	Appearance	smooth	Smooth
3	Phase separation (centrifugation at 1000 rpm for 1hour)	-ve	-ve

The results are depicted in Table 4, both FCA and FCB were yellow in colour consistently smooth in appearance and found to be stable on centrifugation at 1000 rpm for 1hour.

pH

Table 5: pH values of FCA and FCB

Parameter	Formulation Code	
	FCA	FCB
pH	7.53	7.61
	7.55	7.59
	7.59	7.59
Mean	7.55	7.59
S.D (±)	0.0305	0.011

The values of pH shown in Table 5 indicate both formulation (FCA and FCB) has pH near as that of pH of lachrymal fluid (pH-7.4). FCA and FCB were found suitable for ophthalmic use depicted from the standard deviation as per as the pH is concern.

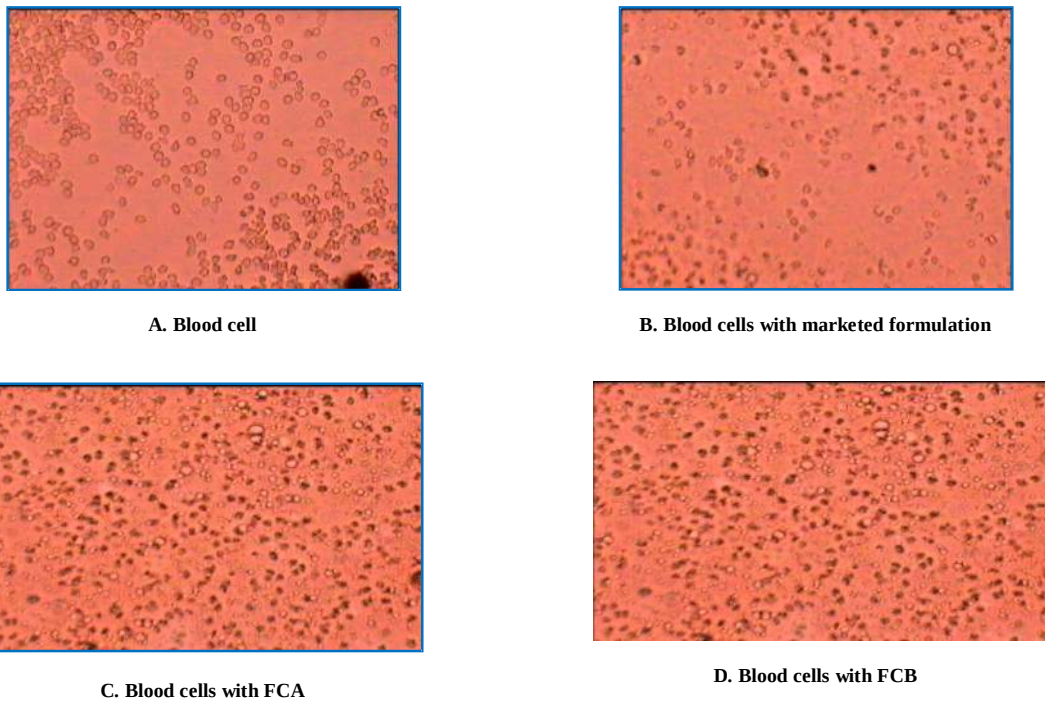
Freeze thaw cycle

Table 6: Observations of Freeze Thaw Test of FCA and FCB

Formulation	Temp	Observation(24 hrs)	
		Creaming	Cracking
FCA	4˚ C	-ve	-ve
	R T	-ve	-ve
	50˚C	-ve	-ve
FCB	4˚ C	-ve	-ve
	R T	-ve	-ve
	50˚C	-ve	-ve

Results from Table 6 inferred that FCA and FCB are thermodynamically stable. This prognosticates that all the components of the system are compatible with each other and form a single homogeneous phase. This may be due to nearly the same density of all ingredients which leads to physical compatibility results in stable ophthalmic preparation.

Isotonicity studies



A. Blood cell

B. Blood cells with marketed formulation

C. Blood cells with FCA

D. Blood cells with FCB

Figure 5: Photographs of blood cells during isotonicity test

Figure 5 indicate that FCA and FCB does not change the shape of blood cells (bulging or shrinkage) which reveals that both formulation were isotonic. The result are also compaired with that of marketed opthalmic ointment of ciprofloxacin and blood cells**.**

Chemical evaluation
Assay (Drug content)

Table 7: % Drug content of ketoconazole in FCA and FCB

Sr. No.	% Drug content	
	FCA	FCB
1	99.71	98.42
2	100.0	99.71
3	99.130	100.28
Mean	99.61	99.47
S.D.(±)	0.44	0.52

The drug content in FCA and FCB shows good agreement of result as per the % label claim is concern. The S.D. values are also below the limit

In vitro Antifungal activity

Table 8: Results of in vitro antifungal activity of FCA and FCB

Microorganism used	Zone of inhibition (mm)			
	Standard (100µg/ml)	Sample		
		FCA	FCB	Control
Candida albicans	27.33±0.57	24.66±0.47	21.33±0.65	13±0.76

The minimum inhibitory zone of ketoconazole solution was greater than FCA and FCB, may be due to direct exposure of ketoconazole to the fungi. In comparison of FCB, FCA shows most promising results. as per as the MIZ is concern, greater the area of MIZ obtained greater will be the infusibility and penetrability of ketoconazole from its formulation.

Biological evaluation
In vitro drug release studies

Table 9: Results of average % release of ketoconazole from ketoconazole solution through goat corneal membrane

Time(min)	Average % release Mean ± S.D
30	0.90 ± 0.138
60	7.77 ± 0.236
90	18.81 ± 0.15
120	30.41 ± 0.21
150	40.08 ± 0.105
180	60.13 ± 0.236

Table 10: Results of average % release of ketoconazole from FCA through goat corneal membrane

Time(min)	Average % release Mean ± S.D
30	2.15 ± 0.121
60	18.60 ± 0.433
90	27.84 ± 0.433
120	48.05 ± 0.320
150	61.38 ± 0.236
180	69.56 ± 0.180

Table 11: Results of average % release of ketoconazole from FCB through goat corneal membrane

Time(min)	Average % release Mean ± S.D
30	0.27 ± 0.120
60	7.77 ± 0.523
90	19.09 ± 0.315
120	32.56 ± 0.669
150	41.87 ± 0.625
180	59.23 ± 0.320

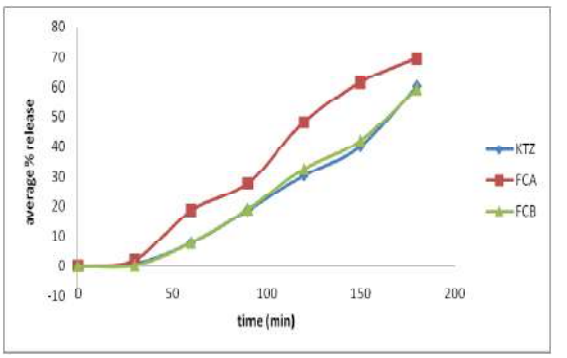


Figure 6: Graph showing comparative account on % release of ketoconazole solution, FCA and FCB

Table 9, 10 and 11 shows the results of an average % release of ketoconazole from ketoconazole solution, FCA, and FCB respectively and Figure 6 compare the release of ketoconazole from the system with time. The study revealed that the average % release of ketoconazole at 30 min and 180 min of FCA were 2.15 ± 0.121 and 69.56 ± 0.180 respectively. This may be attributed that incorporation of cow ghee in FCA facilitates the penetration of ketoconazole through corneal membrane. The S.D. was found to be ± 0.121 and ± 0.180 also support the assumption that cow ghee enhances the penetration of ketoconazole from FCA significantly. In support to average % release of ketoconazole from different system, apparent permeability coefficient of ketoconazole was also calculated. As per results are depicted in Table 10 and from Figure 6. it was observed that FCA has significantly greater penetration than FCB and ketoconazole solution at 30 mins. and 180 mins.

In - vivo eye irritancy test (Draize test in rabbit)
The scoring of the ocular lesions was done as per the follows

Table 12: Rabbit cornea observations for opacity and area of cornea involved

Opacity	Normal Rating For Opacity	Rating for FCA	
		R1	R2
No opacity	0 none	0	0
Diffuse area ,details of iris clearly visible	1 slight	0	0
Easily visible translucent areas, details of iris slightly obscure	2 mild	0	0
Opalescent areas, no details of iris visible,	3 moderate	0	0
Opaque, iris- invisible	4 severe	0	0
Area of cornea involved	**Normal Rating for corneal area involved**	**Rating for FCA**	
		R1	**R2**
25% or less (not 0)	1	0	0
25% to 50%	2	0	0
25% to 75%	3	0	0
Greater than 75%	4	0	0

R = Rabbit

Table 13: Scoring of conjunctiva

Redness	Normal Rating	Rating for FCA	
		R1	R2
Vessels normal	0 none	0	0
Vessels definitely injected above normal	1slight	0	0
More diffuse, deeper crimson red with individual vessels not easily dissemble	2 moderate	0	0
Diffuse beefy red	3 severe	0	0

R = Rabbit

Table 14: Scoring of iris

Values	Normal Rating	Rating for FCA	
		R1	R2
Normal	0 none	0	0
Fold above normal, congestion, swelling, iris react to light	1slight	0	0
No reaction to light, hemorrhage, gross destruction	2 severe	0	0

R = Rabbit

The total score for the eye is the sum of all scores obtained for the cornea, iris, and conjunctivae. The possible score would be 110. From the maximum score of 110 points, 80 points (73% of the total score) can result from the severity and size of the corneal opacity, 20 points from the conjunctiva irritation, and 10 points from the severity of iris.

From Table 12, 13 and 14 reveled that, the zero score in formulation FCA shows no irritation with no ocular damage or abnormal clinical signs to the cornea, iris or conjunctivae. Hence the formulation is suitable for the eye instillation.

Accelerated Stability study

Table 15: Accelerated Stability studies of FCA at 40˚C ± 2˚Cwith 75 ± 5% RH

Sr. No.	Parameters	One month		
		0 day	15 day	30 day
1	Appearance	No change	No change	No change
2	pH	7.53	7.52	7.54
3	Drug content	99.61	99.42	99.22

One month accelerated stability studies of FCA At 40˚C ± 2˚C and 75 ± 5% RH inferred that FCA is stable aesthetically as well as thermodynamically. The pH and drug content were also quite stable up to one month.

CONCLUSION

The present work comprises the formulation and evaluation of ophthalmic ointment of ketoconazole by using cow ghee ($\geq 40^0$c) as a base. The overall results suggest that, all evaluation parameters are satisfactory for ophthalmic ointment. The in-vitro diffusion study of ointment through goat cornea shows that the increase rate of permeation of ointment by using cow ghee as a base than petrolatum base.

Hence it may be concluded that cow ghee is a good penetration enhancer in ophthalmic ointments with cow ghee ($\geq 40^0$c) are suitable for formulation of ophthalmic ointment of ketoconazole as a base inferred from interaction studies, pH, viscosity, isotonicity studies, in-vivo eye irritancy test and stability studies.

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