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Formulation and Evaluation of Topical Anti Fungal Gel Containing Econazole Nitrate

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ABSTRACT

Objective: Thepresent researchhasbeen undertakenwiththe aimtodevelop a topicalgelformulation ofEconazole Nitrate.Econazole Nitrateisan imidazolederivativeandusedforthetreatmentoflocalandsystemicfungalinfection.TheoraluseofEconazole Nitrate isnotmuchrecommended..CommerciallyEconazole Nitratetopicalgelpreparationarenotavailableinthemarket,thusthisformulationismadeforbetterpatient compliance andtoreduce thedoseofthedrugandtoavoidthesideeffectslikeliverdamageandkidneydamage.

Methods: Thegelwasformulatedbychangingthepolymerratio.Variousformulation(F1 to F12)weredevelopedbyusingasuitable polymer(carbopol934p,Sodium alginate, DMSO ,HPMC, Triethanolamine).Theformulation wasevaluatedfor % drug content, Clarity, ph,spreadability,Extrudability andviscosityinvitrodrug releasestudy,stabilitytesting.

Results: ViscositystudiesofvariousformulationsrevealedthatformulationF5wasbettertocomparetoothers.FromamongallthedevelopedformulationF7 showsbetterdrugdiffusion,didgoodRheologicalproperties.pHoftheF9formulationissufficientenoughtotreattheskininfections.
Resultsindicatedthattheconcentrationofcarbopol-934andHPMCK4Msignificantlyaffectsdrugreleaseandrheologicalpropertiesofthegels.

Conclusion: ItwasconcludedthatformulationF2 AND F7wasthebestformulationamongthisformulation.

Keywords:Econazole Nitrate, Carbopol934p,HPMC ,DMSO

I. INTRODUCTION

Fungalinfectionoftheskinisnowadaysoneofthecommon dermatologicalproblems.Thephysicianshaveawidechoicefor treatmentfromsoliddosagetosemisoliddosageformandtoliquiddosageformulation. Among thetopical formulation, clear transparentgelshavewidelyacceptedinbothcosmetics and pharmaceuticals[1].Topicaltreatmentofdermatologicaldiseaseas wellasskincare,awidevarietyofvehicleranging fromsolidstosemisolidsandliquidspreparationsisavailabletocliniciansand patients.Withinthemajorgroupofsemisolidpreparations,theuseoftransparentgelshasexpandedbothincosmeticsandin pharmaceuticalpreparation[2].Formanydecadestreatmentofan acutediseaseorachronicillnesshasbeenmostlyaccomplishedbydeliveryofdrugstopatientsusingvariouspharmaceuticaldosageforms,includingtablets,capsules, pills,suppositories,cream,gel, ointments,liquids,aerosolsandinjectable,asdrugcarriers.Deliveryofdrugstotheskinisaneffectiveandtargetedtherapyforlocal dermatologicaldisorders.Thisrouteofdrugdeliveryhasgained popularitybecauseitavoidsfirst-passeffects,gastrointestinal irritation, andmetabolicdegradation associatedwithoral administration.Duetothefirstpasteffect,only25-45%oftheorally administereddosereachesthebloodcirculation.Inordertobypass thesedisadvantages,thegelformulationshavebeenproposedasa topicalapplication.Gelsaredefinedas“semisolidsysteminwhicha liquidphaseisconstrainedwithinapolymericmatrixinwhicha highdegreeofphysicalandchemicalcross-linkingintroduced”.

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Econazole Nitrateisasyntheticantifungalagentoftheimidazoleclass;it worksbyslowingthegrowthoffungithatcauseinfection.Itisused totreatfungalinfection.Triazoledrugtargetsthefungal-specificsynthesisofmembranelipids.Alkylation of imidazole (2) with bromoketone (1) prepared from o,p-dichloroacetophenone affords the displacement product(3).Reduction of ketone with sodium bromohydride gives the corresponding alcohol(4). Alkylation of the alkoxide from alcohol with p-chlorobenzyl chloride leads to Econazole (5).

II. MATERIALS AND METHODS[5,6]

Material

Econazole Nitrate,HPMC,carbopol934,triethanolamine,Methyl paraben,DMSO,Sodium alginate, water.

Method

It is performed by cold mechanical method Polymer(likeCarbopol934porHPMC)andpurifiedwaterwere takeninabeakerandallowedtosoakfor2h.Tothisrequired amountofdrug(2gm)wasdispersedinwaterandthenCarbopol 934porHPMCwasthenneutralizedwithsufficientquantityofTriethanolamine.Then approx. quantity of DMSO was added which behaves as penetration enhancer. Methylparaben as preservativeswereaddedslowlywithcontinuousgentlystirringuntilthehomogenous gelwasformed.

Table1:Optimizedformulaeof Econazole Nitrate gel

Constituents	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Econazole nitrate (gm)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Alginate (gm)	1	-	-	0.5	0.25	0.75	-	-	-	0.5	0.25	0.75
HPMC K4M (gm)	-	1	-	0.5	0.75	0.25	0.5	0.25	0.75	-	-	-
Carbopol 934 (gm)	-	-	1	-	-	-	0.5	0.75	0.25	0.5	0.75	0.25
Triethanolamine(ml)	.023	.023	.023	.023	.023	.023	.023	.023	.023	.023	.023	.023
DMSO (ml)	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Methyl Paraben (mg)	15	15	15	15	15	15	15	15	15	15	15	15
Water upto 100ml												

EvaluationofEconazole Nitrate gels

Drugcontent

Weighed10gmofeachgelformulationweretransferredin250ml ofthevolumetricflaskcontaining20mlofalcoholandstirredfor30min.Thevolumewasmadeupto100mlandfiltered.1mloftheabovesolutionwasfurtherdilutedto10mlwithalcoholandagain1mloftheabovesolutionwasfurtherdilutedto10mlwithalcohol.

Theabsorbanceofthesolution wasmeasuredspectrophotometricallyat260nm.Drugcontentwascalculatedbythefollowingformula

DeterminationofPh

Weighed50gmofeachgelformulationweretransferredin10mlof thebeakerandmeasureditbyusingthedigitalpHmeter. pHofthe topicalgelformulationshouldbebetween3–9totreattheskin infections.

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Spreadability
Thespreadabilityofthegelformulationwasdetermined,by measuringthediameterof1gmgelbetweenhorizontalplates(20×20cm2)after1minute.Thestandardizedweighttiedonthe upperplatewas125gm.

Extrudability
Thegelformulationswerefilledintoacollapsiblemetal tubeor aluminiumcollapsibletube.Thetubewaspressedtoextrudethe materialandtheextrudabilityoftheformulationwascheckked.

Viscosityestimation
TheviscosityofgelwasdeterminedbyusingaBrookfield viscometerDVIImodelwithaT-Barspindleincombinationwithahelipath stand.

a)**Selectionofspindle**:SpindleT95 wasusedforthemeasurement ofviscosityofallthe gels.
b)**Samplecontainersize**:Theviscositywasmeasured using50gm of gel filledin a 100mlbeaker.
c)**Spindleimmersion**:TheT-barspindle(T95)waslowered perpendicularinthecentretakingcarethatspindledoes nottouch thebottomofthejar.
d)**Measurementofviscosity**:TheT-barspindle(T95)wasusedfordeterminingtheviscosity ofthegels.Thefactorsliketemperature, pressureandsamplesizeetc.Whichaffecttheviscosityw asmaintainedduring theprocess. ThehelipathT-barspindlewas movedupanddowngivingviscositiesatanumberofpoin tsalongthepath.
Thetorquereadingwasalwaysgreaterthan10%.Theave rageofthreereadingstakeninoneminutewasnotedasthe viscosityofgels.

Invitrodiffusionstudy
In-vitro diffusion study was carried out for 4 hours using diffusion cell.The cumulative % amount of the drug release from the gel at the end of 240 mins was found to be 99.29 % in formulation F7 containing 0.5%w/w of Carbopol and HPMC K4M each. The cumulative % amount of the drug release from the gel at the end of 240 mins was found to be 75.01 % in formulation F12 containing 0.75% w/w of Sodium alginate and Carbopol 0.25% w/w.Individual gel formulations F1, F2 and F3 prepared by using 1% w/w of Carbopol, HPMC K4M and Sodium alginate. Showing the release of 93.71%, 97.58 and 92.55. Amongst which F2 showed the best and highest release of 97.58% was selected. In combination formulation F4, F7 and F10 (0.5% w/w of Carbopol, HPMC k4M and Sodium alginate) which showed the release of 90.95%, 99.29% and 78.53% out of which F7 was considered the best formulation for showing the release of 99.29%.Combination formulation F5, F8 and F11 (0.25% w/w of Carbopol, HPMC K4M and sodium alginate) which showed the release of 93.16%, 96.38 and 88.43%. out of which F8 showed the best release of 96.38%Combination formulation F6, F9 and F12 (0.75% w/w of Carbopol, HPMCK4M and sodium alginate) which showed the release of 90.14%,89.74% and 75.01%. out of which F6 showed the best release of 90.14%.

III. RESULTS AND DISCUSSION

FORMULATION CODE	% DRUG CONENT
F1	98.5%
F2	98.4%
F3	98.1%
F4	98.3%
F5	98.6%
F6	98.7%
F7	98.4%
F8	98.1%
F9	98.4%
F10	98.5%
F11	98.2%
F12	98.0%

Table2:Percentdrug content ofgelformulations

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FORMULATION CODE	pH
F1	6.8
F2	6.5
F3	6.7
F4	6.9
F5	6.2
F6	6.1
F7	6.6
F8	6.9
F9	6.3
F10	6.6
F11	6.9
F12	6.2

Table3:pHofgelformulations

FORMULATION CODE	VISCOSITY
F1	8952
F2	8120
F3	8631
F4	8222
F5	9321
F6	8887
F7	8140
F8	8824
F9	9113
F10	8871
F11	8952
F12	8761

Table4:Viscosityofgelformulations

FORMULATION CODE	SPREADABILITY
F1	18.60±0.0113
F2	24.9±0.0150
F3	18.03±0.0153
F4	25.80±0.0249
F5	28.20±0.052
F6	22.03±0.0301
F7	27.52±0.0262
F8	25.45±0.0150
F9	18.04±0.0112
F10	23.08±0.0053
F11	22.31±0.022
F12	18.70±0.0200

Table5:Spreadabilityofgelformulations

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Table6:Extrudabilityofgelformulations

FORMULATION CODE	EXTRUDABILITY
F1	++
F2	+++
F3	++
F4	++
F5	++
F6	++
F7	+++
F8	++
F9	+
F10	++
F11	++
F12	++

Table7:Clarityofgelformulations

FORMULATION CODE	CLARITY
F1	++
F2	+++
F3	++
F4	+
F5	++
F6	+
F7	++
F8	++
F9	+
F10	++
F11	++
F12	+

Excellent (+++), Good(++), Average(+), Poor(-)

IV. CONCLUSION

Variousformulation(F1 TO F12)weredevelopedbyusinga suitablepolymer (carbopol934pandHPMC). Preformulation studies on EN comply with the reported literature limits.The adopted method yielded uniform and reproducible release gel prepared using EN.The Average drug content, spreadability, viscosity, extradurbality, washability and in-vitro release were uniform and reproducible.The release was directly proportional to concentration of polymers used.The adopted methods yielded uniform and reproducible gel formulations with all the polymers used.Gel formulations prepared with carbopol 934 and HPMC K4M showed good homogeneity, no skin irritation, good stability, and antifungal activity. However, the carbopol 934 and HPMC k4m based gel proved to be the formula of choice, since it showed the highest percentage of drug release and good rheological properties. In-vitro release rate studies showed that the drug release were maximum from formulations F2 (containing 1% w/w of HPMC polymer) that is 97.58% and F7 (containing combination of 0.5% w/w Carbopol + 0.5 % w/w HPMC K4M polymers) that is 99.29%.It can be concluded from the present investigation that proper selection of polymers and drug is a prerequisite for designing and developing a topical drug delivery system. The IR and UV studies suggest that polymer selected i.e Carbopol 934, HPMC, sodium alginate were found to be compatible with the drug EN. The varying concentrations of the three polymers were found to affect the gel parameters like drug release, spreadability and its viscosity. Overall formulation F2 (containing 1% of HPMC polymer) and F7 (containing combination of 0.5% Carbopol + 0.5 % HPMC K4M polymers) based on diffusion release , viscosity and antifungal activity were found to be an excellent gels.The Selected best formulations F2 and F7 were found to follow zero order release followed by non fickian diffusion control mechanism (Higuchi's model).The combination of EN Carbopol 934, HPMC with DMSO provides results and no side effects such as skin irritation. All formulation containing triethanolamine, which act as a not only preservative but it also, acts as slight penetration enhancer didn't show any kind of interaction.Anti-fungal effects of gels had been observed just in 72 hours after inoculation. The % zone of inhibition of selected formulation F2 and F7 tested in Candida albicans was found to be good when compared to econazole nitrate alone.All the formulations were found to be stable over the storage period.

V. SUMMARY

In the present study an attempts were made to formulate and evaluate topical gels of Econazole Nitrate. In our preliminary study the standardization of Econazole Nitrate was carried out for purity and identity. Estimation of Econazole Nitrate was done in phosphate buffer pH 7.4 spectrophotometrically at 220nm. The formulation studies include identification, melting point, pH, solubility and In-vitro release studies were carried out.The gels of all formulation have acceptable physical parameters. The gels prepared by cold mechanical method showed drug content in the range of 98 ±0.0147 %, 98.9 ±0.0146%, in-vitro diffusion release of 88.43% to 99.29 %, viscosity was found in between 8874 cps to 9856 cps, Spreadability was found to be between 18.08 ±0.0152 to 27.72 ±0.0264,pH ranging between 6 to

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6.9. All the gels were evaluated for their appearance, pH, drug content, rheological properties,in-vitro release, stability studies and anti-fungal activity. Visually Carbopol gels were sparkling & transparent, HPMC gels were translucent, sodium alginate gels were translucent. The pH range of Carbopol gels, HPMC gels and sodium alginate gels were found to be suitable for topical application.The drug content of formulated gels found in the range of 98.1% and 98.96% respectively.The viscosity measurement was done for selected gels using Brookfield viscometer at room temperature.Which was found between8874 cps to 9856 cps.Anti-fungal activity of selected best gels was compared with Econazole nitrate using Candida albicans using cup plate method. The percentage of zone of inhibition observed for carbopol and HPMC in 0.5%w/w each and carbopol 1% w/w alone showed good results

SCOPE OF STUDY

Further studies can be carried out by using different proportions and different combination of natural, synthetic and semisynthetic polymers with econazole nitrate by other methods method.

The work can be extended to in-vivo studies by using Rabbit as animal model.

AUTHORSCONTRIBUTIONS

All the authorhavecontributedequally

CONFLICTOFINTERESTS

Declared none

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