International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1248-1268 www.ijprajournal.com ISSN: 2249-7781

# Design, Development and Evaluation of Microsponge Based Topical Drug Delivery System by Using Ciclopirox Olamine

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Date of Submission: 01-08-2021 Date of Acceptance: 18-08-2021

**ABSTRACT: -**
The present study involves design, development, and evaluation of Micropsonge based topical drug delivery system by using Ciclopirox Olamine as the active drug ingredient. The micro sponge formulation was prepared by Quasi- solvent diffusion method which contains internal, External phase and use of polymer. The optimized internal phase consists of Ethanol: Dichloromethane as a solvent in which drug get dissolved properly. Polyvinyl alcohol in water used as external phase and ethyl cellulose with optimized concentration was used as a polymer. Further the evaluation of the micropsonge was carried out by its particle size, production yield and loading efficiency. The Factorial design was carried out and the F5 batch was selected as the final batch among them, where the F5 batch showed the better results in comparison to its loading efficiency, production yield and particle size and in vitro dissolution study. The optimized micropsonge formulation were selected for preparation of gel using Carbopol 940 and evaluated for on pH, viscosity, spread ability and diffusion study. Based on results, the micro sponge-based topic gel of Ciclopirox olamine shows percent drug release of 94 % up to 8 hrs. The data obtained in this study shows that micropsonge based topical gel formulation are promising for controlled drug delivery, which can reduce dosing frequency and increase patient acceptance and bioavaibility.

**Keywords:** -Micropsonge, Formulation and Process variables, Factorial designing, Evaluation of micropsonge, Micropsonge loaded gel, Topical controlled release dosage form.

## I. INTRODUCTION: -

Fungal infections have become an issue of great concern round the world; it was estimated that over 40 million people do in fact suffer fungal infections both in developed and in developing countries (Gungor et al. 2013). The incidence of fungal infections is increasing at an alarming rate, presenting an enormous challenge to healthcare professionals (Espinel-Ingroff 2009; Garber 2001). The delivery of drugs through most used conventional preparations viz. creams, gels, lotions, emulsion, etc. limits the effectiveness of actives due to barrier properties i.e., epidermis of the skin which hinder the drug deposition. Thus, selection of proper carrier's extremely important by considering the view in the mind that they should increase drug deposition through topical formulations (Gennaro 2000; Allen et al. 2005). Topical agents are mainstays in both cosmetics and the treatment of dermatological disorders. Conventional dermatological products provide active ingredients in relatively high concentrations, but for a short duration. This may lead to a cycle of short-term over medication followed by long-term under medication (Maiti et al. 2011).Rashes or other serious side effects can occur when a more active ingredient penetrates into the skin (Amrutiya et al. 2009). Various controlled drug-delivery systems, such as microcapsules, microspheres, Nanoemulsion, liposomes and niosomes, have been investigated in order to maximize the duration of active ingredients being present either on the epidermis or within skin layers, while minimizing their transdermal penetration into the body. However, the release rate ofactive drugs from microcapsules cannot be controlled once the capsule wall is ruptured. Similarly, liposomes are relatively expensive, difficult to manufacture and have a low holding capacity of the active drug (Barel et al. 2005).

One of the novel techniques used to control the release of active ingredients from topical formulations is polymeric microspongebased drugdelivery(Chadawar and Shaji 2007). Microsponges are polymeric, porous, and tiny, sponge-like spherical particles. This system provides maximum efficacy, reduced irritancy, extended product stability, enhanced formulation flexibility, increased elegance and better esthetic properties. This delivery system contains a huge number of interconnecting voids within a non-collapsible structure that imparts a

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Volume 6, Issue 4 July-Aug 2021, pp: 1248-1268 www.ijprajournal.com ISSN: 2249-7781

large porous surface. It can absorb or entrap a wide range of pharmaceutical active ingredients and can be formulated into gels, creams, liquids, and powders (Nokhodchi et al. 2007). Being relatively large (5–300 um), upon topical application, microsponges do not pass-through SC and remain on the skin surface. The porous nature of microsponges favors controlled release of the encapsulated drug, leading to minimal accumulation of the drug in the epidermis and dermis.

Ciclopirox Olamine is a broad-spectrum antifungal agent active against a wide variety of fungi and yeasts. Ciclopirox olamine is a hydroxypyridone antifungal agent that acts by thought to act through the chelation of polyvalent metal cations, such as Fe3+ and Al3+. These cations inhibit many enzymes, including cytochromes, thus disrupting cellular activities such as mitochondrial electron transport processes and energy production.The current formulations of ciclopirox olamine has short biological half-life. Due to short biological half-life frequent dosing is required to achieved desired pharmacological effect. The current study was aimed to develop topical gel containing microsponge of Ciclopirox Olamine for controlled release of the drug with improved solubility, site specificity and patient acceptance.This investigation consisted of preparation,optimization, and evaluation of Ciclopirox olamine microsponges. $3^2$ Factorial design or response surface methodology was used to study the effect of factors (formulation and process variables) influencing responses {particle size, entrapment efficiency, and production yield} by carrying out limited no. of experiments. Further optimized microsponge formulation incorporate into hydrogel system to developed microsponge loaded topical drug delivery system.

## II. MATERIALS AND METHODS: -

**Materials:**

Ciclopirox Olamine IP was received as a gift sample from SrinivasaOrganics; Dichloromethane, Ethyl cellulose & Ethanol was supplied by S.D. Fine Chemicals, Mumbai; PolyvinylAlcohol, Sod. Hydroxide, MethylParaben, Triethanolamine,B.H.T&Carbopol 940 were supplied by Loba Chemicals, Mumbai; Glycerine supplied by MM Supplier; all other chemicals and solvents were of analytical grade.

**Method:**

**Methodof preparationof ciclopiroxolamine loaded microsponge**

Microspongewerepreparedbyquasiemulsionsolvent diffusionmethod(Jelvehgari et al. 2006)inwhichtwoimmiscible phases (internal and external phases) are emulsified with the aid of surfactant byreducingtheinterfacial tension. The quasi ESD method seemed to be promising for the preparation of Ciclopirox olamine loaded micropsonge as it is easy, reproducible, rapid and has the advantage of avoiding solvent toxicity (Comoglu et al 2003). In this present study, Dichloromethane: Ethanol was used as the solventwhich is capable of dissolving both drug and polymer ethyl cellulose. The internal phase consists of ethylcellulose (200 mg)which dissolves in Dichloromethane: Ethanol (6:6 ml) and actual amount of the drug (100mg) wasaddedtothissolution. This solution requires ultrasonicationfor20minutestoobtainhomogeneous solution.Add Glycerin (1 ml) to homogeneous solution which acts as a plasticizer. Thisinternal phase was added to 200 ml of distilled water containing PVA (50 mg) (which act as external phase)under stirring for 3 hrs. atroomtemperature at500 rpm tofacillated the evaporation of solventand formation of micro sponges. After evaporation ofDichloromethane: Ethanol, the micro sponges formed were filtered and washedwith distilled water. micro sponges were dried at room temperature for 12 hrs. and stored inclosedglass tubes.

**Optimization of Microsponges:**

**A. RationalforSelectionofIngredientsandProcess:**

Ethylcelluloseisaratecontrollingelement,itisinsolubl e, nonerodable andnon-degradable.Itisporousinnatureandallowsdiffusionan ditspH rangeisfrom6-7.Henceit‘s selected for preparation of micropsonge. Polyvinyl alcohol is used as the dispersion mediaor external phase. Glycerin was used as a plasticizer. quasi emulsion solvent diffusionmethod was chosen since it yields more uniform particles. The method is referred as O/W (oilinwater)sinceapolymericsolutioninorganicsolve ntisconsideredasaoilinmicroencapsulationterminolo gy.

**B. SelectionofIndependentVariables:**

Followingaretwoindependentvariables,whichweres electedinthisstudy-

1. Polymerconcentration(i.e., Ethylcellulose)
2. Stirringspeed

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Volume 6, Issue 4 July-Aug 2021, pp: 1248-1268 www.ijprajournal.com ISSN: 2249-7781

Polymer concentration (i.e., Ethyl cellulose) affects the particle size, % entrapment efficiencyand drug release characteristics of drug. Stirring speed affect also particle size, productionyield etc. A significant decrease in the rate and extent of drug release was observed withincrease in polymer concentration in micropsonge could be attributed to increase on densityof polymer matrix and increases in the diffusional path length which the drug moleculeshave to traverse. Therefore, these parameters are chosen for optimization of micropsongecharacteristics.

## C. OptimizationofProcessParameters:

Duringoptimizationofvariousparameters,theprocess parameterswhoseeffectwasmeasuredarevariedwhile otherprocessparametersaremaintainedconstantdurin gpreparation of micropsonge. The final product was evaluated for their morphology, physicalcharacteristics, production yield, actual drug content, entrapment efficiency and mean particlesize.

**1)Selection of Internal Phase:**

**A]Experimental**

For the selection of the internal phase, the various investigations were carried out usingdifferent internal phase solvent with constant drug to polymer ratio of 1:1 and the stirringspeedof500rpmforaperiodof3hrs.Thecompos itionofexternalphasewaskeptconstantfor all batches i.e., 0.025%PVA solution in 200ml distilled water. Initial selections of theinternal phase solvent were based on the solubility of theCiclopirox olamine and Ethylcellulosepolymer.

### 1) Effectofvolumeof theInternalPhase:

**A]Experimental**

Five different volumes 4,6 and 8 ml were taken to study the effect of volume of internalphase solvent (dichloromethane and combination of dichloromethane and ethanol) on the micropsonge formulations A-1, A-2, A-3,A-4, A-5andA-6. Themicropsongepreparedwereevaluatedfortheirmor phology,physicalcharacteristics,particlesize,product ionyield and entrapmentefficiency.

**Tableno.1:Formulationtableof batchestostudyeffectofvolumeof theinternalphase**

| **Components** | **Formulationcodeandamount** | | | | | |
|---|---|---|---|---|---|---|
| | **A-1** | **A-2** | **A-3** | **A-4** | **A-5** | **A-6** |
| Ciclopiroxolamine(mg) | 100 | 100 | 100 | 100 | 100 | 100 |
| Ethylcellulose(mg) | 100 | 100 | 100 | 100 | 100 | 100 |
| **Dichloromethane(ml)** | **4** | **6** | **8** | **4** | **6** | **8** |
| **Ethanol (ml)** | **0** | **0** | **0** | **4** | **6** | **8** |
| Glycerin (%) | 1 | 1 | 1 | 1 | 1 | 1 |
| Polyvinylalcohol(mg) | 50 | 50 | 50 | 50 | 50 | 50 |
| DistilledWater(ml) | 200 | 200 | 200 | 200 | 200 | 200 |

### 2) Selection and study of the effect of External Concentration – Polyvinyl Alcohol [PVA]:

**A]Experimental:**

Toknowtheoptimumconcentrationofsurfact antrequiredfortheformationofmicropsonge; different concentration of polyvinyl alcohol such as 25mg, 50mg, 75mgand100mg in 200 ml of distilled water was used as external phase. Also, one formulation wasprepared without using PVA. Drug to polymer ratio and stirring speed and other parameterswere kept constant. These formulations were coded as B-1, B-2, B-3, B-4 andB-5.

**Tableno.2:FormulationtableofbatchestoStudytheeffectofSurfactantConcentration as External Phase**

| **Components** | **Formulationcodeandamount** | | | | |
|---|---|---|---|---|---|
| | **B-1** | **B-2** | **B-3** | **B-4** | **B-5** |

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| | | | | | |
|---|---|---|---|---|---|
| Ciclopiroxolamine(mg) | 100 | 100 | 100 | 100 | 100 |
| Ethylcellulose(mg) | 100 | 100 | 100 | 100 | 100 |
| Dichloromethane(ml) | 6 | 6 | 6 | 6 | 6 |
| Ethanol (ml) | 6 | 6 | 6 | 6 | 6 |
| Glycerin(%) | 1 | 1 | 1 | 1 | 1 |
| **Polyvinylalcohol(mg)** | **00** | **25** | **50** | **75** | **100** |
| DistilledWater(ml) | 200 | 200 | 200 | 200 | 200 |

**3) EffectofdrugtoPolymerRatio:**

**A]Experimental**

The drug and polymer in the ratios 1:1, 1:2, 1:3,1:4 and 1:5 was taken to prepare differentmicropsongeformulations.Ineachformulation,theamountsofdrug(100mg),dichloromethane and ethanol(6ml),PVA(0.025%w/v)werekeptconstant.Thehemicropsongeformulations were prepared using mechanical stirrer (Remi RQT127-D) at a stirring rate of500 rpm for 3 hours. The prepared batches C-1, C-2, C-3, C-4and C-5wereanalyzedforphysicalproperties,particlesize,productionyield,andentrapmentefficiency.

**Tableno.3:Formulationtabletostudyeffectofdrugtopolymer ratio**

| **Components** | **Formulationcodeandamount** | | | | |
|---|---|---|---|---|---|
| | **C-1** | **C-2** | **C-3** | **C-4** | **C-5** |
| Ciclopiroxolamine(mg) | 100 | 100 | 100 | 100 | 100 |
| **Ethylcellulose(mg)** | **100** | **200** | **300** | **400** | **500** |
| Dichloromethane(ml) | 6 | 6 | 6 | 6 | 6 |
| Ethanol (ml) | 6 | 6 | 6 | 6 | 6 |
| Glycerin(%) | 1 | 1 | 1 | 1 | 1 |
| Polyvinylalcohol(mg) | 50 | 50 | 50 | 50 | 50 |
| DistilledWater(ml) | 200 | 200 | 200 | 200 | 200 |

**Optimization of formulation using$3^2$factorialdesigns:**

**Tableno.4:Variables in$3^2$factorialdesigns**

| **IndependentVariables** | **LevelsUsed** | | |
|---|---|---|---|
| | **-1** | **0** | **+1** |
| X1= Polymer concentration | 100 | 200 | 300 |
| X2=Stiringspeed | 300 | 500 | 700 |

**ResponseVariables:**

Y1 = Mean Particle SizeY2=PercentageYield
Y3=EntrapmentEfficiency

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**Tableno.5.:ExperimentalRuns For$3^2$FactorialDesign**

| Batch Code | X1 | X2 | Ethyl Cellulose Concentration(mg) | StirringSpeed (rpm) |
|---|---|---|---|---|
| F1 | -1 | -1 | 100 | 300 |
| F2 | 0 | -1 | 200 | 300 |
| F3 | +1 | -1 | 300 | 300 |
| F4 | -1 | 0 | 100 | 500 |
| F5 | 0 | 0 | 200 | 500 |
| F6 | +1 | 0 | 300 | 500 |
| F7 | -1 | +1 | 100 | 700 |
| F8 | 0 | +1 | 200 | 700 |
| F9 | +1 | +1 | 300 | 700 |

**Tableno.6.:Bill of Material for Ciclopirox olamine loaded microsponge formulation**

| Sr. No | BOM | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| **Internal Phase** | | | | | | | | | | |
| 1 | Drug (mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Ethyl cellulose (mg) | 100 | 200 | 300 | 100 | 200 | 300 | 100 | 200 | 300 |
| 3 | Glycerin (ml) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | DCM (ml) | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 5 | ETOH (ml) | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| **External Phase** | | | | | | | | | | |
| 6 | PVA (mg) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 7 | Water (ml) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| **Process Parameters** | | | | | | | | | | |
| 1 | Stirring Time(RPM) | 300 | 300 | 300 | 500 | 500 | 500 | 700 | 700 | 700 |

**Characterisationofmicrosponges:**

**1. Visual appearance**

Themicro spongeswereobservedfortheircolor.

**2. Theoretical tiled**

Theoretical Yield= Actual amount of drug added+ Actual amount of polymer added

**3. Practical yield**

Determination of dried micro sponges recovered form batch.

**4. PERCENTYIELD**

Thepercentageofproductionyield(wt/wt)wascalculatedfromtheweightofdriedmicro sponges (W1) recovered from batches and the sum of initial dry weight of startingmaterials(W2) as the following equation:

$$\%\text{Productionyield} = \frac{W1 \times 100}{W2}$$

theyields of production were calculated as the percentage weight of the final product afterdrying, with respect to the initial total amount of Ciclopirox olamine and polymers used forpreparation.

**5. Particle size analysis**

Determinationofaverageparticlesizeofmicro spongeswascarriedoutbyopticalmicroscopy in which stage micrometer was employed. A minute quantity of micro spongeswas spread on a glass slide and average size of 200 micro sponges was determined in eachbatch.

**6. Theoreticaldrugloading**

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Theoretical drug loading was determined by calculation assuming that the entire Ciclopiroxolaminepresentinthepolymersolutionused wasentrappedinCiclopiroxolaminemicro sponges and no loss was observed at any stage of preparation of Ciclopirox olaminemicro sponges

**7. Actualdrug loading**

Weighed amount ofCiclopirox olamine micro sponges equivalent to 100 mg of Ciclopiroxolaminewasdissolvedin100mlofphosphat ebufferpH6.8.Thissolutionwaskeptovernight for the complete dissolution of ciclopirox olamine in phosphate buffer pH6.8. Thissolution was filtered and diluted to make a conc. of 6 µg/ml solution. The absorbance of thesolutions was measured at 311nm using double beam UV- Visible spectrophotometer againstphosphate buffer pH 6.8 as blank and calculated for the percentage of drug present in thesample.

**8. Entrapmentefficiency**

**Entrapmentefficiency=Actualdrugloading× 100**
**Theoreticaldrugloading**

**9. Invitrodrugreleasestudy**

In the present study, the USP apparatus II was used. The micro sponges equivalent to 100 mgCiclopirox olamine were placed directly in a dissolution chamber. The dissolution test wasperformed using 900 ml of phosphate buffer pH 6.8, at 37±0.5$^0$ C and 100 rpm. A sample of 5ml of the solution was withdrawn from the dissolution apparatus at certain intervals for 8 hrs and diluted to 10 ml,andthe samples were replaced with fresh dissolution medium to maintain sink condition. thesamples were filtered through 0.45-micron filters. Absorbance of these solutions measured at311nm.Cumulativepercentagedrugreleasewascalc ulatedusinganequationobtainedfromastandardcurve.

**10. Model fitting**

The Model fitting for % cumulative release was done using PCP Disso software to find thebestfits kineticequation for thedissolution profile.

**Kineticsofdrugrelease:**

To understand the mechanism and kinetics of drug release, the results of the in vitrodissolution study of the optimized batch of micro sponges (batch) were fitted with variouskineticequations. The coefficient of correration (R2) values were calculated forthe linear curves obtained byregressionanalysis of the aboveplots.

**Characterization of final optimized batches**

**a. Compatibilitystudy by FTIR**

FTIR measurements of drug, Ethyl cellulose and optimized micro sponge formulation (F5) was obtainedon FTIR 8400S Shimazdu. Samples were prepared by mixing with KBr (2mg sample in 200mgKBr) and placing in the sample hold (Orlu et al. 206). The spectra were scanned over the wave numberrangeof 4000-400 cm$^{-1}$at ambient temperature and shown in **figure no.9, 10 and figure no 11 respectively.**

**b. Differentialscanningcolometry(DSC):**

Thermalanalysisofdrug and final optimized micropsonge formulationwascarriedoutusingaMettlerToledoCom pany,Model–SW920. The thermal endotherm was shown in **figure no. 12 & 13**

**c. X-RAYpowderdiffractometry(XRD)**

X-Ray Diffractometry (XRD) was carried out to investigate the effect of micropsonge processon crystallinity of drug. Powder (XRD) patterns were recorded on Bruker D8 Advanced analyticalinstruments pvt. Ltd, Pune D2 phaser-based diffractometer. The XR patterns of drug and micro sponge wererecorded and shown in **figure no. 14 and 15 respectively.**

**a. Surfacemorphology(SEM)**

Scanning electron microscopy has been used to determine particle size distribution, surfacetopography, texture and to examine the morphology of fractured or sectioned surface. SEM isprobably the most commonly used method for characterizing drug delivery systems, owing inlarge to simplicity of sample preparation and ease of operation. SEM studies were carried outby using JEM 6100 (JEOL) scanning microscope (Chandigarh). Dry micro sponges were placedon an electron brass stub and coated with in an ion sputter. Picture of Drug and micro sponges weretaken byscanning of stub. And shown in **figure no. 16 (A), (B), (C), (D) respectively.**

**Formulationofgelofoptimizedbatch:**

**MethodofPreparation:**

All the ingredients were accurately weighed. Carbopol 940 was soaked overnight withdistilled water to hydrate and then hydrated Carbopol was again dispersed in distilled water bystirringonmagneticstirrerforabout1hour,thenprop yleneglycolalongwithotherexcipientssuchasButylat edHydroxyTolueneandMethylparabenwereaddedwi thcontinuous stirring to the Carbopol 940 solution. Then mixture was neutralized by drop-wiseaddition of triethanolamine whichactas neutralizing agent. Mixing was continued untiltransparent gel appeared, while amount of base was adjusted to achievea gel with pH valueofabout 6.1.

A] IncorporationofMicro spongesintotheGel:

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The prepared Micro sponges equivalent to 100 mg was weighed anddispersed into Carbopol gel with continuous stirring on magnetic stirrer for 20 minutes to getuniformlydistributed micro sponges into the gel base. (Shaikh et al. 2010)

**Table.no.6:Formulationtableforgel**

| Sr.no. | Components | Micropsonge Batch |
|---|---|---|
| 1 | Micro sponges equivalent to 100 mg drug (F5)(mg) | 300 |
| 2 | carbopol-940(mg) | 800 |
| 3 | propyleneglycol(gm) | 2.0 |
| 4 | ButylatedHydroxyToluene(mg) | 10 |
| 5 | Methylparaben(mg) | 10 |
| 6 | Triethanolamine | Qs |
| 7 | DistilledWaterup to10ml | Qs |

**Evaluation of gel:**

**1. Physicalexamination:**

Thepreparedgelformulationswereinspectedvisuallyfortheircolor,homogeneity,consistency,and appearance.

**2. pH:**

ThepHvaluesof1%aqueoussolutionsofthepreparedgelsweremeasuredbyaDigitalpHmeter.

**3. Viscosity:**

ViscosityofpreparedgelsweremeasuredbyBrookfield-DV-II+ProViscometer.

Apparentviscositymeasured at 25°C byrotating the spindleno.7 at0.5 rpm.

**4. Spread ability:**

It was determined by wooden block and glass slide apparatus. It consists of two parallelplaced platforms to hold the glass slides. It is because of these parallel placed platforms thatthe upper slide will be pulled in a straight line when force is applied. A pulley is centrallyattached to the upper slide. Scale is fixed on one of the platforms to measure the time taken tomove the slide a fixed distance. Weights about 20g were added to the pan and the time werenotedfor upper slide(movable) to separatecompletelyfrom thefixed slides.

**5. In-vitrodiffusionstudy:**

**A]Experimental:**

Thediffusionstudywascarriedoutbyusing Franzdiffusioncellandbyusingcello phonic membrane. The vertical type of Franz diffusion cell was designed, fabricated, andvalidated.Beforediffusionstudythecello phonicmembraneofapproximately2.5cm²areawas taken and these slices were hydrated in phosphate buffer (pH-6.8) overnight prior to use.The whole cell was assembled, then 100 mg of gel sample was applied on the surface of themembranewhichistiedtothelowerendofdonorcompartment. Thevolumeofthereceptor was kept 25ml.The cell was assembled in such way that, the membrane surface just flushed tothe surface of the permeation fluid (phosphate buffer pH-6.8) maintained at 37°±1°C andstirred continuously on magnetic stirrer at 50 rpm. The aliquot of 1ml was withdrawn andanalyzed for the drug content by spectroscopic method. The volume of the fluid was replacedwith the same volume of fresh buffer after each sampling. The samplings were done at 0.5, 1,2, 3, 4, 5, 6, 7, and at 8 hours for each gel formulation. The cumulative percentage drugdiffusedacross themembranewascalculated ateach samplingpoint and recorded.

## III. RESULT AND DISCUSSION: -

**Drug Authentication:**

The ciclopirox olamine observes as white crystalline molecule with melting point of $143^0$c and solubility was determine using shake flask method in distilled water (1 mg/ml),

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dichloromethane (17 mg/ml), ethanol (20 mg/ml). The calibration curve was plotted at 311 nm in water and phosphate buffer pH 6.8.

**Optimization of Micro sponges**

**C) Optimizationofprocessparameters**

**1) Selectionof internalphases:**

Theeffectof4differentsolventsystemswhich werepriorselecteddependinguponsolubility of drug as well as polymer: namely Ethanol, Dichloromethane, Acetone and combinationofEthanol and Dichloromethane.In case of Acetone, there is no formation of small, discrete, spherical, polymericparticles. The product obtained was in the form of lump or irregular in shape. In case of Dichloromethane, the yield was good, but it is notconsistent. While in case of Ethanol and Dichloromethane; the characteristic product was formedwhicharespherical, uniform, smalland freeflowing in nature.

**Discussion**

The solvent used as internal phase for dissolving the polymer as well as drug is very criticalstepintheformulationbecausethenatureandmiscibility oftheinternalphasesolventinfluences the diffusion process which further affect the formation of small discrete micro-particles. From result obtained it was found that combination of ethanol and dichloromethane as an internal phase givecharacteristic product, thus it was selected as internal phase solvent for the preparation ofmicro spongesofCiclopirox olamine.

**2) Effectofvolumeof theinternalphase:**[49]

**Tableno.7.:Effect ofvolumeoftheinternalphase**

| Analytical Data | Formulation Code (For optimization of Internal Phase) | | | | | |
|---|---|---|---|---|---|---|
| | A1 | A2 | A3 | A4 | A5 | A6 |
| **Analytical Data** | | | | | | |
| Visual Appearance | Drug and Polymer does not get properly dissolved. | | | Drug and polymer get dissolved properly | Drug and polymer get dissolved properly. When poured in PVA uniform fine complexation observed. | Drug and polymer get dissolved properly but when added in PVA it causes more dispersion. |
| Theoretical Yield (D+P) | 200 | 200 | 200 | 200 | 200 | 200 |
| Practical Yield (mg) | 96 | 87 | 67 | 126 | 131 | |
| Production Yield | 48.5 | 43.5 | 33.5 | 63 | 65 | |
| Theoretical drug content (%) | 50 | 50 | 50 | 50 | 50 | |
| Actual Drug Content (%) | Not done | | | 30.05 | 33.9 | |
| Encapsulation efficiency | | | | 60.1 | 67.8 | |
| Particle Size | 65 um | 80 um | 105 um | 38 um | 24.3 um | Not done |

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**Discussion:**

As increase in DCM content decrease in practical yield and increase in Particle size due to more emulsification and only solidification of drug and polymer. While in DCM and Ethanol Ratio (4:4), particle size is greater than 6:6 ratio is due to might be solubilization of drug and polymer in internal phase. (As drug and polymer get easily dissolved in 6:6 ratio than in 4:4 ratio so Batch A5 is selected for further study) Even we tried 8:8 ratio of DCM and ethanol but more dispersion observed with solidification of drug and polymer.

**3) Studytheeffectofsurfactantconcentration–polyvinylalcohol[PVA]:**

**Tableno.8:Effectofsurfactantconcentration–polyvinylalcohol[PVA]**

| Analytical parameters | Formulation Code (For optimization of Internal Phase) | | | | |
|---|---|---|---|---|---|
| | **B1** | **B2** | **B3** | **B4** | **B5** |
| **Analytical Data** | | | | | |
| Visual Appearance | No Yield | Micro sponge formed | | | |
| Theoretical Yield (D+P) | | 200 | 200 | 200 | 200 |
| Production Yield | | 78.16 | 73.12 | 65.77 | 48.05 |
| Theoretical drug content (%) | | 50 | 50 | 50 | 50 |
| Actual Drug Content (%) | | 41.08 | 34.23 | 31.18 | 29.8 |
| Encapsulation efficiency | | 81.08 | 68.46 | 62.36 | 59.11 |
| Particle Size | | 45.21 | 21.52 | 54.88 | 62.14 |

**Discussion:**

ThePVAsignificantlypreventedtheaggregationofthe dropletswithsolidifiedoutershellduringprocess. Thedispersion oftheinternal phasecontaining drugand polymer; intothe droplets depended on concentration of PVA in the external phase medium; hence when PVAconcentration was increased in dispersed phase, the particle size of micro sponges decreasedbut up to certain concentration of PVA; further increased in PVA concentration; increasesviscosity of external phase which lead to formation of larger globules during dispersion ofsolvents,thusresultedinincreasedparticlesizeofmicropsonge.IncreasedPVAconcentrationincreasessolubilizationofdrugintoexternalphase.Duetoincreasedsolubilization of drug in water, less amount of drug is made available for encapsulation thusdecreases productionyield and encapsulation efficiency so the 50 mg concentration of PVAin 200 ml Distilled water was found to be optimum and selected for further formulation ofmicro sponges.

**4) Effectofdrugtopolymerratio:**

**Tableno.9.:Effectofdrugtopolymerratio**

| Analytical Parameters | Formulation Code (For optimization of Internal Phase) | | | | |
|---|---|---|---|---|---|
| | **C1** | **C2** | **C3** | **C4** | **C5** |
| **Analytical Data** | | | | | |
| Visual Appearance | Micro sponge formed | | | | |
| Theoretical Yield (D+P) | 200 | 300 | 400 | 500 | 600 |
| Practical yield (mg) | 134 | 212 | 295 | 396 | 495 |
| Production Yield (%) | 67 | 70.66 | 73.75 | 79.2 | 82.5 |
| Theoretical drug content (%) | 50 | 33.33 | 25 | 20 | 16.66 |
| Actual Drug Content (%) | 34.88 | 27.5 | 21.5 | 18.09 | 15.21 |
| Encapsulation efficiency | 69.76 | 82.5 | 86 | 90.45 | 91.29 |
| Particle Size | 23.14 | 30 um | 68 um | 135 um | 205 um |

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**Discussion:**

Increased Production yield & Entrapment is due fact that the amount of polymeris increasedwith increased ratio of drug to polymer[57]. It was observed that as drug to polymer ratioincreases the particle size increased; this is probably due to fact that at higher relative drugcontent; the amount of polymer available per micropsonge to encapsulate the drug becomemore,thusincreasesthicknessofthepolymer wallandhencelargerthesizeofmicro sponges.

**Characterizationofmicrosponges:**

**Table No. 10 Characterization of factorial batches**

| Sr. No | Analytical Parameters | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| **Analytical Parameters** | | | | | | | | | | |
| 1 | Description | **Themicro sponges were foundtobe in white in color.** | | | | | | | | |
| 2 | Theoretical Yield (mg) | 200 | 300 | 400 | 200 | 300 | 400 | 200 | 300 | 400 |
| 3 | Practical Yield (mg) | 110 | 177 | 248 | 121 | 208 | 284 | 86 | 146 | 218 |
| 4 | Percentage Yield (%) | 55 | 59 | 62 | 60.5 | 69.33 | 71 | 43 | 48.66 | 54.5 |
| 5 | Theoretical Drug Content (%) | 50 | 33.33 | 25 | 50 | 33.33 | 25 | 50 | 33.33 | 25 |
| 6 | Actual Drug Content (%) | 31.82 | 23.75 | 21.29 | 33.57 | 26.21 | 22 | 31.47 | 23.4 | 19.54 |
| 7 | Encapsulation Efficiency (%) | 63.64 | 71.25 | 85.16 | 67.14 | 78.63 | 88 | 62.94 | 70.20 | 78.16 |
| 8 | Particle Size (um) | 24.5 | 27.84 | 61.3 | 22.4 | 25.3 | 65.2 | 28.5 | 31.6 | 69.3 |

**3. Practical yield:**

The practical yield was influenced by the polymer concentration and the stirring speed in the formulation.

**Effect of polymer concentration:** As drug: polymer ratio increased the practical yield also increased due to the reduced diffusion rate of internal phase from concentrated solution into aqueous phase this provide more time for the droplet formation and improve yield of micro sponges.

**Effect of stirring speed:** It was observed that at higher stirring rates due to the turbulence created within the external phase, polymer adhered to the paddle and practical yield decreases.

**4. Percentageyield**

The percentage yield was influenced by the polymer concentration and the stirring speed in the formulation.

**Effect of polymer concentration:** As drug: polymer ratio increased the % yield also increased due to the reduced diffusion rate of internal phase from concentrated solution into aqueous phase this provide more time for the droplet formation and improve yield of micro sponges.

**Effect of stirring speed:** It was observed that at higher stirring rates due to the turbulence created within the external phase, polymer adhered to the paddle and production yield decreases.

**5. Particle size analysis**

The mean particle size ranged from 22.40 µm-69.30 µm. The mean particle size was influenced by the polymer concentration and the stirring speed in the formulation.

**Effect of polymer concentration:**In high drug: polymer ratio, the amount of polymer per micro sponges is more. when dichloromethane: ethanol diffuses out nearly all of the dispersed phases is converted to the form of solid micro sponges and separated particles appear. Therefore, in high drug: polymer ratio more polymer surrounded the drug and increases the particle sizes of micro sponges

**Effect of stirring speed:**As agitation speed increases the size of micropsonge was reduced for

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until some speed e.g when the rate of stirring increased from 300-500 rpm the mean particle size was decreased but as again agitation increases more than 500 rpm particle size increases

**7. Actualdrug loading**

The Actual drug loading was influenced by the polymer concentration and the stirring speed in the formulation.

**Effect of polymer concentration:** As drug: polymer ratio increased the drug loading also increases up to certain level

**Effect of stirring speed:** It was observed that at higher stirring rates due to the turbulence created within the external phase, polymer adhered to the paddle and production yield decreases as well as coating is observed proper so drug get release easily through polymer coating.

**8. Entrapmentefficiency**

Entrapmentefficiencyofallformulationareshowninta ble.TheEntrapmentefficiencywasinfluencedbytheet hylcellulosepolymerconc.andstirringspeed. EntrapmentEfficiencyimprovedbygreaterproportion ofpolymerwithrespecttoamountofdrugavailable,hen cemorepolymerscan entrapmoredrugparticle, i.e. moreamount of polymerpresentper unitdrug.

**9. InVitroDrug Releaseand releasekineticstudy:**

**Tableno 11:InVitroDrugReleaseprofileforciclopiroxolaminemicrosponge**

| Time (hrs.) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 19.45 ±0.487 | 10.58 ±0.612 | 7.12 ±0.545 | 9.23 ±0.675 | 5.10 ±0.522 | 4.68 ±0.486 | 11.74 ±0.635 | 5.85 ±0.701 | 4.99 ±0.548 |
| 1 | 31.12 ±0.476 | 18.1 ± 0.533 | 12.83 ± 0.856 | 23.11 ± 0.726 | 10.94 ±0.491 | 11.58 ±0.509 | 20.03 ±0.593 | 13.03 ±0.720 | 10.23 ±0.631 |
| 2 | 48.01 ±0.521 | 28 ±0.507 | 29.03 ±0.646 | 41.18 ±0.837 | 19.65 ±0.632 | 20.08 ±0.577 | 41.06 ±0.538 | 29.14 ±0.788 | 16.58 ±0.575 |
| 3 | 64.23 ±0.651 | 38.52 ±0.482 | 36.39 ±0.751 | 63.56 ±0.589 | 29.60 ±0.752 | 28.57 ±0.750 | 59.62 ±0.715 | 36.74 ±0.904 | 25.12 ±0.761 |
| 4 | 79.12 ±0.631 | 51.02 ±0.306 | 41 ±0.811 | 73.74 ±1.378 | 38.30 ±0.544 | 46.85 ±0.541 | 65.37 ±0.664 | 41.06 ±0.969 | 35.63 ±0.718 |
| 5 | 86 ±0.876 | 60.23 ±0.556 | 54.68 ±0.794 | 82.46 ±0.808 | 51.98 ±0.762 | 53.49 ±0.753 | 79.16 ±0.821 | 51.67 ±0.806 | 48.09 ±0.918 |
| 6 | 94.92 ±0.892 | 74.61 ±0.663 | 69.41 ±0.574 | 87.47 ±0.734 | 66.90 ±0.145 | 61.59 ±0.596 | 86.05 ±0.542 | 66.02 ±0.876 | 59.6 ±0.512 |
| 7 | - | 80.43 ±0.694 | 74.75 ±1.064 | 93.32 ±0.572 | 80.58 ±0.688 | 72.34 ±0.772 | 92.12 ±0.671 | 71.29 ±0.809 | 70.22 ±0.954 |
| 8 | - | 89.88 ±0.519 | 81.91 ±0.880 | - | 96.75 ±0.725 | 80.21 ±0.580 | - | 78.8 ±0.948 | 75.6 ±0.827 |

Where±SD=standarddeviation(n=3)

Decrease in the rate and extent of drug release was observed with the increase in polymerconcentration in micropsonge and is attributed to increase in the density of the polymermatrix and an increase in the diffusional path length which the drug molecules have totraverse

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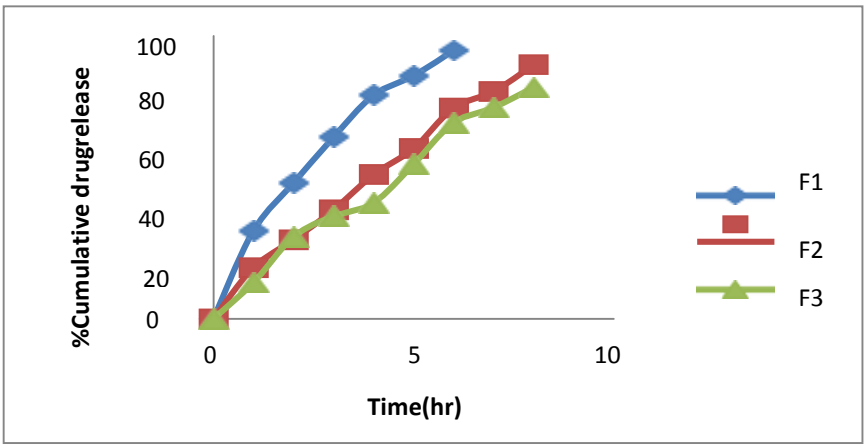
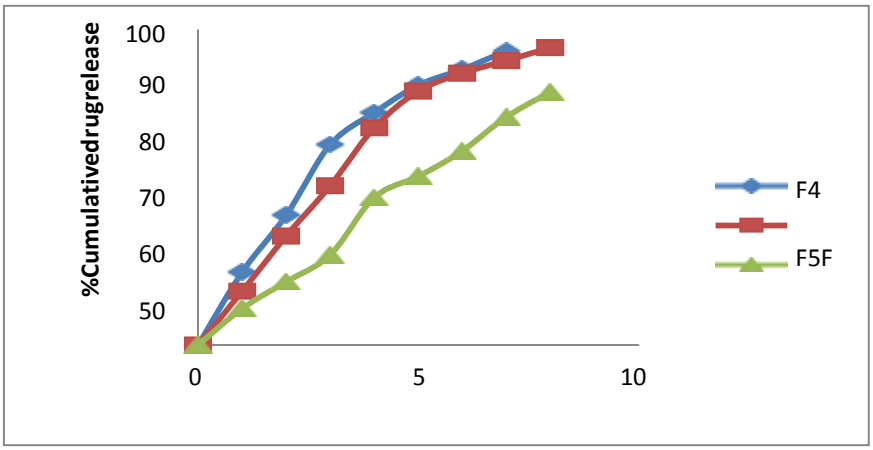
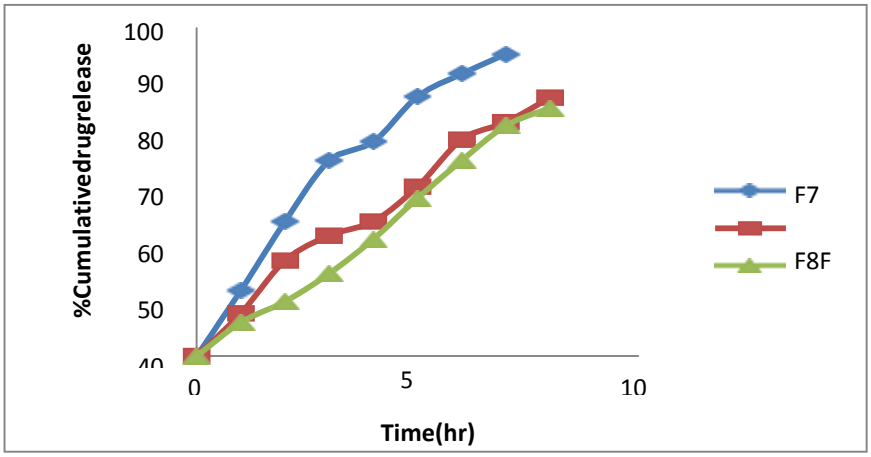



**Figureno.1:Invitrodrugreleaseprofileofciclopiroxolamine (batchF1toF3)**




**Figureno.2:Invitrodrugreleaseprofileof ciclopiroxolamine (batchF4toF5)**




**Figureno.3:Invitrodrugreleaseprofileof ciclopiroxolamine (batchF7toF9)**

**Discussion:**

Drug release from the formulations decreased with increasein the amount of polymer in themicro sponges. The present study showed that

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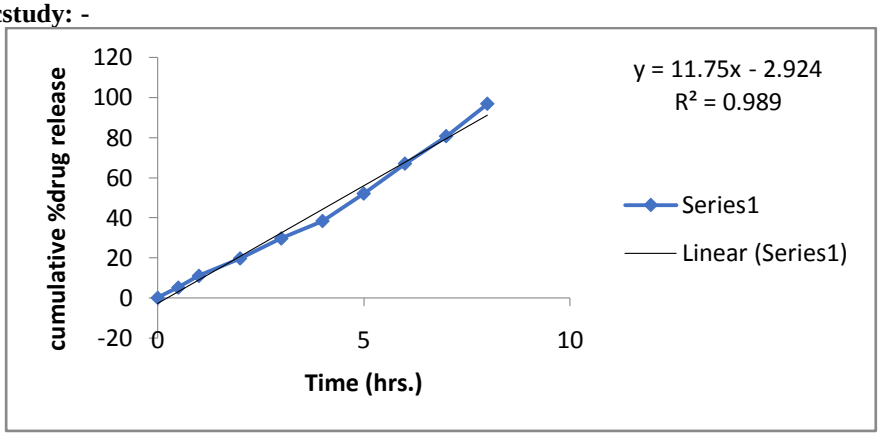
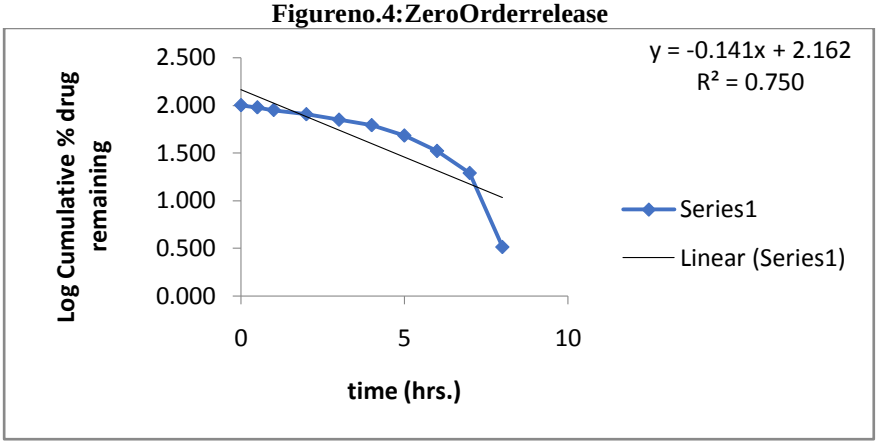
increase in the ratio of drug: polymer resulted indecreases in release of ciclopirox olamine from micro sponges. While higher concentration ofpolymer decreases release of drug from micro sponges; this could be due to formation of athickermatrixwallinmicro spongeswithsmallerdrug: polymerratiosleadtoalongerdiffusion path, and consequently slower drug release rate. batch F5 shows 96.75 % drugreleaseat8 hours,it indicatedthat the formulationF5 foundto beoptimizedbatchfollowed by otherformulation.FormulationF1, F4andF7showedanunsatisfactorydrugreleasepattern . But F2, F3, F6, F8, F9 gives a release rate up to 8 hrs. but it is from 89 to 75 %due toincreasesin theconcentration ofpolymer.

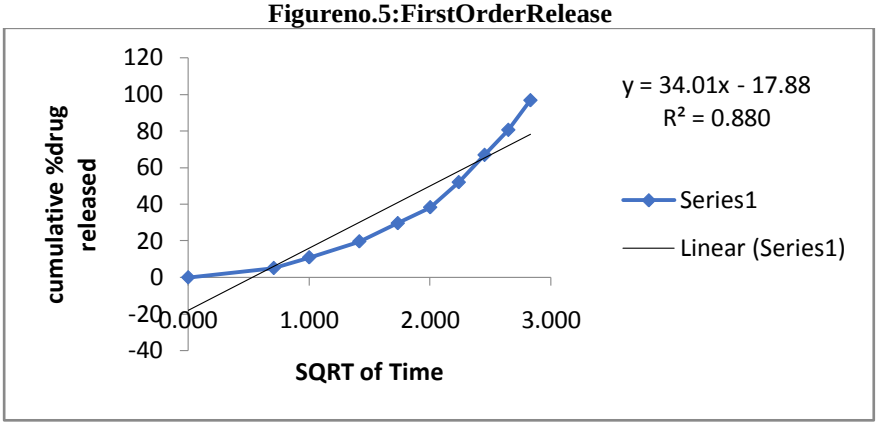
**Releasekineticstudy: -**




**Figureno.4:ZeroOrderrelease**




**Figureno.5:FirstOrderRelease**




**Figureno.6:HiguchiMatrixModel**

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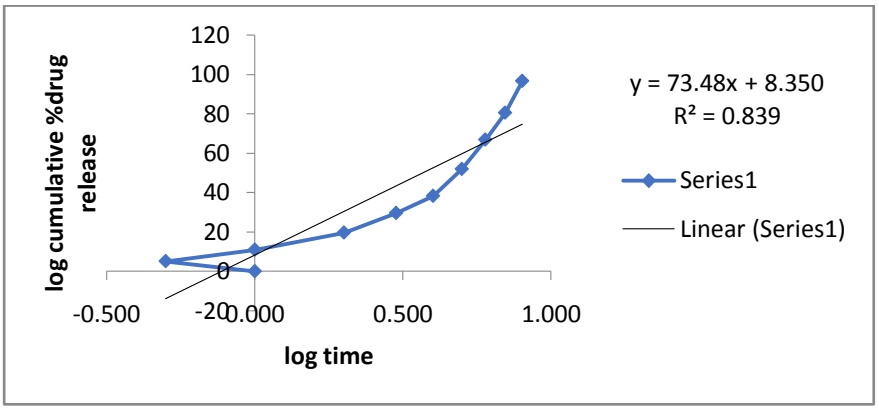
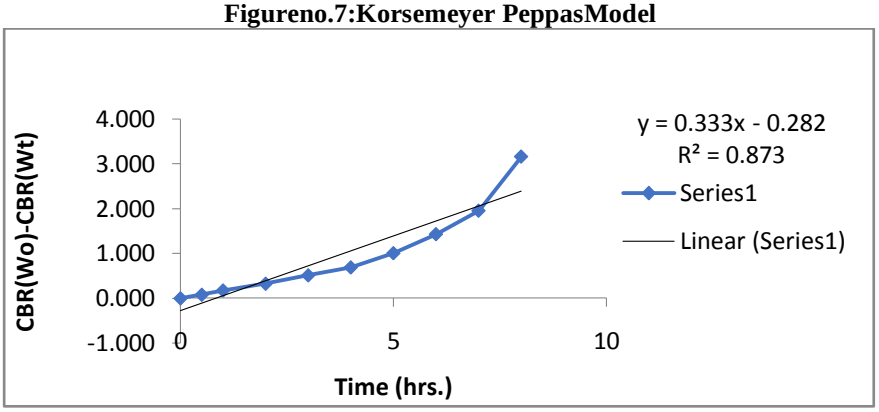



**Figureno.7:Korsemeyer PeppasModel**




**Figureno.8:HixsonModel**

**Tableno.12:Releasekineticdataof Ciclopiroxolamine micro sponges**

| Formulation | ZeroOrder | FirstOrder | HighuchiMatrix | KorsemeyerPeppas | Hixson Model |
|---|---|---|---|---|---|
| F5 | 0.9891 | 0.7504 | 0.8808 | 0.8393 | 0.8732 |

TheoptimizedbatchevaluatedkineticallybyZeroOrder,FirstOrder,HighuchiMatrix,KorsemeyerPeppas Model. Themodel withhigher correlation coefficient ($R^2$)was considered the best fit as presented in **Table no 12**formulation f5 fitted well to Zero order releasemodel,thismodelsuggestedthatthedrugrelease wasbydiffusionmechanism. Diffusion of drug from the formulation into the diffusion medium depends uponthe concentration. As gradient varies, the drug is released, and the distance for diffusionincreases.

**Characterization of final optimized batches: -**

**1. Compatibilitystudy by FTIR**

To investigate the possible chemical interactions of the drug with polymer, we have analysed Drug (Ciclopirox olamine), Polymer (Ethyl cellulose), and Micro sponge (Final formulation F5) using FTIR spectra as shown in **Figure 9**. The infrared spectrum of the F5 formulation has shown no significant shifting of bands when compared with individual spectra of pure ciclopirox olamine and ethyl cellulose spectra. Peaks appearing for Ciclopirox olamine have also appeared in a formulation indicating the compatibility of drug–polymer compatibility.

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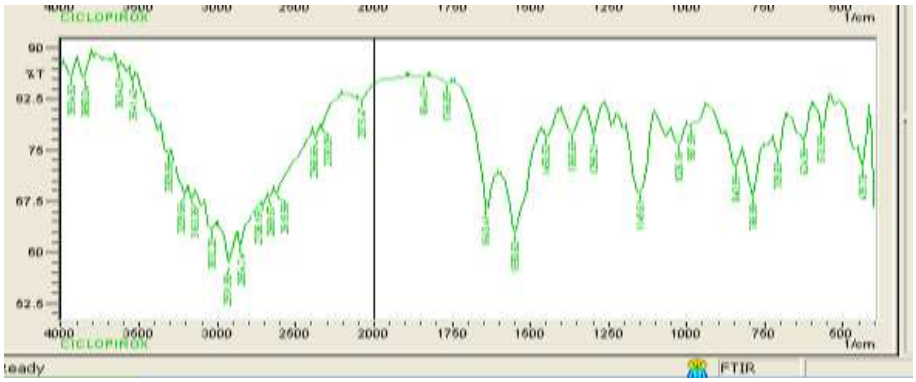
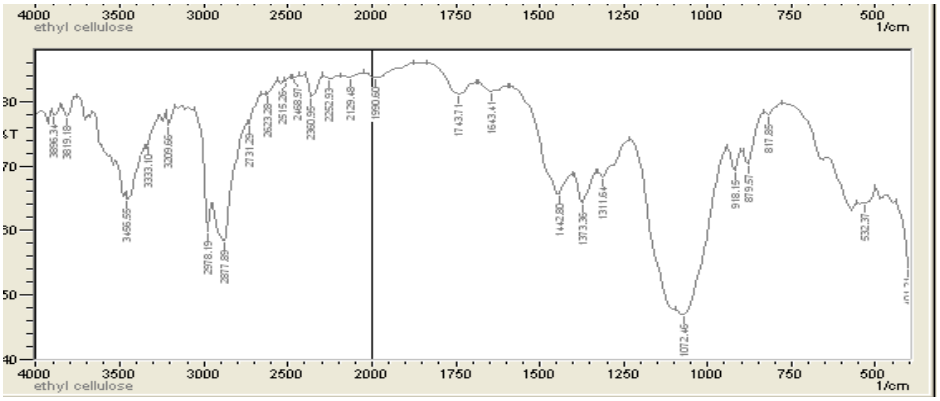
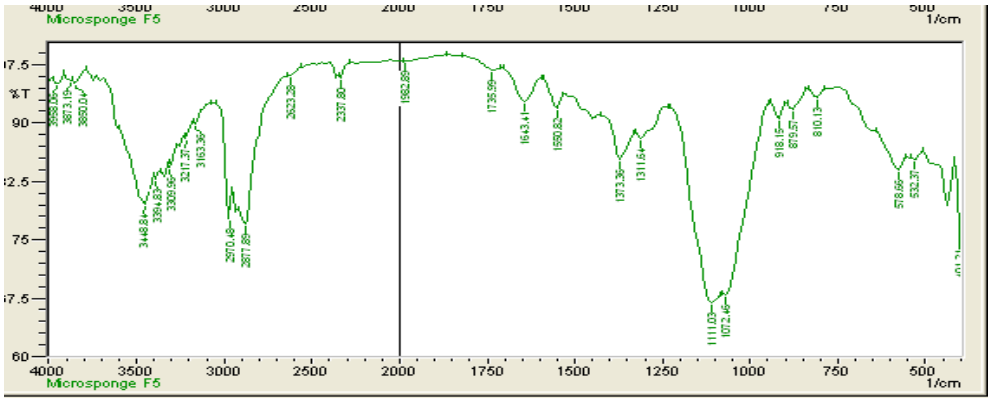



**Figureno.9: IRspectraofCiclopirox Olamine**




**Figureno.10: IRspectraofEthyl Cellulose**




**Figureno.11: IRspectraofMicro sponge (F5)**

**2. DifferentialScanningColorimetry(DSC):**

DSCprovidesinformationaboutthephysical propertiesofthesampleascrystallineoramorphous nature and demonstrates a possible interaction between drug and other excipients inmicro sponges.Thethermalbehaviourof final microsponge formulation (F5) and endothermic pic for final microsponge formulation (F5) was found to contain peak at 149.50°C which is shown in **figure 13**. This peak does not deviate much frompeak of standard ciclopirox olamine (146.82°C). Therefore, polymer and drug were found to be compatiblewitheach other.

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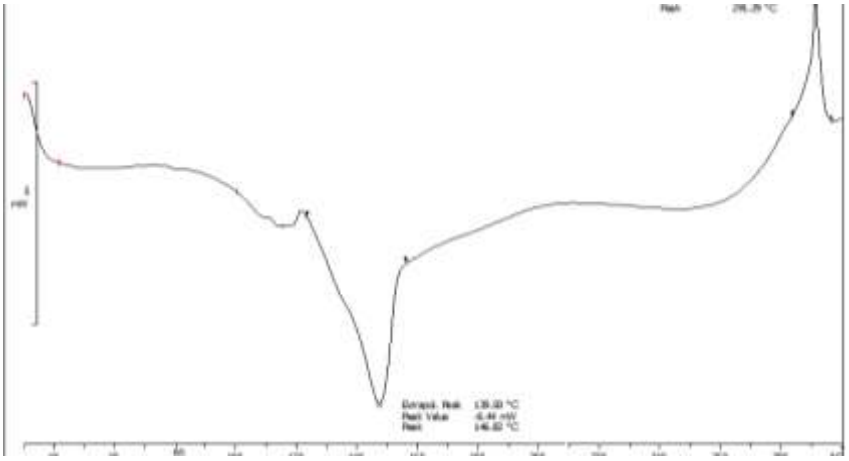
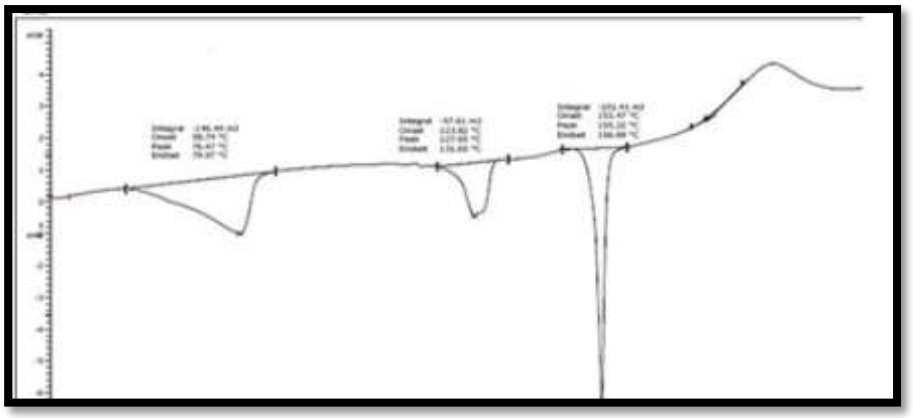


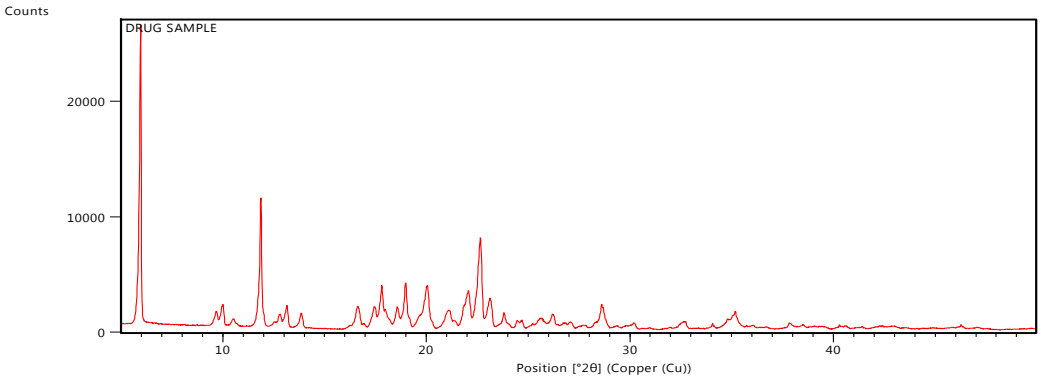
**Figureno.12: DSC Thermogram of Ciclopirox olamine**



**Figureno.13: DSC Thermogram of Microsponge (F5)**

**3. X-RAYPOWDERDIFFRACTOMETRY(XRD)**

The XRPD pattern of final formulation shows the intense peaks**.** It defines that intensity of formulation was decreases than pure drug, so formulation exhibits greater solubility than drug. The XRPD patterns of drug and final formulation is recorded which is shown in **Figure15**




**Figureno.14: XRD Pattern for Ciclopirox olamine**

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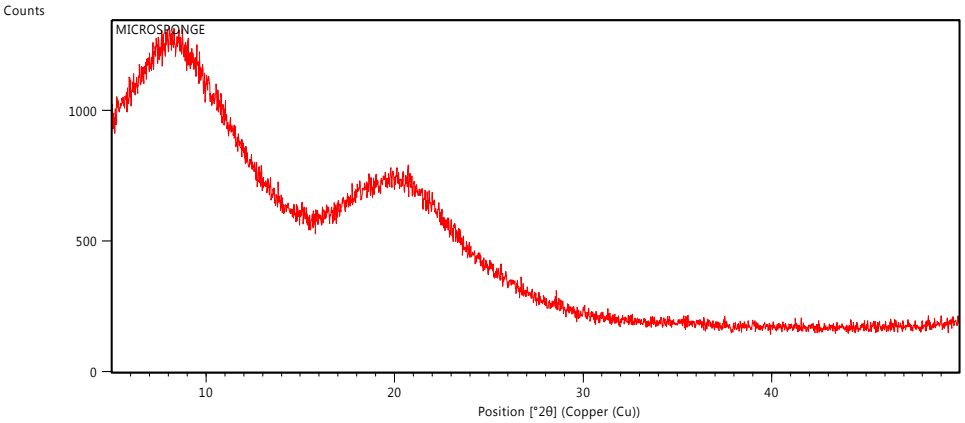


**Figureno.15: XRD Pattern for Micro sponge (F5)**

## 4. SURFACEMORPHOLOGY(SCANNIN GELECTRONMICROSCOPY)

Sample of pure drug and final formulation F5 were mounted onto the stubs using double-sided adhesive tape and then coated with gold palladium alloy (150-200 Å) using fine coat ion sputter (Joel, JEM 6100). The samples were subsequently analysed under the scanning electron microscope for external morphology. The morphology characterized by SEM for drug and final formulation F5 is recorded which is shown in **Figure No.16 SEM for Drug (A), (B), Figure 16 for Microsponge (F5) (C), (D).**

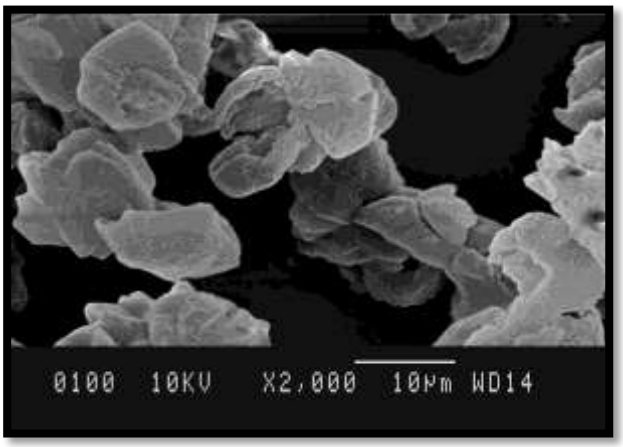


**Figure16 SEM For Drug (A)**

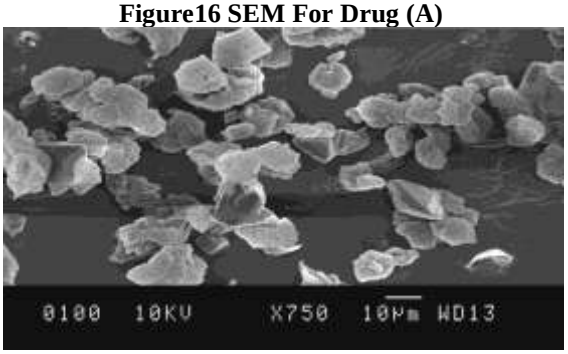


**Figure 16 SEM For Drug (B)**

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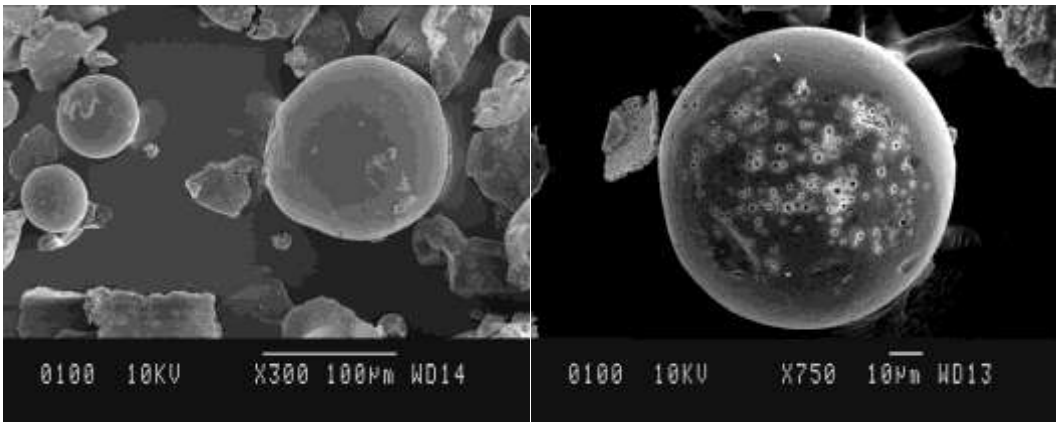


**Figure 16 SEM for Microsponge F5 (C)** **Figure 16 SEM for Microsponge F5 (D)**

**EvaluationofGelparameters:**

**1. Appearance**

Formulatedgelwasfoundtobetransparent, elegance,homogeneous, andconsistentinnature.

**2. pH**

pHofformulatedbatchwasfound tobe6.1.

**3. Viscosity**

Viscosityof formulatedbatch was found to be6,72,475 cps.

**4. Spredability**

Spredabilityofformulatedbatch wasfound tobe10.02gm.cm/sec.

**5. Invitrodiffusionstudy**

**Table 13:Invitrodiffusion study**

| Time(hr.) | Drugrelease (%)ofbatchF5 |
|---|---|
| 0.5 | 10.04 ± 0.480 |
| 1 | 18.65±0.529 |
| 2 | 30.94±0.428 |
| 3 | 45.08±0.719 |
| 4 | 56.68±0.544 |
| 5 | 69.18±0.669 |
| 6 | 78.42±0.475 |
| 7 | 86.09±0.655 |
| 8 | 94±0.716 |

Where±SD=standarddeviation(n=3)

## IV. CONCLUSION: -

It was concluded that it is possible to optimize the release of Ciclopirox olamine forbetter therapeutic efficacy. Ciclopirox olaminemicro sponges were prepared successfullyusing the quasi-emulsion solvent diffusion method. the micro sponges prepared using ethylcellulose polymer was found to be suitable to for the sustained release formulation andCiclopirox olamine micro sponges containing gel also showed the sustained release action.Thus, drug as in the form of microsponge can prevent direct contact of drug with skin thusreducingsideeffect to a great extentand henceimprovepatient compliance.

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## REFERENCES: -


[1]. MichaelJ. Rathbone,Jonath Hadgraft,'Modified Release Drug Delivery technology-Dermaland Transdermal delivery, Marcell Dekkar,New-York,2002, page no.471-475.

[2]. Valerie C. Scanlon, Tina Sanders, 'Essentials of Anatomy & Physiology', F. A. DavisCompany,Fifth Edition, 2007, pageno. 88-101.

[3]. Kenneth A. Watters, Michael S. Roberts 'Dermatological and Transdermal formulations -Structureand Function of Skin' MarcelDekkar ,New-York, 2002.

[4]. Xiaoling Li, Bhaskara R. Jasti, 'Design of Controlled Release Drug Delivery Systems-Physiological and Biochemical Barrier to Drug Delivery' McGraw-Hill Publication, U.S.A,2006,pageno. 52-55.

[5]. Andre O. Barcel, Mark Paye, Howard I. Maibach, Bozena B. Michniat-Kohn, 'Handbookof Cosmetic Science And Technology-Skin: Physiology & Penetration Pathways' MarcellDekkar, New-York, 2001, pageno. 19-25.

[6]. Meyer R. Rosen, 'Delivery System Handbook for Personal Care and Cosmetic Products'WilliamAndrew Publishing, USA, 2005, pageno.78-82.

[7]. Kenneth A. Watter, Michael S. Robert, Sheree Elizaberth Cross and Mark A. Pellett,'DermatologicalandTransdermalFormulations-SkinTransport,MarcellDekkar,New-York

[8]. Kingsley H.N. Chan, 'Skin Diseases- More than Skin Deep',Published by Federation ofMedicalSocieties ofHongKong. Editorial,Vol.15(11),2010,pageno.105.

[9]. Hywel Williams, Michael Bigby, Thomas Diepgen, Andrew Herxheimer, Luigi Naldi,BertholdRzany,'Evidence-basedDermatology'BMJPublishingGroup2003,pageno.1-7.

[10]. JamesJ.Leyden,'New Understandingof PathogenesisofAcne',Journalof theAmerican Academyof Dermatology, vol.32, no.5, Part-3, May1995, pageno. S.15-S.25.

[11]. MuhammadTahir,'ReviewArticlePathogenesisofAcneVulgaris:simplified',JournalofPakistan Association of Dermatologists, Vol.20, 2010, pageno.93-97.

[12]. YvonaLovečková, IlonaHavlíková,'AMicrobiologicalApproach toAcneVulgaris',Biomed.Papers Vol.146 (2), 2002, pageno. 29–32.

[13]. VyasS.,KharR.,Targetedandcontrolleddrugdeliveryovelcarriersystem.CBSpublication, New Delhi,1st edition, (2002),pageno.453.

[14]. Kaity, S., et al., Microsponges: A novel strategy for drug delivery system. J Adv PharmTechnolRes, 2010. **1**(3):pageno. 283-90.

[15]. Aritomi H., Yamasaki Y., Yamada K., Honda H., Koshi M.,Development of sustainedreleaseformulationofchlorpheniramine maleateusingpowdercoatedmicrosponges preparedbydryimpactblendingmethod.JournalofPharmaceuticalSciencesandTechnology,56(1),1996,pageno. 49-56.

[16]. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Control of Prolonged Drug Releaseand Compression Properties of Ibuprofen Microsponges with Acrylic Polymer, Eudragit RS,by Changing Their Intraparticle Porosity. Chemical & pharmaceutical bulletin 1992;40(1),pageno.196-201.

[17]. D' souza J., Masvekar R., Pattekari P., Pudi S., More H., Microspongic Delivery OfFluconazoleForTopicalApplication,1stIndo-JapaneseInternationalConferenceOnAdvances In Pharmaceutical Research And Technology, Mumbai, India, vol.12(1)2005,pageno.25-29.

[18]. Wester R., Patel R., Nacht S., Leydan J., Malendres J., Maibch H.,Controlled release ofbenzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy. J.Am.Acad. Dermatol,vol. 24,1991, pageno.720-726.

[19]. TanselC.,Preparationandinvitroevaluationof modifiedreleaseketoprofenmicrosponge IIFarmaco,vol 58,2003, pageno.101-106.

[20]. Embil K., Nacht S., The Microsponge Delivery System (MDS) - a topical delivery systemwithreducedirritancyincorporatingmultipletriggeringmechanismsforthereleaseofactives.JMicroencapsul,vol.13(5),1996,pageno. 575-88.

[21]. http://www.pharmainfo.net/files/images/stories/article_images/ReactionVesselForMicrospongePreparation.jpg.

[22]. Tansel C¸ Omoglu, Nurs¸In Gonu, Tamer Baykara: The effects of pressure and directcompression on tablet-ting of microsponges, International Journal of Pharmaceutics, vol.242,2002,pageno.191–195.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1248-1268 www.ijprajournal.com ISSN: 2249-7781

[23]. AndersonD.L.ChengC.H.NachtS;FlowCharacteristicsofLooselyCompactedMacroporous Microsponge(R) polymeric systems. Powder Technology, vol.78,1994, pageno.15-18.
[24]. Comoglu T, Gonul N, Baykara T, Preparation and in vitroevaluation of modified releaseketoprofenmicrosponges,IIFarmaco,vol.58, 2003,pageno. 101-106.
[25]. Kirtideshmukh:SolidPorousMicrosphere:EmergingTrendinPharmaceuticalTechnology., International Journal of Pharma and Bio Sciences,Vol 2,(1), 2011 ,page no .75-79.
[26]. Khopade AJ, Jain sanjay, Jain NK. "The Microsponge". Eastern Pharmacist, 1996, pageno.49-53.
[27]. Rahul Nair,et al,formulation and evaluation of microemulsion based vaginal gel-in vitroandin vivoevaluation, scholars researchlibrary,vol. 2(6),2010,pageno.99-105.
[28]. NoltingS.Openstudiesofciclopiroxnaillacquer inonychomycosis:a review.In:ShusterS,editor.Hydroxy-pyridonesasantifungalagentswithspecialemphasisononychomycosis. Berlin: Springer-Verlag; 1999. pageno.75-80.
[29]. Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. Part I. J Am AcadDermatolvol.30,1994, pageno.677-700.
[30]. Saroj Kumar Pradhan, 'Microsponges as the versatile tool for drug delivery system',International Journal of Research in Pharmacy and Chemistry, Vol.1 (2), 2011, page no.243-258.
[31]. 'The United State Pharmacopoeia', USP22/NF-22, 2004, United State PharmacopoeialconventionInc., USA, pageno. 448-449.
[32]. Tripathi K D, Antimicrobial drugs, Essentials Of Medical Pharmacology, Jaypee BrothersMedicalPublishers, NewDelhi,Sixth Edition, 2008,pageno. 766.
[33]. Raymond C.R., Sheskey P.J., Sian C. Owen, ' Handbook of Pharmaceutical Excipients',Fifthedition,PharmaceuticalPress &TheAmericanPharmacistAssociation2006, 2006,pageno.278-282.
[34]. Ghulam Murtaza, Ethylcellulose Microparticles: A Review, Acta Poloniae PharmaceuticaDrugResearch, Vol. 69(1),2012, pageno. 11-22.
[35]. The UnitedState Pharmacopoeia',USP30/NF-25,2006,United State PharmacopoeialconventionInc., USA, pageno. 2072,3971.
[36]. Raymond C.R., Sheskey P.J., Sian C. Owen, ' Handbook of Pharmaceutical Excipients',Fifthedition,PharmaceuticalPress &TheAmericanPharmacistAssociation2006, 2006,pageno.592-593,796-797.
[37]. 'IndianPharmacopoeia2007',IndianPharmacopoeialCommission,Govt.ofIndia-Ministryof Health &FamilyWelfare,Vol.II, pageno. 475-476.
[38]. Mohamed walash et.al Spectrofluometric determination of Ciclopirox Olamine ternarycomplexwith Tb (III)and EDTA, actapharma56, ( 2006),pageno. 431-440.
[39]. Junmei Li, et. Al. fast and simple method for assay of Ciclopirox Olamineby micellarelectrokineticscapillarychromatography,Journalofpharmaceuticalandbiometalanalysis,47(2008) ,pageno. 929-933.
[40]. Ruba T. et.al. physicochemical studies on Ciclopirox OlamineComplexes with divalentmetalions ,vol. 289(1-2)2005,pageno.179-187.
[41]. ShrivastavaRishabh,et.al,ColonicLuminalSurfaceRetentionOfMeloxicamMicrospongesDeliveredByColonTargetedMatrixTablet,InternationalJournalOfPharmaceutics,Elsevierpublication, 427,2012,pageno.153-162.
[42]. Netal Amrutiya,et.al Development Of Microsponges For Topical Delivery Of Mupirocin,AAPSPharmaSci Tech,Vol.10(2)2009, pageno.402-409.
[43]. NevineSAbdelmalak,et.al,TopicalFluconazoleMicrospongeLoadedHydrogel,International Journal Of Pharmacy And Ppharmaceutical Science, Vol4(1),2012, page no.460-468.
[44]. Vikas Jain, Ranjit Singh, 'Development & characterization of Eudragit RS 100 loadedMicrosponge and its colonic delivery using natural polymer', Acta poloniac Pharmaceutica-DrugResearch, Vol.67,No.4, 2010, pageno. 407-415.
[45]. Katkade Mayor, et.al, Ethyl Cellulose based microsponges delivery system for anti fungalvaginal gel of Tioconazole, journal of delivery and therapeutics, vol.3(6),2013,page no. 14-20.
[46]. AliNokhodchi,et.al.,'TheEffectofFormulationTypeontheReleaseofBenzoylPeroxide from Microsponges', Iranian Journal of Pharmaceutical Science, vol. 1(3), 2005,pageno. 131-142.
[47]. Vikas Jain, Ranjit Singh, 'Development & characterization of Eudragit RS 100 loadedMicrosponge and its colonic delivery

using natural polymer', Acta poloniac Pharmaceutica-DrugResearch, Vol.67,No.4, 2010, pageno. 407-415.

[48]. .D. Perumal, 'Microencapsulation of Ibuprofen and Eudragit RS 100 by the emulsionsolventdiffusiontechnique',InternationalJournalofPharmaceutics,vol.218,ElsevierScience,2001, pageno.1–11.

[49]. Jelvehgari M, et.al., 'The microsponge delivery system of benzoyl peroxide: preparation,characterization and release studies', International Journal of Pharmaceutics , 2006, 308, pageno.124-32.

[50]. Orlu M, Cevher , Araman A. , 'Design and evaluation of colon specific drug deliverysystem containing flurbiprofen microsponge', International journal of pharmaceutics, 2002,pageno.191–195.

[51]. TanselC,et.al.,'Preparationandinvitroevaluationofmodifiedreleaseketoprofenmicrosponges' Il Farmaco, 58,2003, pageno.101-06.

[52]. AliNokhodchi,et.al.,'Factorsaffectingthemorphologyofbenzoylperoxidemicrosponges'.Journal of Microencapsulation,2007, 38, pageno.834-40.

[53]. D'souza J.I., More H.N., 'Topical Anti-Inflammatory Gels of Fluocinolone Acetonideentrapped in eudragit based microsponge delivery system', Research J. Pharm. And Tech.,Vol1(4), 2008, pageno.502-506.

[54]. Vikrant Chadawar, Jessy Shaji., 'Microsponge delivery system.Current Drug Delivery',2007, Vol. 4, pageno 123-129.

[55]. Rekha U, Manjula BP., 'Formulation and evaluation of microsponges for topical drugdelivery ofmometasonefuroate',InternationalJournalofPharmacy andPharmaceuticalSciences, Vol.3,Issue-4,2011, pageno. 133-137.

[56]. Saboji J. K., et.al.,'formulation and evaluation of ketoconazole microsponge gel by quasiemulsion solvent diffusion', Journal of Cell and Tissue Research Vol. 11(1),2011, page no.2691-2696.

[57]. Viral Shaha, et.al., 'Microsponge drug delivery: A Review', Int. J. Res. Pharm. Sci. Vol-1,Issue-2, 2010, pageno. 212-218.