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DESIGN, DEVELOPMENT AND EVALUATION OF ETHOSOMAL GEL OF FLUCONAZOLE FOR TOPICAL FUNGAL INFECTION

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ABSTRACT

Due to an increase in host predisposition factors, the increasing occurrence of fungal infections has become a worrying public health concern.Despite the abundance of medications available to treat these illnesses, their efficacy is in doubt and their adverse effects cannot be neglected.In light of this, it is crucial to create novel drug delivery systems for these medications in order to combat developing fungal infections as well as prevent the spread of drug-resistant strains.New nano-based drug delivery systems, new cellular targets, and even chemicals with antifungal potential are presently being researched, despite the fact that it has proven to be a challenging task. This article will provide a summary of the state-of-the-art strategies that have been studied in order to improve drug permeability and solubility, and lessen side effects and dosage requirements of conventional drugs.

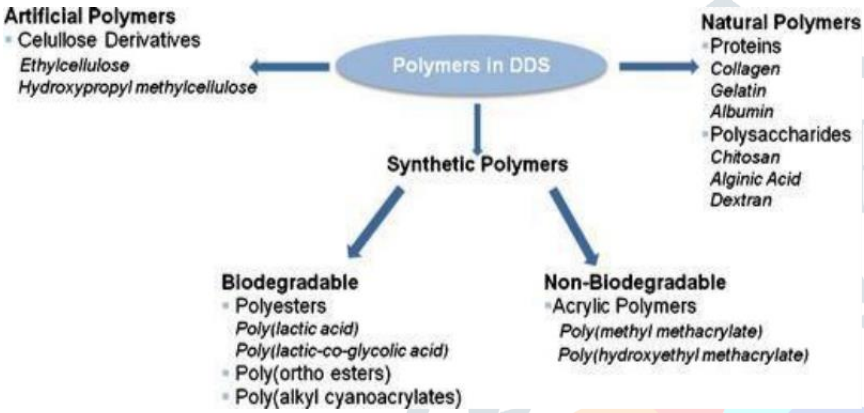
INTRODUCTION

The term "drug delivery system" describes a method of giving medication an apparent, positive therapeutic impact on the body. Patients' responses to medical drugs are influenced by both the dosage and the mode of delivery. Technologies that change patterns of absorption, distribution, and excretion are used to create pharmaceutical products. Patient comfort and adherence are increased, and the final product is more dependable and secure. The factors that affect drug release include affinity-based mechanisms, degradation, swelling, and diffusion, to name a few. Inhalation, topical (on the skin), transmucosal (nasal, buccal/sublingual, vaginal, ocular, and rectal), and peroral are the most often utilised non-invasive administration methods (through the mouth). 1

Pharmaceutical compounds are currently created in targeted delivery systems, which confine the medication's action to a certain part of the body, and sustained release formulations, which allow the medication to be released from a formulation over time in a regulated manner (such as cancerous tissues, the brain, or the colon).

2. NOVEL DRUG DELIVERY SYSTEM

The Novel Medication Delivery System aims to efficiently and quickly deliver the required drug concentration to the targeted physiological location. Throughout the recommended treatment period, the medication must be released through the drug delivery system at a pace set by the body.



ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM[4]

- Minimising medication loss and degradation.
- A decrease in the dosage regimen
- The shelf life and bioavailability of the drug are enhanced.
- Reducing harmful drug side effects
- A reduction in the variability of medication concentrations in the blood.
- Changes in drug consumption.
- More adherence from the patient.

DISADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM[4]

- The cost of the finished item was fair.
- Patients' discomfort while utilising the DDS device
- The potential toxicity of the medications.
- Adverse effects of degradation
- System application or removal requires surgical intervention.

TYPES OF NANOPARTICLES

Quantum Dot

Each of the three spatial orientations is fixed for an exciton, an electron-valence band hole couple, an electron in the conduction band, or a hole in the conduction band. This uses quantum dots, a form of semiconductor nanostructure.

1. Nanocrystalline silicon

Nanocrystallinesilicon(**nc-Si**) - amorphous phase is equivalent to that of amorphous silicon (a-Si). Due to the presence of microscopic crystalline silicon grains, the nc-Si amorphous phase sets itself apart from the other two phases.

1. Photonic crystal

Photonic crystals are periodic metallo- or dielectric-dielectric formations at the nanoscale.
intended to specify the permissible and desirable electronic energy bands, which will affect how electromagnetic waves (EM) travel, much as how a semiconductor crystal's periodic potential affects electron mobility.

4. Liposomes

Medicines or genetic material can be delivered into a cell using a spherical vesicle with a phospholipid bilayer membrane.

5. Gliadin nanoparticles

To boost the bioavailability of drug's anti-H. pylori effects, mucoadhesive gliadin nanoparticles (GNP), which can carry drugs to the sites of infection, were developed. A GNP containing clarithromycin and omeprazole was produced utilising the desolvation method.

6. Polymeric Nanoparticles

Polymeric nanoparticles have been produced by Speiser et al. They present a fascinating alternative to liposomes as drug delivery mechanisms. They generally have excellent storage stability and a lengthy shelf life

7. Solid Lipid Nanoparticles (SLN)

As an innovative delivery technique to take the place of traditional polymeric nanoparticles, solid lipid nanoparticles have been created. SLNs are physiological, lipid-based colloidal carriers that range in size from 50 to 1000 nm and are dispersed in water or an aqueous surfactant solution.

Ethosomal:

Before being included in a dosage form, various chemicals can be suspended or encapsulated in ethosomals, which are tiny nanoporous structures that resemble meshes. They have been demonstrated to be spherical colloids, and based on their inclusion and exclusion behaviour, it is possible that they have a very high capacity to saturate insoluble drugs.

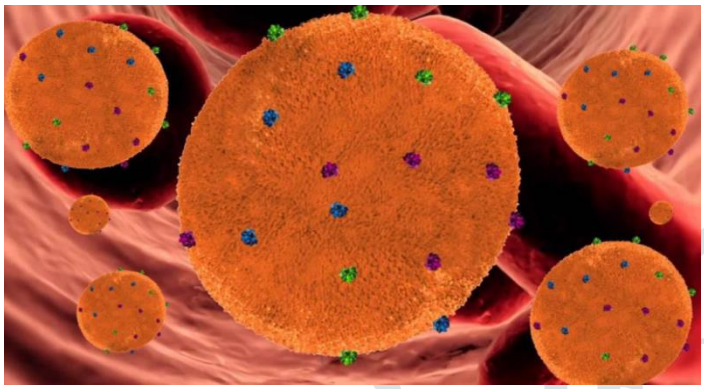


Figure-4 : STRUCTURE OF Ethosomal

Advantages of Ethosomal:[18]

1.Targeted site specific drug delivery.

2. Can be used to mask unpleasant flavours and to convert liquid substances to solids.

3. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).

4.Ethosomal particles are soluble in water, so the hydrophobic drugs can been capsulated with in the Ethosomal, after mixing with a chemical called an adjuvant reagent.

5. Particles can be made smaller or larger by varying the proportion of cross-linkerto the polymer.

Disadvantages

1. The main disadvantage of these Ethosomals is their ability to include only small molecules.

2. The Ethosomals could be either Para crystalline or in crystalline form. The loading capacity of Ethosomals depends mainly on degree of crystallization. Para crystalline Ethosomals can show different loading capacities.

3. The Ethosomals can be synthesized to be of specific size and to release drugs overtime by varying the proportion of cross linker to polymer.

Characteristic features of Ethosomals.

- Ethosomals exhibit a range of dimensions (1 µm or less) with tunable polarity of the cavities. Ethosomals of specific size and adjustable polarity can be synthesized by varying the crosslinker to polymer proportion.

- They could be either para-crystalline or in crystalline form, depending on the process conditions. Crystal structure of Ethosomals plays a very important role in their complexation with drugs.

- The drug loading capacity of Ethosomals mainly depends on the degree of crystallization. Para-crystalline Ethosomals have shown various drug loading capacities.

- They are nontoxic, porous particles insoluble in most organic solvents and stable at high temperatures up to 300 °C.

- Ethosomals as formulations are stable over the pH range of 1 to 11 and temperature up to 130 °C.

FACTORS AFFECTING DRUG RELEASE FROM EthosomalS:

- Physical and chemical properties of entrapped actives.

- Physical properties of sponge system like pore diameter, pore volume, resiliency etc.

- Properties of vehicle in which the sponges are finally dispersed.

- Particle size, pore characteristics, composition can be considered as imperative parameters.

- External triggers like temperature, pressure, and solubility of actives.

Pressure: Pressure or rubbing can release active ingredient from Ethosomals onto skin.

Temperature: Some entrapped actives can be too viscous at room temperature to flow spontaneously from sponges onto the skin but increased skin or environment can result in increased flow rate and ultimately drug release.

Solubility: Sponges loaded with water soluble drug like antiperspirants and antiseptic release the ingredients in the presence of water.

REVIEW OF LITERATURE

DrPrathimasrinivas*et al* formulated and Evaluated VoriconazoleEthosomals for Oral and topical Delivery as Tablets and Gel. VoriconazoleEthosomals were prepared by Emulsion Solvent Evaporation Technique with three different Polymers.

Raja CH. NV. *et al* fabricated and Evaluated Ciprofloxacin loaded Ethosomals for sustained release. Five batches of Ethosomals using different proportion of Ethyl cellulose were prepared by solvent evaporation method.

GautamSeema*et al*developed and evaluated curcumin loaded Ethosomals for colon drug delivery. Six batches of Ethosomals were prepared and zeta potential, Drug content, Drug entrapment efficiency, Surface characteristic by SEM, Particle size, FTIR, DSC, Stability studies.

P.Suresh Kumar *et al* formulated and evaluated Miconazole nitrate Loaded Ethosomals for vaginal drug delivery. Ethosomals were prepared using different ratios of beta cyclodextrin and Di phenyl carbonate.

Renuka Sharma *et al*fabricated and Evaluated Econazole nitrate Ethosomals as topical hydrogel. EconazoleEthosomal were prepared by using various concentration of ethyl cellulose and evaluated for entrapment efficiency, *in -vitro* drug release size measurement, Rheological properties. For hydrogel the Equilibrium swelling study, viscosity analysis, texture analysis, *in-vitro* permeation study has evaluated.

Fei Wang, et al[38] formulated Hydrogel Retaining Toxin – Absorbing Ethosomals for Local Treatment of Methicillin Resistant Staphlococcus aureus infection. The Staphlococcus aureus which are resistant to the methicillin due to their toxin activity towards the drug.

Gouri Shankar and Y.K. Agarwal40 formulated and Evaluated -cyclodextrinEthosomals of a poorly water soluble drug. -cyclodextrinEthosomal were prepared and Simavastatin was added to it.

Monica R. P. Rao et al developed and Evaluated the Ethosomal- based Pediatric-controlled release dry suspension of Gabapentin for reconstitution. Ethosomal of Gabapentin were formulated using -cyclodextrin by melt method. The Ethosomal drug complex were characterized by FT-IR, DSC and PXRD as well as evaluated for taste and saturated solubility.

Kurhe, et aldescribes Scaffold based drug delivery system :A Special emphasis on Ethosomal. Ethosomals were prepared to have ability to encapsulate either hydrophilic or lipophilic drug and release the drug in a controlled and predictable fashion at the target site.

ShastrulagariShivani et al reviewed Ethosomal – novel emerging drug delivery system. Types of Ethosomal, advantages, Polymers and cross linker used are reviewed. Method of preparation of Ethosomal, Factors influencing Ethosomal, characterization and applications.

Candida albicans

It is a diploid yeast with two pairs of 8 chromosomes. Its genome size is about 16 Mb. It possesses 6,159 coding genes. It is the predominant cause of invasive fungal infections. People at risk include those suffereing from HIV, cancer and intensive care unit patients for example those undergoing major surgery and organ transplants.

Candida glabrata (Torulopsisglabrata)

It is a small, haploid, monomorphic yeast with 13 chromosomes and a genome sizeof 12.3 Mb. It possesses 5283 coding genes. It has become important because of its increasing incidence worldwide and decreased susceptibility to antifungals. Its emergence is largely due to an increased immunocompromised patient population and widespread use of antifungal drugs. In many hospitals, *C. glabrata* is the second most common cause of candidemia.

Candida tropicalis

It is a diploid, with 10 to 12 chromosomes and a haploid genome size of 15 Mb. It possesses 6258 genes. *C. tropicalis* is the third or fourth most commonly recovered *Candida* species from blood cultures. *C. tropicalis* has progressively been observed to be the commonest cause of invasive candidiasis in neutropenic patients such as those with acute leukaemia or those who have under- gone bone marrow transplantation.

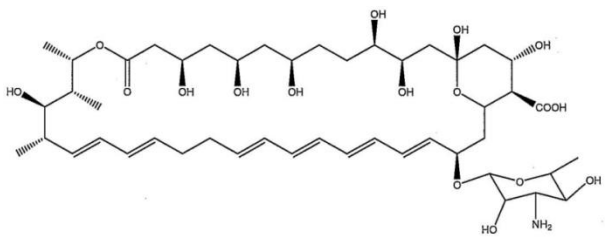
Candida parapsilosis

It is a diploid or aneuploid with 14 chromosomes and a genome size of 16 Mb. It possesses 5733 genes. It is one of the principal causes of invasive Candidiasis. In most parts of the world, it is the third most common cause of candidemia especially in patients with intravenous cathe- ters, prosthetic devices, and intravenous drug use. It is one of the most common causes of candidemia in neonatal intensive care units.

DRUG PROFILE

NYSTATIN

Structural formula



CAS Number[61]

1400-61-9

Synonyms[25]

Mycostatin, Nistatina,NYS,Nystatin, Nystatine and Nystatinum.

Empirical formula[25]

C47H75NO17

Chemical name

(21E,23E,25E,27E,31E,33E)-20-{[(3S,4S,5S,6R)-4-amino-3,5-dihydroxy-6-methyloxan-2-yl]oxy}-4,6,8,11,12,16,18,36-octahydroxy-35,37,38-trimethyl-2,14-dioxo-1-oxacyclooctatriaconta-21,23,25,27,31,33-hexaene-17-carboxylic acid

Molecular weight : 926.1

Description

Nature: A Yellow to slightly brown powder, Hygroscopic.

Odour : Characteristic.

Pharmacokinetics

Nystatin has negligible intestinal absorption. The majority of orally taken Nystatin is eliminated in the faeces unaltered. Nystatin plasma concentrations that are clinically relevant can occasionally be seen in individuals with renal insufficiency who are taking oral medications in accordance with standard dosage forms. Rapid action onset, unknown peak and half-life, and 6 to 12 hours of action time.

Medical indications

Nystatin is suggested for the treatment of cutaneous or mucocutaneousmycotic infections brought on by Candida albicans and other susceptible Candida species. It comes in the form of a topical powder, cream, or ointment. dosage and management

The typical adult dosage for cutaneous candidemia

Use topical nystatin cream, ointment, or powder as needed to completely cover the afflicted area and any nearby skin 2 to 4 times each day. The powder formulation can be used to treat lesions or wet areas.

Depending on the type and severity of the illness, the course of therapy should last anywhere from 2 to 8 weeks. The typical adult dosage for vaginal candidiasis For a total of 14 days, place one Nystatin vaginal pill (100,000 units) vaginally, ideally before bed. Common dosage for cutaneous candidiasis in children

Use Nystatin topical cream, ointment, or powder 2–4 times a day, enough to cover the affected area and the skin just around it. The powder formulation can be used to treat lesions or wet areas. Depending on the type and severity of the illness, the course of therapy should last anywhere from 2 to 8 weeks.

EXPERIMENT

COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS

Before creating the formulation dosage form, preformulation studies were performed to make sure there would be no drug-excipient interaction. It gives the information required to choose the excipients that will be used in conjunction with the drug for making ethosomal. Physical compatibility between the medication and excipients was examined. The possibility of pharmacological excipient interactions with ethyl cellulose and polymethyl methacrylate was investigated utilising an FT-IR Spectrum analysis.

Physical Compatibility

Drug and excipient physical admixtures were tested at room temperature and at 40 C2 C/75 5 percent RH (in days) to determine their physical compatibility.

Fourier Transforms Infrared (FT-IR)Spectroscopic studies

The spectroscopic investigations were conducted using an FT-IR spectrophotometer to determine how the pure medication, excipients, and its physical mixture interacted. The compatibility of the excipients and drug is next evaluated by comparing the IR spectra of the physical mixture with the spectrum of the drug (Nystatin). The resolution is 4 cm-1, and the scanning range is 450-4000 cm-1.

PREPARATION OF PHOSPHATE BUFFER pH 5.5

Solution I – 13.612 g of Potassium dihydrogen phosphate in 1000 ml of Distilled

Water.

Solution II – 35.08 g of Disodium hydrogen phosphate in 1000 ml of Distilled Water.

96.4 ml of Solution I and 3.6 ml of Solution II were mixed together

STANDARD CURVE OF NYSTATIN

100mg of drug was accurately weighed and dissolved in 30 ml methanol and made up to 100ml with phosphate buffer pH 5.5. Calibration curve was prepared in a mixture of phosphate buffer and methanol (7:3) at λ max 305 nm.

FORMULATIONDEVELOPMENT

FORMULATION OF NYSTATIN LOADED Ethosomal

Nystatin ethosomals were made utilising the emulsion solvent evaporation method. Two different polymers were used in the formulation. Methyl methacrylate (PMMA) and ethyl cellulose were the polymers used (EC). Distilled water and polyvinyl alcohol make up the aqueous phase. The polymers (1:1, 1:2, 1:3, 1:4, and 1:5) have been dissolved in dichloromethane, and the medication has been dissolved in the required solvent (dimethyl sulfoxide). All of the components were properly shaken before the drug solution was added to the polymer solution. The drug polymer combination was then added to the aqueous phase while being homogenised at a high speed of 1500 rpm for two hours at 35 °C. The made ethosomals were spun in a high-speed cooling centrifuge, and the scraps were then freeze-dried.

RESULT

Table-21 : *in-vitro* drug release of pure drug, marketed sample (Nistatina cream) and Nystatin Ethosomal gel (EC and PMMA) G1 and G2

Time in hours	Pure drug	Marketed cream	Ethosomal Gel G1	Ethosomal Gel G2
0	0	0	0	0
1	0.61	0.9	2.73	3.18
2	0.66	1.2	5.18	5.36
3	0.84	1.39	7.39	7.28
4	1	1.51	8.62	9.73
5	1.17	1.64	9.28	10.73
6	1.31	1.79	11.03	11.37
7	1.58	1.92	12.66	14.3
8	1.74	2.11	14.24	16.06
9	1.8	2.33	15.05	17.28
10	1.91	2.5	15.81	18.17
11	2	2.66	16.59	19.1
23	2.54	2.87	21.75	26.04
24	2.63	3.01	23.15	28.88

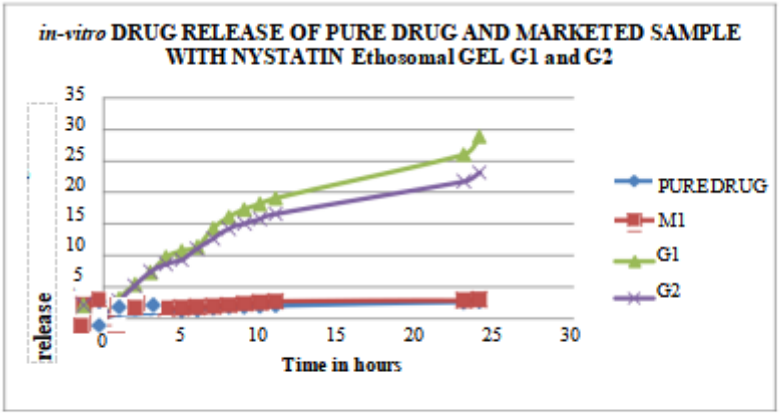


Figure-27: *in-vitro* drug release of Pure drug, Marketed sample (Nistatina cream) and Nystatin Ethosomal gel G1 and G2

Table -2| : Release kinetics of NystatinEthosomal Optimized formulation F3

Time in Hours	%cum drug release	% drug remaining	Log%cum drug remaining	Square root of time	Log time	Cube root of % drug remaining	Log %cum drug release
0	0	100	2	0		4.641589	
1	2.84	97.16	1.98748	1	0	4.597225	0.453318
2	5.06	94.94	1.97744	1.41421	0.30102	4.561941	0.704151
3	8.41	91.59	1.96184	1.73205	0.47712	4.507641	0.924796
4	10.69	89.31	1.95090	2	0.60205	4.469922	1.028978
5	13.06	86.94	1.93921	2.23606	0.69897	4.430028	1.115943
6	14.55	85.45	1.93171	2.44949	0.77815	4.404575	1.162863
7	16.75	83.25	1.92038	2.64575	0.84509	4.366445	1.224015
8	18.6	81.4	1.91064	2.82842	0.90308	4.333859	1.269513
9	19.71	80.29	1.90466	3	0.95424	4.314069	1.294687
10	22.51	77.49	1.88924	3.16227	1	4.263326	1.352375
11	24.44	75.56	1.87829	3.31662	1.04139	4.227633	1.388101
23	31.92	68.08	1.83302	4.79583	1.36172	4.083255	1.504063
24	36.28	63.72	1.80427	4.89897	1.38021	3.994158	1.559667

Table-3 : Release kinetics of Nystatin Ethosomal Optimized formulation F7

Time in Hours	%cum drug release	% drug remaining	Log% cum drug remaining	Square root of time	Log time	Cube root of % drug remaining	Log %cum drug release
0	0	100	2	0		4.641588	
1	4.14	95.86	1.981637	1	0	4.57663	0.617
2	7.3	92.7	1.96708	1.414214	0.30103	4.525777	0.863323
3	10.16	89.84	1.95347	1.732051	0.477121	4.478747	1.006894
4	14.13	85.87	1.933841	2	0.60206	4.411779	1.150142
5	15.94	84.06	1.924589	2.236068	0.69897	4.380561	1.202488
6	18.69	81.31	1.910144	2.44949	0.778151	4.332261	1.271609
7	20.72	79.28	1.899164	2.645751	0.845098	4.295903	1.31639
8	23.2	76.8	1.885361	2.828427	0.90309	4.250634	1.365488
9	27.06	72.94	1.862966	3	0.954243	4.178193	1.432328
10	29.16	70.84	1.850279	3.162278	1	4.137704	1.464788
11	35.58	64.42	1.809021	3.316625	1.041393	4.00873	1.551206
23	41.45	58.55	1.767527	4.795832	1.361728	3.883073	1.617525
24	45.66	54.34	1.73512	4.898979	1.380211	3.787679	1.659536

SUMMARY AND CONCLUSION

The aim of this study was to prepare nystatin-loaded ethosomal gel for sustained drug release, improve drug permeability and solubility, and lessen side effects and dosage requirements.

The results of the FTIR studies demonstrated that the drug and polymers did not interact.

Using a variety of polymers, Ethosomal was prepared using a homogenization technique followed by centrifugation.

Different polymers (Ethylcellulose and polymethyl methacrylate) were used to create the formulation in a variety of ratios (drug:polymer-1:1, 1:2, 1:3, 1:4 and 1:5). a crosslinker and solvent both using dichloromethane. Drug entrapment effectiveness was assessed for the formulations. The formulations' observed entrapment efficiencies ranged from 97.85 to 99.21. For the formulations F3 and F7, the highest entrapment efficiency was observed at 99.21 and 98.94. Drug content in the formulations was identified. It was determined that the formulations' drug content ranged from 82.90 to 95.71. The average particle size of Nystatin-loaded Ethosomal F3 and F7 was 231.1 nm and 370.3 nm, respectively, according to the Malvern Zeta sizer's analysis of particle size. The spherical surface of the particles is visible in the Ethosomal SEM analysis.

REFERENCES

- Jorge F. Coelho, Drug delivery systems: Advanced technologies potentially applicable in personalized treatments. EPMA J. 2010 Mar; 1(1): 164–209. Published online 2010 Apr 10. doi: 10.1007/s13167-010-0001-x
- Suryavanshi Kiran, *et al.*, Fundamentals of drug delivery systems. free ebooks.net
- P. Dwarakanadhar eddy *et al.*, Recent advances in Novel drug delivery system. Int.J. PharmTech Res.2010; 2(3).
- Aarti P. Nikam**,**Mukesh. P. Ratnaparkhiand, Shilpa P. Chaudhari.
- Nanoparticle – An Overview. International Journal of Research and Development in Pharmacy and in Life Sciences, Aug –Sep 2014; Vol - 3, No - 5, pp 1121-1127,ISSN:2278-0238.
- Wim H De Jong *et al*., Drug delivery and Nanoparticles: Applications and
- hazards. Int J Nanomedicine. 2008; Jun; 3(2): 133–149.
- V.J.Mohanraj*et al.*, Nanoparticle – A Review. Tropic Journal of Pharmaceutical research, June 2006; 5(1):561-573.
- KonwarRanjit, Ahmed abdulBaquee. Nanoparticle – An overview of preparation, characterization, and application. Int. Res. J. Pharm.2013; 4(4).
- GautamSeema., Singh Arun Kumar., BhardwajManoj., Development and Evaluation of Curcumin Loaded Ethosomals for Colon Drug Delivery. World Journals of Pharmaceutical Research ., ISSN 2277-7105 Vol 4, Issue , 1650-1666.
- Renuka Sharma and KamlaPathak., Polymeric Ethosomals as an alternative carrier for improved retention of Econazole Nitrate onto the Skin through topical Hydrogel formulation. Pharmaceutical Development and Technology, 2011; 16(4):
- Suvakanta dash, Padalanarasimhamurthy, Lilakantanath, and Prasantachowdhury. kinetic modeling on drug release from controlled drug delivery systems. ActaPoloniaePharmaceutica ñ Drug Research, Vol. 67 No. 3 pp. 217-223, 2010.
- CH.N.V.Raja, G. Kiran Kumar., Kotapatianusha., Fabrication and Evaluation of Ciprofloxacin Loaded Ethosomals for Sustained Release. International Jouanal of Research in Pharmaceutical and Nano Sciences.2(1),2013,1-9.
- P.Suresh Kumar, N.Hematheerthani.,J.VijayaRatna.,and V.Saikishore., Formulation and Evaluation of Miconazole Nitrate Loaded Ethosomals for Vaginal Drug Delivery. IAJPS 2015,Volume2 (6), 1028-1037.
- FeiWang,Weiweigao, SorachaThamphiwatana, Brian T. Luk, PavimolAngantikul, Qiangzhe Zhang. et al. Hydrogel Retaining Toxin – AbsorbingEthosomals for Local Treatment of Methicillin ResistantStaphlococcusaureus infection.www.Materialviews.com. 2015.Doi:10.1002/adma.201501071.