DEVELOPMENT AND EVALUATION OF MICONAZOLE NITRATE ENTRAPPED POLYMERIC NANOPARTICLE LOADED GELS

Jyoti Saxena*, Pranshu Tangri
Department of Pharmacy, GRD (PG) IMT, Dehradun-248197, Uttarakhand, India.
E-mail ID-jyotisaxena6july1996@gmail.com

ABSTRACT
The present study has aimed to investigate the effective transdermal delivery of anti-fungal miconazole nitrate (MN) by formulating as polymeric nanoparticle loaded gels or Nanogels (NG). Miconazole Nitrate is an imidazole derivative and used for the treatment of candidial skin fungal infection. The Nanoparticles were prepared by Nanoprecipitation method so as to avoid both chlorinated solvents and surfactants to prevent their toxic effect on the body and the corresponding gel were prepared using carbopol 934 P. Nanoparticles of Miconazole Nitrate were prepared by using hydrophilic polymers such as chitosan and carbopol 934 P. These polymers were incorporated into Eudragit RS 100 polymer loaded nanogel to modify the rate of drug. The prepared formulations were then characterized for particle size, zeta potential, loading efficiency, encapsulation efficiency and drug-excipient compatibility. FT-IR study confirmed the purity of drug and revealed no interaction between the drug and excipients. Nanogel formulations were characterized for drug content, pH determination and drug entrapped efficiency. The prepared nanogel formulations with different polymers ratio have shown particle size in the range of 250.12-743.07 nm, zeta potential in the range of -14.2 to +33.2 mV, entrapped efficiency in the range of 49.25 & 49.8% for F1 & F10 formulations. Among the selective two formulations, F1 was selected as the best formulation as its %CDR, drug content and drug loading polymers for 12 hrs was 97.8%,98.5 & 3% and F10 was selected as the best formulations its %CDR, drug content and drug loading polymer ratio for 12 hrs was 98.9%, 99.6% & 3:3. F1& F10 formulation did not show any skin irritation. Gel formulation F1& F10 were found to be stable at 40 ±2°C and 75 ± 5% RH.
Keywords: Miconazole Nitrate, Nanoparticles, Nanogel, pre & post formulation studies.

I. INTRODUCTION OF NANOPARTICLES [1-6]

Nanoparticles are generally defined as particulate matter particulate dispersions or solid particles with at least one dimension that is less than 100 nm. Nanoparticles are generally defined as particulate matter particulate dispersions or solid particles with at least one dimension that is less than 100 nm. This definition puts them similar size domain as that of ultrafine particles (air borne particulates) and places them as a sub-set of colloidal particles. Nanoparticles are one of the different types of nano-sized carriers that being developed for drug delivery applications. Drug delivery systems (DDS) have been expand in order to

control pharmacological parameters such as bioavailability, biodistribution and pharmacokinetics of the administered substances. It can help to keep drug levels in the therapeutically desired range by releasing the substance over a predefined period of time.

The major objective in designing nanoparticles as a delivery system are to manage particle size, surface properties and to free of pharmacologically active ingredients in order to attain the target -specific action of the drug at the therapeutically optimal rate and dose regimen. The drug molecule is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation of nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are complex in which the drug is cramped to a cavity surrounded by an individual polymer membrane, while nanospheres are matrix complex in which the drug is physically and invariably dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly(ethylene glycol) (PEG) known as long-circulating particles, have been used as prospective drug delivery devices because of their capability to pass on for a prolonged period time target a particular organ. Most current nanoparticles and nano structured materials can be classified into four material based. (i) Carbon-based nanomaterials: Overall, these nanomaterials contain carbon, and are found in morphologies such as hollow tubes or spheres. Fullerenes (C60), carbon nanotubes (CNTs), graphene (Gr), and carbon anions are included under the carbon-based NMs category. (ii) Inorganic-based nanomaterials: These NMs add metal and metal oxide NPs and NSMs. These NMs can be combined into metals such as Au or Ag NPs, metal oxides such as TiO2 and ZnO NPs.(ii) Composite-based nanomaterials: Composite NMs are polyphase NPs and NSMs with single phase on the nanoscale dimension that can either merge NPs with other NPs or NPs cooperated with larger or with bulk-type materials (e.g., hybrid nanofiber) or more complex structures. The composites may be any mixture of carbon-based, metal-based, or organic-based NMs with any form of metal, ceramic, or polymer bulk materials. Nanoparticles offers various advantage in drug delivery system. These advantages include:

- Nanoparticles have many remarkable advantages over conventional and traditional drug delivery system.
- Nanoparticles are sustained release form at the site of localization, they change organ distribution of drug substances. They increase drug flow in blood, bioavailability, therapeutic effectiveness and lower easily penetrates to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
- Nanoparticle increases the aqueous solubility of poorly soluble drug, which upgrade bioavailability of drug.
- As a targeted drug transporter nanoparticles decrease drug toxicity and enhance effective drug distribution.
- By using polymers drug release from nanoparticles can be modified which construct polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.
- Useful to determine various diseases.
- Increased stability of ingredients.
- Extend shelf life.

- Used in dental surgery also as filling the cavities in teeth.
- Change the method of drug delivery to improve customer acceptance or decrease manufacturing costs.
- Nanoparticles can be deliver by various routes including oral, nasal, parenteral, intra-ocular etc.
- In the minute areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a specific cell type or receptor.
- Due to small particle size nanoparticles overcome resistance by physiological barriers in the body.

MECHANISM OF DRUG RELEASE

The polymeric drug transporter delivers the drug at the tissue site by any one of the 3-general physical-chemical mechanisms.

1.By the swelling of the polymer nanoparticles by hydration followed by freeing through diffusion.

2.By an enzymatic reaction break off in rupture of the polymer at site of delivery, there by releasing the drug from the entrapped inner core.

3.Detachment of the drug from the polymer and release from the swell on nanoparticles.

Nanoparticles can be ready from a several materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix substances is dependent on many characters including:

(a) Size of nanoparticles need;
(b) Intrinsic properties of the drug, e.g., aqueous solubility and stability;
(c) Surface factors such as charge and permeability;
(d) Level of biodegradability, biocompatibility and toxicity;
(e) Drug release profile desired; and
(f) Antigenicity of the final product.

The term ‘nanogels’ defined as the nanosized particles developed by physically or chemically crosslinked polymer lattice that is swell in a good solvent. Sudden outburst in the field of nanotechnology have introduced the require for developing nanogel systems which proven their potential to deliver drugs in controlled, sustained and targetable mode. With the growing field of polymer sciences it has now become unavoidable to prepare smart nano-systems which can prove effective for treatment as well as clinical trials progress. A gel is a colloidal system formed by continuous solid phase dispersed in fluid phase. If fluid is water and known as the gel is hydrogel. A hydrogels are three dimensional network structures obtained from polymers which can absorb and keep big amount of water. So they are biocompatible. Nanogels are nanosized hydrogels in 10-100nanometers in diameter. Nanogels are cross linked nanoscale particles assemble of flexible hydrophilic polymers. They are soluble in water and allow voluntary loading of drug in aq. Media.

PROPERTIES OF NANOGEL [39-42]

- **Biocompatibility and Degradability**

  Nanogel is build up of either natural or synthetic polymers. They are highly biocompatible and biodegradable thereby avoiding its collection in the organs. Chitosan, ethyl cellulose,

methyl cellulose and various polysaccharide-based polymers like dextran, pullulan and dextrin can be used to produce the Nanogel. Polysaccharides are mainly carbohydrate-based polymers, formed of replicated monosaccharide units connected by glycosidic bonds. These polymers are stable, non-toxic, hydrophilic and biodegradable in nature.

- **Swelling Property in Aqueous Media**
  Nanogels are very small, soft materials, they have the capability to absorb the water in presence of an aqueous medium. It is considered to be the fundamental property influencing the mechanism of action followed by this drug delivery system.
- **Higher Drug Loading Capacity**
  Nanogels are await to have greater loading capacity compared to conventional dosage forms. This is mainly due to the swelling property which allows the formulation to absorb large quantity of water. Loading takes place through three methods:
  Physical entrapment- it can refer to the connection between hydrophilic chains and hydrophobic regions of the polymer .Covalent bond of bioactive molecules which guides to the formation dense drug-loaded core. Controlled self-assembly-which is generally for polyelectrolyte-based Nanogel. The high loading efficiency is allocate to interaction between oppositely charged Electrolytes.
- **Permeability and Particle Size**
  Nanoparticles are capable of permeation by diffusion through tissues or compromised areas of endothelium and in some cases through a particular transport system, they produces a challenge crossing Blood Brain Barrier (BBB). So, in order to control such dilemma, Nanogels were formulated. It's small enough to cross (BBB) and in the same time to keep away from fast clearance mechanisms. **Classified Based On Their Behaviour Towards A Specific Stimuli**
  Non-responsive Nanogels: When non-responsive Nanogels come in contact with water, they absorb it, resulting in swelling of the Nanogel.
  Stimuli-responsive Nanogels: Any modification in any of these environmental factors i.e temp. pH etc., which act as stimuli, will lead to adjustment in the behaviour of the Nanogels as a response, hence the term stimuli-responsive Nanogels.
  Classified Based On the Type of Linkages PresentIn the Network Chains of Polymeric Gel Structure
  Physical Cross-Linked Gels
  Physical gels or pseudo gels are formed by weaker linkages through either:
  □ Van der Waals forces,
  □ Hydrophobic, electrostatic interactions, or
  □ Hydrogen bonding.
  A few simple methods are available to obtain physical gels.
  Liposome Modified Nanogels
  These liposomes go through chain fusion below pH 5.5 that has been shown to capable deliver calcein to the cytoplasm. Liposomes anchored by or modified with poly(N isopropylacrylamide)-basedcopolymeric groups are acceptable for thermo- and pHresponsive Nanogels, which are being explore for transdermal drug delivery.
  MicellarNanogels

Micellar Nanogels are manufactured by supramolecular self-assembly of both hydrophilic and hydrophobic blocks in an aqueous solution. Micellar Nanogels contain of a hydrophilic shell (corona), made of polymer blocks, surrounding a hydrophobic core, and stabilizing the whole micelle.

The motive of this conformation is to supply enough space to contain drugs or biological macromolecules just by physically entrapping these particles inside the borders of the shell, thereby acting as a drug delivery system.

As the micelle enters the body, the hydrophilic shell interconnects with the aqueous media by forming hydrogen bonds in order to shields the hydrophobic core that brings the drug to its target cells. This process protects the drug molecules from being hydrolyzed or degraded by enzymes.

ADVANTAGES OF NANOGELS

Nanogels are observed advantages over other drug delivery systems for a number of reasons, including:

1. High biocompatibility, which manufactured nanogels a very promising approach to drug delivery systems.

2. High biodegradability, which is pivotal to avoid assemble ofnanogel material in the bodily organs, thereby leading to toxicity and adverse effects.

3. Nanogels are immobile in the blood stream and the internal aqueous environment, meaning that they do not induce any immunological responses in the body.

4. Extremely small size, which persuades a number of effects such as:

• Enhanced permeation capability.

• Avoidance of quickly renal exclusion. Escaping renal clearance leads to prolonged serum half-life .

• Avoidance of clearance by phagocytic cells and the uptake by reticuloendothelial system, which allows both passive and active drug targeting.

• Capability to cross the Blood Brain Barrier.

• Increased penetration of endothelium in pathological sites like solid tumors, inflammation tissue and contravention areas. Since Tumor tissues have a high capillary permeability, more nanoparticles absorb into the tumor tissue and accumulate there, which increases the amount of drug delivered and the selectivity of the drug delivery.

• Improved capability to entry areas that is not accessible by hydrogels, upon intravenous administration.

• Safe delivery of drug delivernanogel particles into the cytoplasm of target cells, therefore making the perfect for intracellular drug delivery.

• Rapid responsiveness to environmental changes such as pH and temperature.

5. Nanogels are administered along a variety of routes including oral, pulmonary, nasal, parenteral, intra-ocular and topical routes of administration.

6. Nanogels are acceptable to administer both hydrophilic and hydrophobic drugs, as well as charged solutes and other diagnostic agents. This property is highly influenced by the type of functional groups present in the network of polymer chains, the crosslinking density and the type of crosslinking agent incorporated in the polymeric network.

7. Nanogels have a maximum affinity to aqueous solutions, resulting in their ability to swell or deswell, imbibing water when placed in an aqueous medium. This is the most beneficial characteristic of nanogels as it makes them perfect candidates for the uptake and delivery of proteins, peptides, bio-macromolecules as well as bulky drugs.

8. Drug loading in nanogels is moderately high when compared to other nanocarriers and drug delivery systems. This is due to the result of the functional groups present in the polymeric network. By set up hydrogen bonds or other weak linkages within the polymeric network and interconnecting with drug or protein molecules at the interface, functional groups on the polymeric network extremely increase the drug loading capacity of nanogels.

9. Incorporating drug into the nanogels is easy, spontaneous, and does not necessarily need any chemical reactions. This makes the process of preparing nanogels efficient, since the drug is not needed in the initial steps of the manufacturing process and can be introduced to the nanogel network in following steps when the nanogel swell with water or aqueous biological fluids.

10. Nanogels are manufactured to be capable of releasing drug in a controlled and sustained pattern at the target site, thereby enhancing the therapeutic efficacy of the drug and avoiding its adverse reactions.

11. Targeted drug delivery is possible in nanogels due to the presence of functional groups that associate with antibodies and/or drugs, resulting in high selectivity and preventing the accumulation of drug in non-target tissue like muscular and adipose tissue.

Moreover, the chemical modification of nanogels to incorporate ligands leads to targeted drug delivery and triggered drug release.

12. The synthesis of nanogels is generally a stress-free process since mechanical energy is not employed and harsh conditions like sonication or homogenization are not involved. Also, there is no introduction of organic solvents to the process in any of its steps. Hence the drug can be easily loaded without being exposed to any sort of vigorous conditions throughout the preparation process.

13. Nanogel dispersions are known to have and exceptionally large surface area which is crucial for a variety of in vivo applications.

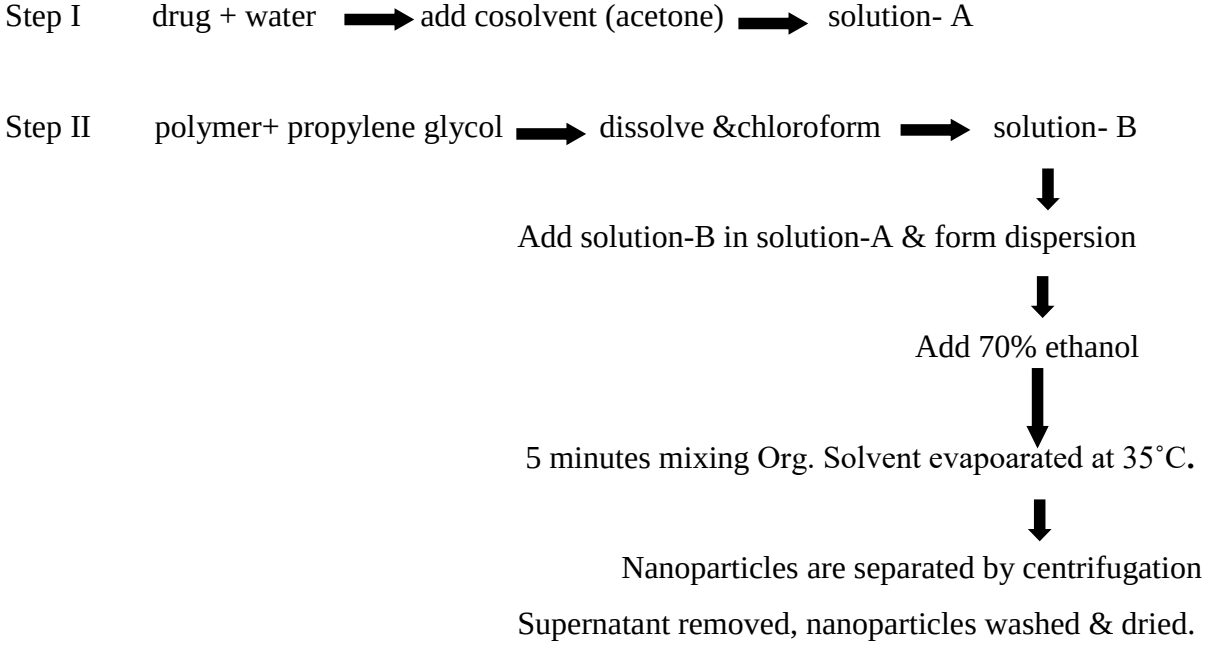
14. Bio-macromolecules as well as fragile compounds with low or high molecular weights can be successfully and efficiently encapsulated in the nanogels for the purpose of prolonging the activity of these molecules in the biological environment.

15. Nanogels can be formulated in the form of polymeric micellarnanogel systems that shows slower rates of dissociation, better stability over the surfactant micelles, lower critical micelle concentrations, and, most importantly, longer retention of loaded drugs.

Formulation and evaluation of Gel containing Fluconazole-Antifungal Agent. In this Fluconazole is an imidazole derivative and used for the treatment of local and systemic fungal infection. The oral use of fluconazole is not much recommended as it has many side effects. Some measures are such as how to increase the bioavailability if the drug without patient inconvenience.Why you choose that drug for this formulation. Etc.

Steps of nanoparticles were drug choosen , polymer choosen and their compatibility, aftr that maethod preparation, trial formulations , worked formulations and conversion of nanoparticle in to nanogel.

Nanoprecipitation method [9]



Result of the topic was that by this method different formulations of nanogel were prepared in which two of the formulations were taken as the best formulations due to its %CDR in 12 hrs and stable at different parameters of the nanoparticles. Thus this process , drug an formulation was recommended by Dr. Pranshu Tangri, Associate Professor , to me and worked on it and found that it is highly useful for all the skin infections as not available in the market as in this form of the drug due its increased bioavailability and its drug potency.

II. RELATED WORK

Formulation and evaluation of polymeric nanoparticles of an antihypetensive drug for gastroretention. In this Carvidolol was used as a gastroretention while is used as to treat cardiac failure. Carvedilol was selected as a suitable drug for gastro- retentive nanoparticles due to its short half life, low bioavailability, high frequency of administration, and narrow absorption window in stomach and upper part of GIT.

Formulation and evaluation of lamivudine loaded polymethacrylic acid nanoparticles. In this lamivudine was used , oral formulations lamivudine are administered multiple times a day (150 mg twice daily) because of its moderate half-life (5-7 hours). Lamivudine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multidose therapy, poor patient compliance, and high cost. The objective of the present study was to prepare nanoparticles of lamivudine to overcome some of these problems.[7-8]

.

III. METHODOLOGY

Preparation of Nanoparticles[9,15-23]

Nanoparticles were prepared according to the nanoprecipitation method. Briefly, 200 mg of polymer (HPMC, chitosan, and gelatin) was dissolved in 25 ml of acetone separately. The miconazole nitrate 100 mg was dissolved in 2 ml of dimethylsulfoxide. Both solutions were mixed and then 50 ml of water was added and stirred for a half hour. Acetone was eliminated

by evaporation under reduced pressure using rotary flash evaporator and the final volume of the suspension was adjusted to 10 ml. Then this suspension was centrifuged at 15000 rpm at 4oC for half an hour. The supernatant was discarded and precipitate was washed 3 times with distilled water. The nanoparticles thus obtained were dried overnight in oven at 60ºC and stored in a desiccator.

Preparation of miconazole nitrate Nanogel [10-14]

Accurately weighed quantity of the nanoparticles and Tween-80 as stabilizer are dissolved in glycerol while stirring. Prepared aqueous phase containing Carbopol-940 dissolved in water with continuous stirring and heat. These drug containing phase is sonicated on Ultra sonic bath sonicator. The drug phase is added drop by drop into the aqueous phase during homogenization to form emulsion. The emulsion converted into nanodroplets by homogenizer which formed O/W emulsion. Homogenization was continued for one hour. Triethanolamine added to form the gel with continuous stirring to nanogel.

For this BIT software and different formulas were used such as in vitro release of the drug , standard deviation of the drug, stability of the formulations, drug content, drug efficiency etc during the experiment in the laboratory of GRD institute of management & technology in the year of 2020.

IV. RESULTS AND DICUSSION

Here, F1 & F10 were suggested as the best formulation due to their some parameter which are given below.

Table:1 Different parameters of all formulations

FORMULATION CODE	Homogenesity	pH	Drug content (%)	Spreadability (g.cm/s)	Extrudability (g)	Entapped efficiency (%)
FNG1	Uniform	5.5	98.5	30.5	18.8	49.25
FNG2	Uniform	4.9	97.3	27.5	18.0	48.65
FNG3	Uniform	5.0	98.1	27.2	18.0	49.05
FNG4	Uniform	5.7	98.3	25.4	18.2	49.15
FNG5	Uniform	6.0	96.2	26.3	18.3	48.1
FNG6	Uniform	6.1	97.8	26.0	18.4	48.9
FNG7	Uniform	5.9	97.9	30.6	18.6	48.95
FNG8	Uniform	6.5	98.0	25.8	18.7	49.0
FNG9	Uniform	5.3	97.9	24.0	18.0	48.45
FNG10	Uniform	5.0	99.6	33.4	18.9	49.8
FNG11	Uniform	4.1	96.8	28.7	18.5	48.4
FNG12	Uniform	6.7	98.2	28.0	18.4	49.10

Figure:1 Zeta potential of F1 formulation

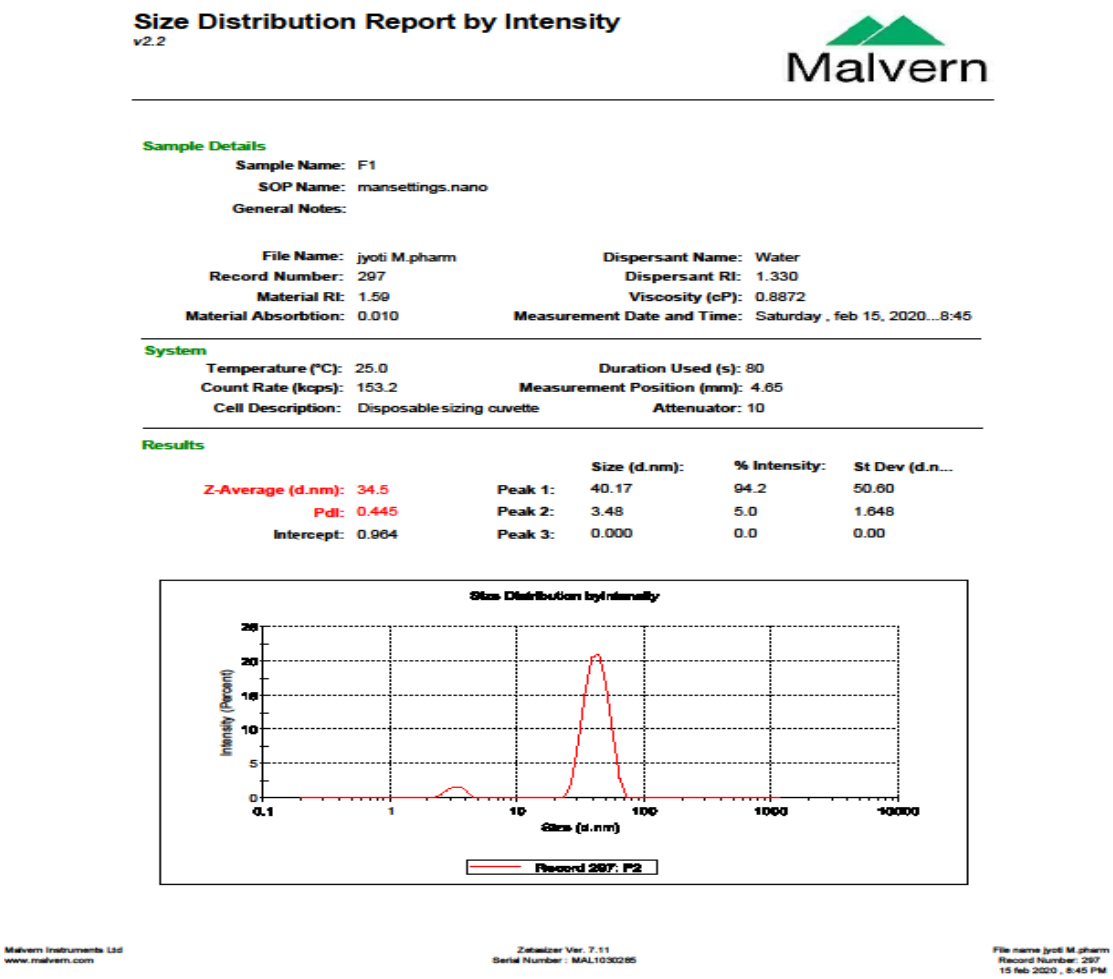
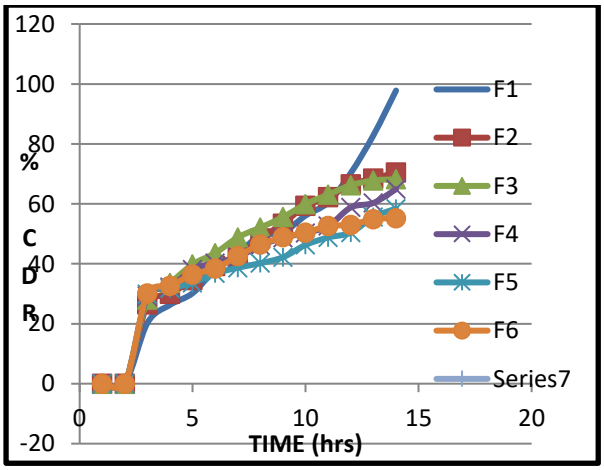


Table : 2 In-Vitro drug release (% CDR) of formulated Nanogels

TIME (Hrs)	FNG1	FNG2	FNG3	FNG4	FNG5	FNG6	FNG7	FNG8	FNG9	FNG 10	FNG 11	FNG 12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	20.3	26.5	28.1	29.2	29.9	30.1	25.8	29.4	32.4	30.3	32.5	36.5
2	26.3	30.0	33.6	32.2	31.8	32.7	29.3	32.7	36.5	37.0	38.4	40.3
3	30.2	34.6	39.8	38.1	33.6	36.4	32.4	35.8	39.6	40.8	45.6	46.5
4	38.1	39.3	43.6	40.3	36.8	38.3	36.8	39.4	42.3	48.8	49.0	59.6
5	43.5	42.1	48.8	42.3	38.2	42.6	40.4	42.4	47.3	52.3	53.3	61.3
6	49.4	48.5	52.1	46.	40.	46.	48.	48.	49.	58.5	56.4	65.4

				1	2	4	5	1	0			
7	50.5	53.4	55.6	48.7	48.2	48.9	50.7	50.9	52.1	64.5	65.6	68.6
8	56.1	59.4	59.9	50.3	46,3	50.4	56.3	54.9	53.7	73.3	72.8	70.8
9	60.5	62.3	63.1	52.6	48.8	52.6	60.4	60.9	59.9	79.7	78.3	74.6
10	70.3	66.5	66.2	58.8	50.4	53.0	70.3	63.8	61.0	85.6	85.2	79.7
11	82.9	68.4	67.8	60.3	55.6	54.9	88.9	70.7	66.8	92.5	89.0	82.9
12	97.8	70.5	68.2	64.9	58.4	55.2	96.8	75.9	69.8	98.9	90.2	85.3

Figure:2 In-vitro release of the formulations (F1-F6) Figure:3 In-vitro release of the formulations (F7-F9)



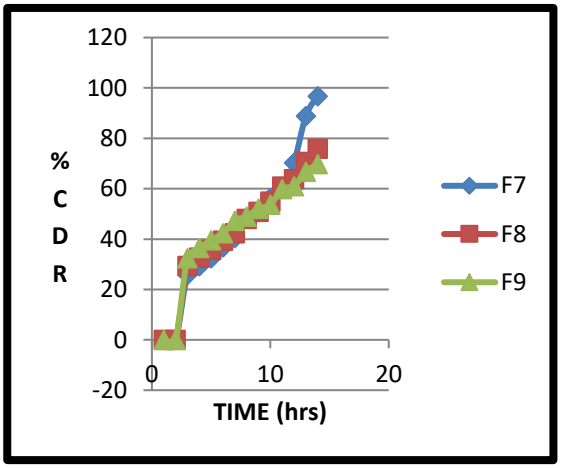


Figure: 4 In-vitro release of the formulations (F10-F12)

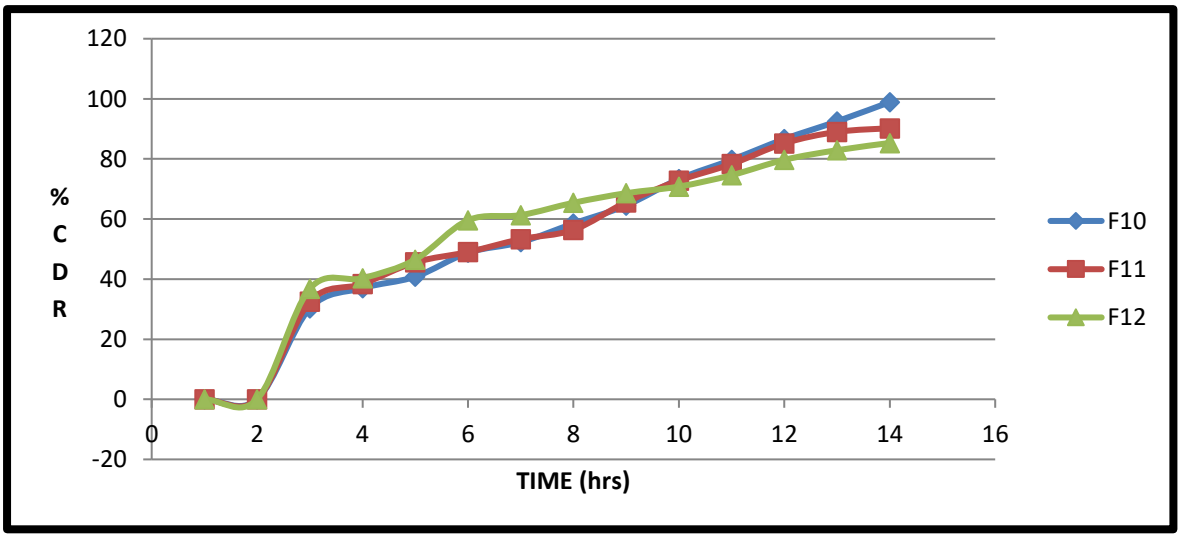


Figure:5 Stability analysis of F1 & F10 formulation after storage

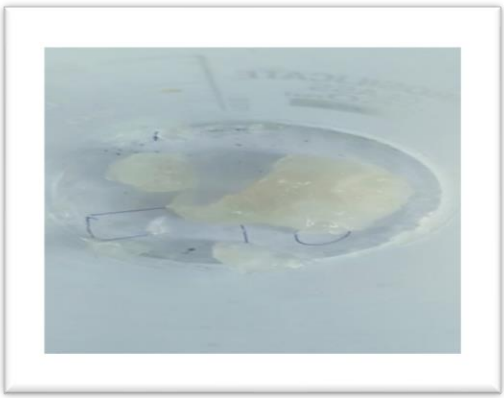


Table: 3 Drug conc. Of formulated nanogel (F1& F10 F10) for 2 months

S.NO.	**DAYS(** F1)	**DRUG CONTENT (%)**	**pH**
1	**INITIAL** 0	98.5	6.0
2	**AFTER STORAGE** (40˚C &75 % RH) 10	98.3	6.0
3	20	98.0	5.9
4	30	97.8	5.8
5	40	97.6	5.7
6	50	97.0	5.7
7	60	96.5	5.6

Table:4 Drug conc. Of formulated nanogel (F10) for 2 months

S.NO.	**DAYS**	**DRUG CONTENT (%)**	**pH**
1	**INITIAL** 0	99.6	6.4
2	**AFTER STORAGE (40˚C &75 % RH)** 10	99.6	6.4
3	20	98.6	6.3
4	30	98.2	6.2
5	40	98.0	6.1
6	50	97.8	6.0
7	60	97.6	6.0

Figure:6 Drug content graph

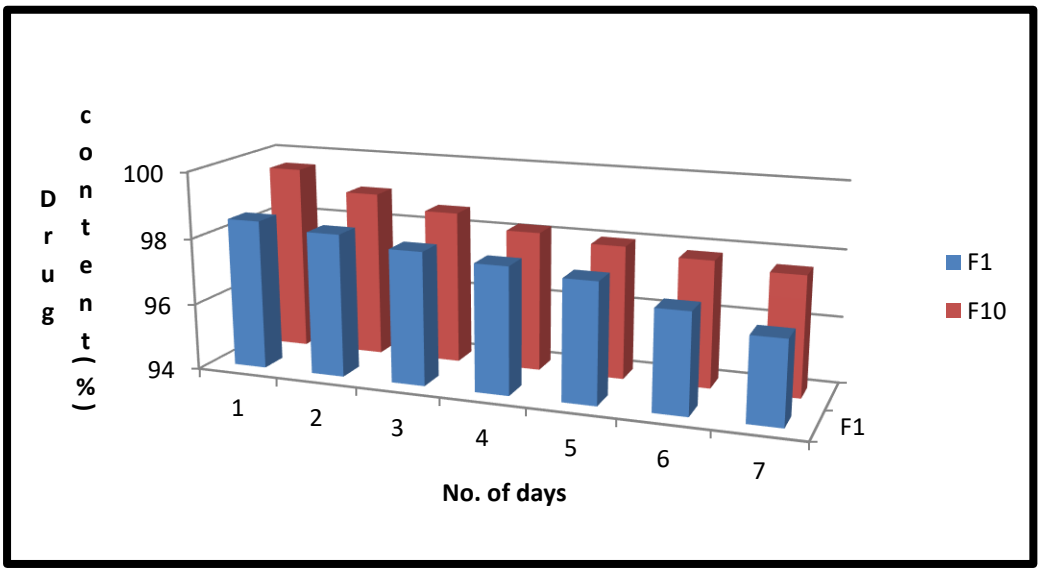


Figure:7 In-vitro release kinetic model of F1 formulation

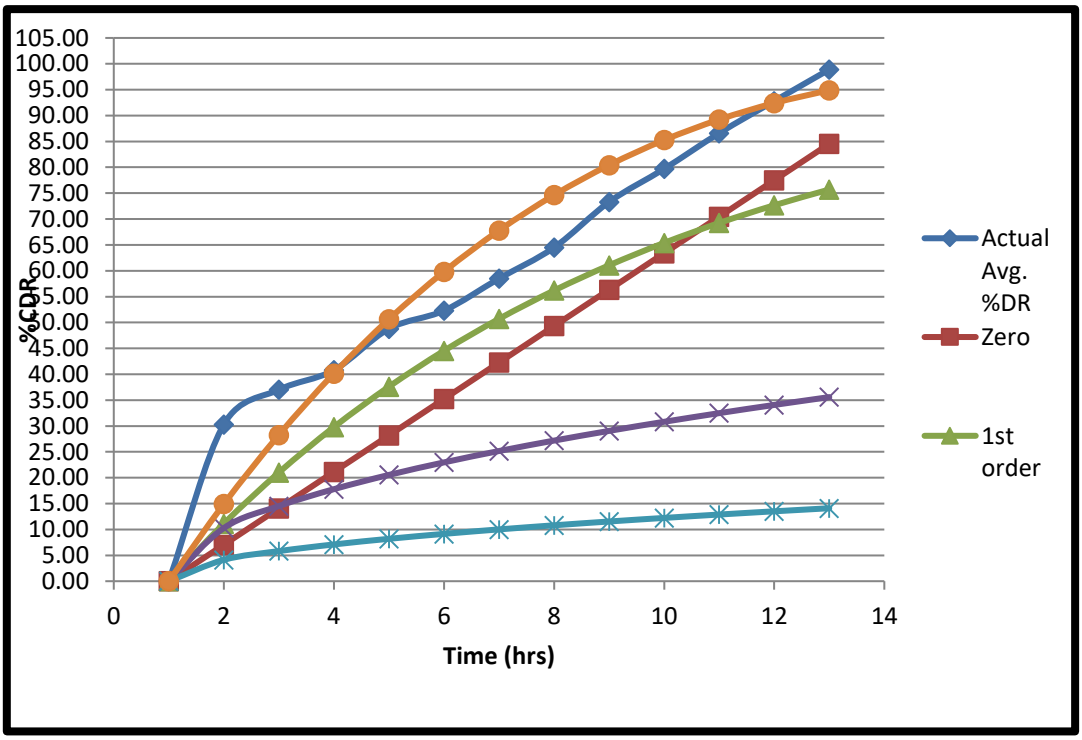


Figure:8 In-vitro release kinetic model of F10 formulation

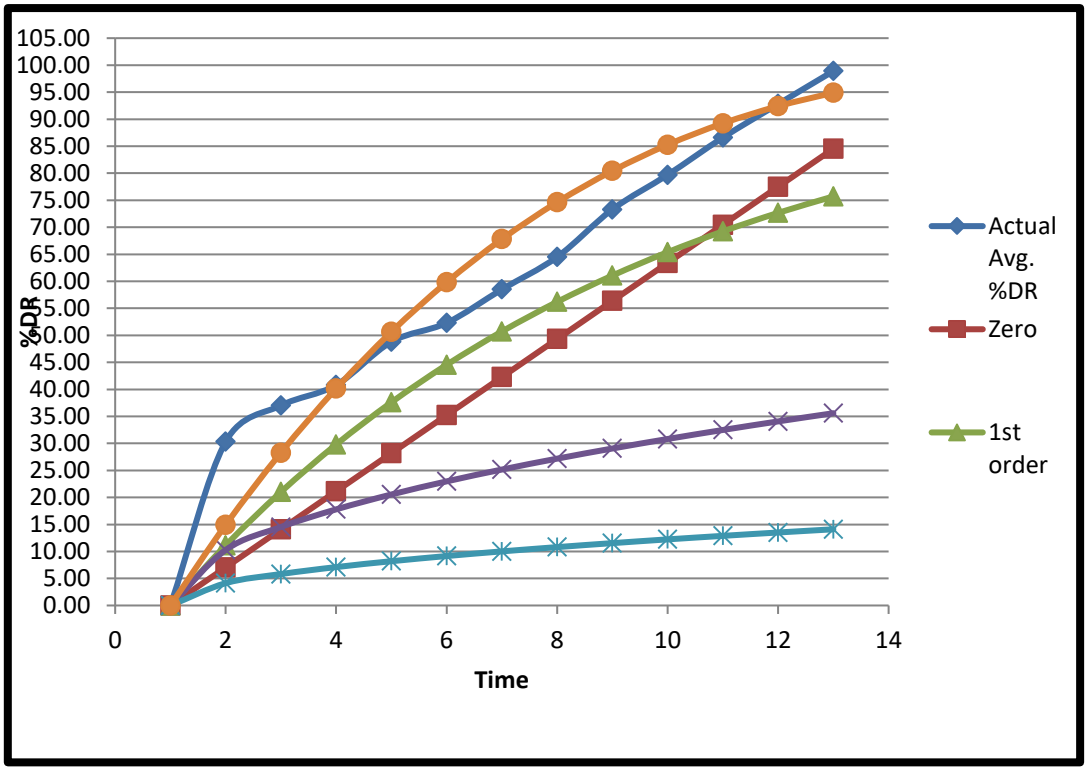


Table : 5 Model fitting release profile of prepared nanogel F1 & F10 formulations

Code	Corelation factor			Korsmeyer &peppas(N)	Mechanism of release	Best fit model
	Zero(R)2	First(R2)	Higuchi(R2)			
F^1	0.9569	0.6378	0.8904	0.6020	Anomalous transport	Zero model
F^{10}	0.9582	0.7666	0.8983	0.4942	Fickian diffusion	Zero model

V. CONCIUSION AND FUTURE SCOPE

Topical nanogel loaded with miconazole nitrate was successfully prepared using modified emulsification diffusion method. Zeta potential studies have revealed that there was no crystalline stryuc ture of drug present in the final nanogel formulation. FTIR studies have revealed that both the dru and polymer had been incorporated in the prepared nanogel. Nanogel physicochemical properties revealed that it was effective for topical delievery of the nanogel. In vitro activity had confirmed the prepared nanogel retarded the growth of candida albicans.

VI. ACKNOWLEDGEMENT

It takes this privilege and pleasure to acknowledge the contribution of many individuals who have been inspirational and supportive throughout my work undertaken and endowed me with the most precious knowledge to see success in my endeavour. My work bears the

imprint of all those people, I am grateful to. It is said that only hard work and will power is not enough for getting success, but the efforts for getting success are to be guided and motivated. I take this pleasant oppourtunity to express my regards and gratitude to his holiness **Shri Raja Singh, GRD (PG) Institute of Management & Technology** for his encouragement and providing facilities that enabled me to complete my project work. I owe my heartiest gratitude to **Dr. N.G. Raghvendra Rao , Director** of Department of Pharmacy, GRD (PG) Institute of Management & Technology, for his valuable guidance, kind help and incessant encouragement. In this regards, it gives me a feeling of great pleasure for expressing my deep gratitude and honour for my respected guide **Dr. Pranshu Tangri, M.pharm, Ph.D, Associate Professor**, Department of Pharmacy, GRD (PG) Institute of Management & Technology, Rajpur Road, Dehradun for his valuable guidance and continuous supervision which enable me in successful completion of my project work. His great encouragement and efforts have provided moral support and confidence to carry on my work.

VII. REFERENCES

1. Langer R. Biomaterials in drug delivery and tissue engineering: one laboratory's experience. Acc Chem Res 2000; 33: 94-101.
2. Bhadra D, Bhadra S, Jain P, Jain NK. Pegnology: a review of PEG-ylated systems. Pharmazie 2002; 57: 5-29.
3. Kommareddy S, Tiwari SB, Amiji MM. Long-circulating polymeric nanovectors for tumor-selective gene delivery. Technol Cancer Res Treat 2005; 4: 61525.
4. Lee M, Kim SW. Polyethylene glycol-conjugated copolymers for plasmid DNA delivery. Pharm Res 2005; 22: 1-10.
5. Vila A, Sanchez A, Tobio M, Calvo P, Alonso MJ. Design of biodegradable particles for protein delivery. J Control Release 2002; 78: 15-24.
6. Tiruwa renu, Indian Journal of pharmaceutical and biological research (IJPBR), Biol. Res., 2015; 4(2): 27-31.
7. Punna R.R., Sindhura G., Saha R.N., Design an Study of Lamivudine Oral Controlled Release Tablet, **AAPS PharmSciTech,** 2007, 8, E1-E9.
8. Jain S , Tiwari AK, Sapra B , Jain AK. Formulation & evaluation of Ethosomes for Transdermal Delivery of Lamivudine, **AAPS PharmSciTech,** 2007, 8, E1-E8.
9. Leena Peltonen., The Effect of Cosolvents on the Formulation of Nanoparticles From LowMolecular-Weight Poly(l)lactide AAPS PharmSciTech., 2002, 3, E1-E7.
10. Vinogradov SV, Batrakova EV, Kabanov AV,Nanogels for oligonucleotide delivery to the brain. Bioconjug Chem. 2004; 15(1):50-60.
11. Sultana F, Manirujjaman M, Imran-Ul-Haque MA, Sharmin S. An Overview of Nanogel Drug Delivery System. Journal of Applied Pharmaceutical Science Vol. 2013;3(8 suppl 1):S95-S105.
12. Sultana F, Manirujjaman, Md Imran-Ul-Haque, Arafat M, Sharmin S An Overview of Nanogel Drug Delivery System. J Appl Pharm Sci 2013; (3):95-105.
13. Vinogradov SV Nanogels in the race for drug delivery. Nanomedicine 2010; (5):165–168.

14. Jung Kwon Oh, Ray Drumright, Daniel J. Siegwart, Krzysztof Matyjaszewski, The development of microgels/Nanogels for drug delivery applications, Prog. Polym. Sci. 2008; (33):448–477.
15. Govender T, Stolnik S, Garnett MC, Illum L, Davis SS. PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. J. Control. Rel. 1999; 57: 171-185
16. Kikwai L, Babu RJ, Prado R, Kolot A, Armstrong CA, Ansel JC, Singh M, In-vitro and in-vivo evaluation of topical formulations of spantide II, AAPS PharmSciTech, 6(4), 2005, 565-572.
17. Saroha K, Singh S, Aggarwal A, Nanda S, Transdermal GelsAn Alternative Vehicle For Drug Delivery, Int Journal of Phr Chemical and Biological Sciences, 3(3), 2013, 495-503.
18. Thakur V, Prashar B, Arora S, Formulation and in vitro Evaluation of Gel for Topical Delivery of Antifungal Agent Fluconazole Using Different Penetration Enhancers, Drug Invention Today, 4(8), 2012, 414-419.
19. Sheikh AA, Ali SS, Siddiqui AR, Zahir Z, Ahmad A, Formulation development and characterization of aceclofenac gel containing linseed oil and ginger oleoresin, Int. J. Pharm. Tech. Res, 3(3), 2011, 1448-1453.
20. Preet L, Topical Gel: A Recent Approach for Novel Drug delivery, Asian Journal of Biomedical and Pharmaceutical Sciences, 3(17), 2013, 1-5.
21. Choukse R, Formulation and Evaluation of Pluronic lecithin organogel of Flurbiprofen, Journal of Biomedical and Pharmaceutical Research, 1(1), 2012, 1-7.
22. Kikwai L, Babu RJ, Prado R, Kolot A, Armstrong CA, Ansel JC, Singh M, In-vitro and in-vivo evaluation of topical formulations of spantide II, AAPS PharmSciTech, 6(4), 2005, 565-572.
23. 29. Saroha K, Singh S, Aggarwal A, Nanda S, Transdermal GelsAn Alternative Vehicle For Drug Delivery, Int Journal of Phr Chemical and Biological Sciences, 3(3), 2013, 495-503.