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Preparation of Clotrimazole-Silver Nanoparticals: Topical Antimycotic Nanogel Delivery

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ABSTRACT
Nanotechnology has unbolted individual platform to explore in a hybrid therapeutic region. At present, nanometal technology is in the embattled field which has some extraordinary advantages of exceptionally very small metal nanoparticle particle sizes. Inthis research we focused on the antimycotic properties of silver nanoparticles with the combination of niosomes and nanogel which shows the synergistic effects with clotrimazole antifungal drug. This topical preparation can used for the treatment against various pathogens. We synthesized silver nanoparticles using Carbopol concentration 0.04, 0.05, 0.06, 0.07, 0.08g/ml which shows orange to brown color after some time it converts into greyish color. UV visible spectra of silver nanoparticles at different concentration were analyzed and drug loading and entrapment efficiency was performed which was found to be fairly good.

Keywords- , clotrimazole UV spectroscopy, nanoparticle, fungal, nanogel

I. INTRODUCTION

Fungal Diseases

A threat of fungal infection on the life of plants and animals are increasingly recognized fact. A study gave information those fungal infections not only limited to animals and crops but also evolving as a pathogen across diverse taxa including soft corals. The latest reports describe the scary and remarkable effects on food safety and ecosystem imbalance of these pathogens. (1, **7**). The fact is, the deaths causes by fungal infection are often overlooked. Neither World Health Organization nor any public health agencies have any program on fungal infections except Centers for Disease Control and prevention (U.S.) do little or no mycological surveillances.

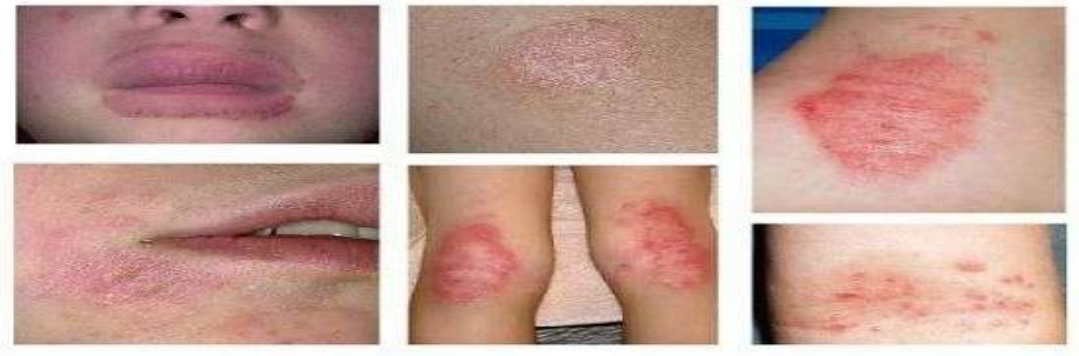

Fig. 1: Symptoms and sign of fungal infections

The rate of invasive fungal disease is less than external diseases, but these diseases are ofmore solicitude because they are associated to a high fatality rate. Various species are accountable for invasive fungal diseases which causes more than 90% of death. Some of them are: Pneumocystis, Aspergillus, Candida and Cryptococcus. Invasive fungal infections occur in approximately six cases among 100000 people in which only half population are detected in their lifespan which are

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suffered from these infections per year. Due to the difficulty in the diagnosis of these infection, rate of detection is very low so it includes radiological, microbiological and clinical findings. (3, 7).

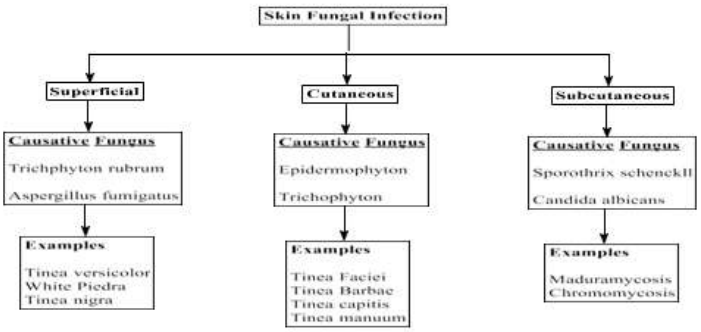

Table 1: Types of fungal diseases

Even though invasive fungal disease has lots of advance treatment, but death rate still continues and the intensities of infections are different. These infections intensity is considered, for examples: C. glabrata infections resistant to azole, C. tropicalis infectionsresistant to multi-azole and co-resistant of echinocandin-azole isolate is noted.

There are many multi-drug resisting fungal species, together with pan-azole resistant they are as follow

Table 2: Ten significant invasive fungal infections Statics

Causative Organism	Location	Estimated life-threatening infections/ year at that location*	Mortality rates (% in infected population s)*
Penicilliosis (*Penicillium marneffei*)	Southeast Asia	>8,000	2–75
Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Brazil	~4,000	5–27
Histoplasmosis (*Histoplasma capsulatum*)	Midwestern United States	~25,000	28–50
Coccidioidomycosis (*Coccidioides immitis*)	Southwestern United States	~25,000	<1–70
Blastomycosis (*Blastomyces dermatitidis*)	Midwestern and Atlantic United State	~3,000	<2–68
Mucormycosis (*Rhizopus oryzae*)	Worldwide	>10,000	30–90
Pneumocystis (*Pneumocystis jirovecii*)	Worldwide	>400,000	20–80
Aspergillosis (*Aspergillus fumigatus*	Worldwide	>200,000	30–95
Candidiasis (*Candida albicans*)	Worldwide	>400,000	46–75
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	>1,000,000	20–70
Endemic dimorphic mycoses*	-	-	-
Opportunistic invasive mycoses	-	-	-

Nanogels

In biomedical field nanogel is pioneering and promising materials. Recent advancement in curing & diagnosing, and new investigating methods of disease like bioimaging techniques, medical tools, pharmaceutical industry is employing nanotechnology as drugdelivery tool for better results. Exclusive properties of nanogel, it is considered as great tool in multidisciplinary fields, and large number of publications evidences in

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preparation, properties and its applications. The term ‘‘Nanogel’’ first introduce in the papers where hydrophilic polymer network was produced. Poly-ethylene imine and poly- ethylene glycol are the chief chemical constituents that were chemically cross linked. For delivering anti-sense oligonucleotides it was used.

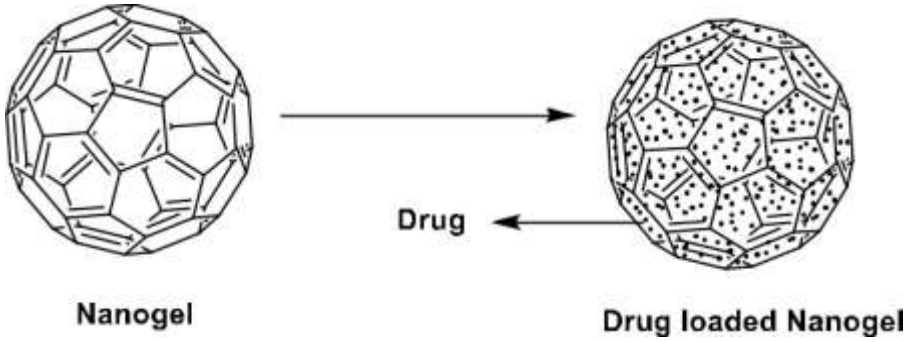
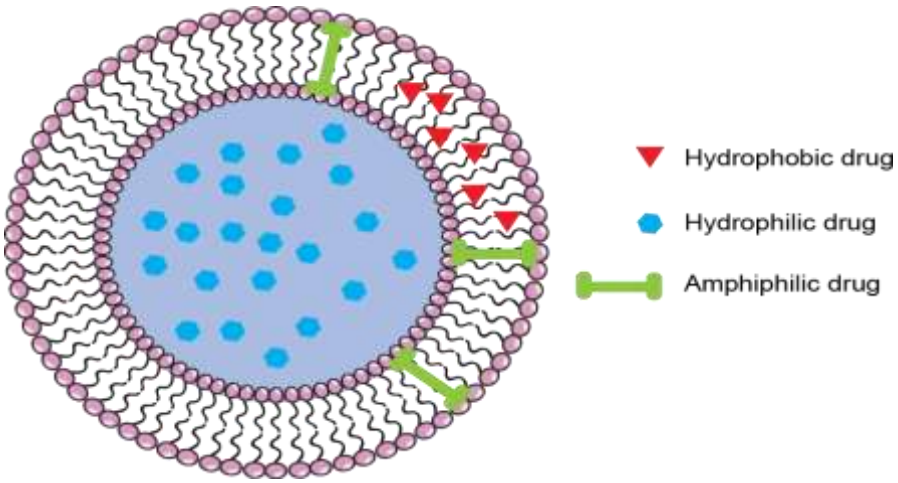


Fig. 2: High drug loading capacity in polymer network of nanogel thus release ofdrug

Nanogels have the distinctive properties like swelling and degradation property; soft and flexible in size, stimuli responsive behavior, large surface area and high water containing capacity. Biological molecules and drugs are encapsulated in nanogel and its network protect drugs or biological molecules from the elimination and degradation in vivo and deliver biological molecule and drugs in sustained and control way.

Why Niosomes?

Requirement of drug targeting is site specific drug release with minimum toxicity and maximum therapeutic action. When encapsulated drug releases to the target site from the vesicle is known as vesicular drug delivery system. Niosomes, vesicular nanocarrier usedas the demand from past 3 decades because of its numerous benefits.



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Advantages

- The medication is given in a controlled way at targeted site.
- As compared to colloidal vesicle carrier noisome is economically cheaper.
- Niosomes found to be more stable than liposomes.
- Both hydrophillic and hydrophobic drugs can incorporate niosomes.

Niosomes Limitations

- Niosomes stand life decreases in the composition.
- It has some problems such as chemical and physical instability, vesicle fusion, formation of aggregation and hydrolysis of encapsulated drug.

Silver Nanoparticles

Nanoparticles (NPs) can be found naturally, incidentally, or tailored substance comprising more than 50 % of particles in 1–100nm range size. It can be categorized extensively as provided under (a) Organic and (b) Inorganic.

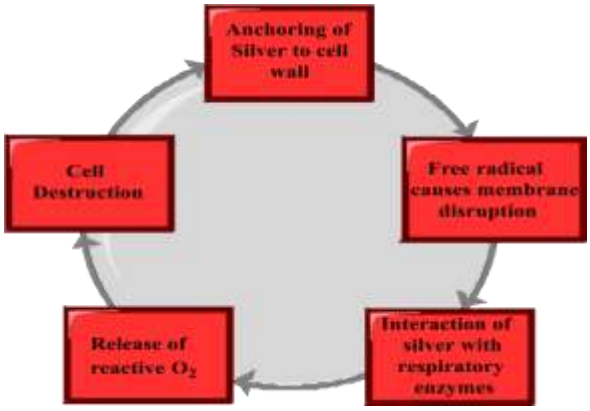

Fig.4: Silver Nanoparticles mechanism of action

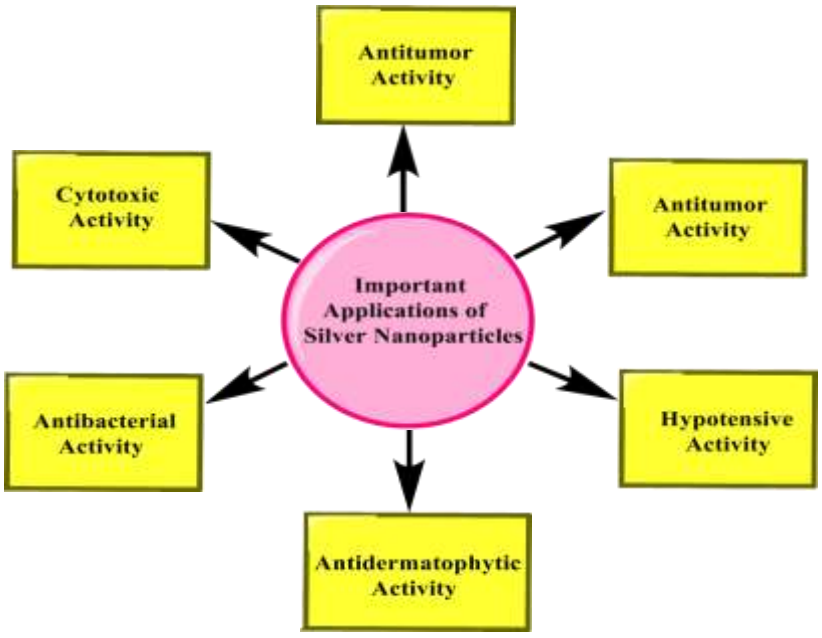

Fig.5: Silver Nanoparticles application in various fields.

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"RESEARCH HYPOTHESEZED

Hypothesis

Nanotechnology becomes an unbolted platform stand to explore inside a heterogeneous therapeutic region. At present, nanometal methodology in the objective domain has some outstanding benefits of unusually very tiny range of particle range of Metal nanoparticles.

- We choose the three combination of **"N" NANO (Niosomes, Nanogel and Nanoparticles)** in this research. Clotrimazole is mainly applied for its Antimycotic factor but there are some limitations-
- Clotrimazole is a poorly water-soluble drug.
- It has poor penetration, dermal bioavailability, limited permeation, andchangeable medication levels bound the performance with a longer duration of therapy.
- It requires a proper vehicle to raise the right levels of topical absorption.
- Conventional gel, cream have problem of leakage of the formulation.

Nanogels are vigorous nanoparticles that can be taken in use to delivery drug compounds in controlled manner. Silver Nanoparticles Whose antifungal activity is well documented and Silver ion possessed documented antifungal properties along with clotrimazole it shows synergistic effect hence enhance the therapeutic effects of the combination .

Niosomes are more effective vesicular carrier and also cheaper. It is very good in drug delivery at target site and less toxic. Nanogel decreases premature dug release and its particle size and great loading capacity of drug is controlled because of polymeric network. For maximizing the therapeutic effectiveness of drug AgNPs is combined with nanogels and niosomes to increase the targeted drug delivery and enhance the permeation.

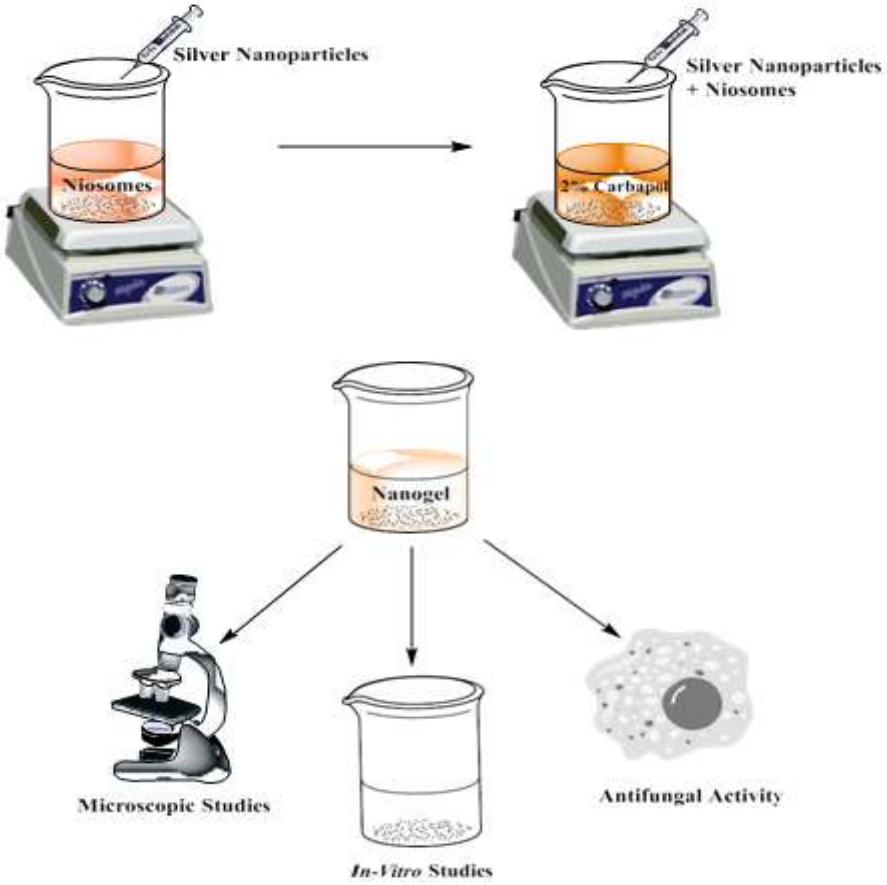

Fig. 6: Schematic Representation of Plan of Work

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DRUG PROFILE

Clotrimazole

Clotrimazole is an imidazole ring derivative used primarily in the treatment of topical dermal, oral infections and to fight with vaginal candida infections. Is a broad spectrum antimycotic agent with lipophilic nature. Several fungal strains are seen to affect by clotrimazole lie those causing causes stubborn candidiasis in the vagina such as C. topicalis & C. albicans.

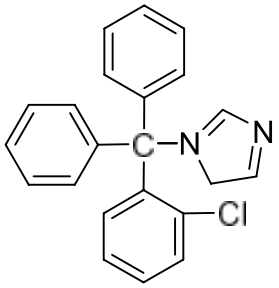

Fig. 7: Clotrimazole chemical structure

Chemical formula: $C_{22}H_{17}ClN_2$

IUPAC Name: (1-[(2-chlorophenyl) diphenylmethyl]-1H-imidazole)

Molecular weight: 344.8 g/mol

Uses: Antifungal agent, anti-malaria, sickle cell anemia

Mode of action

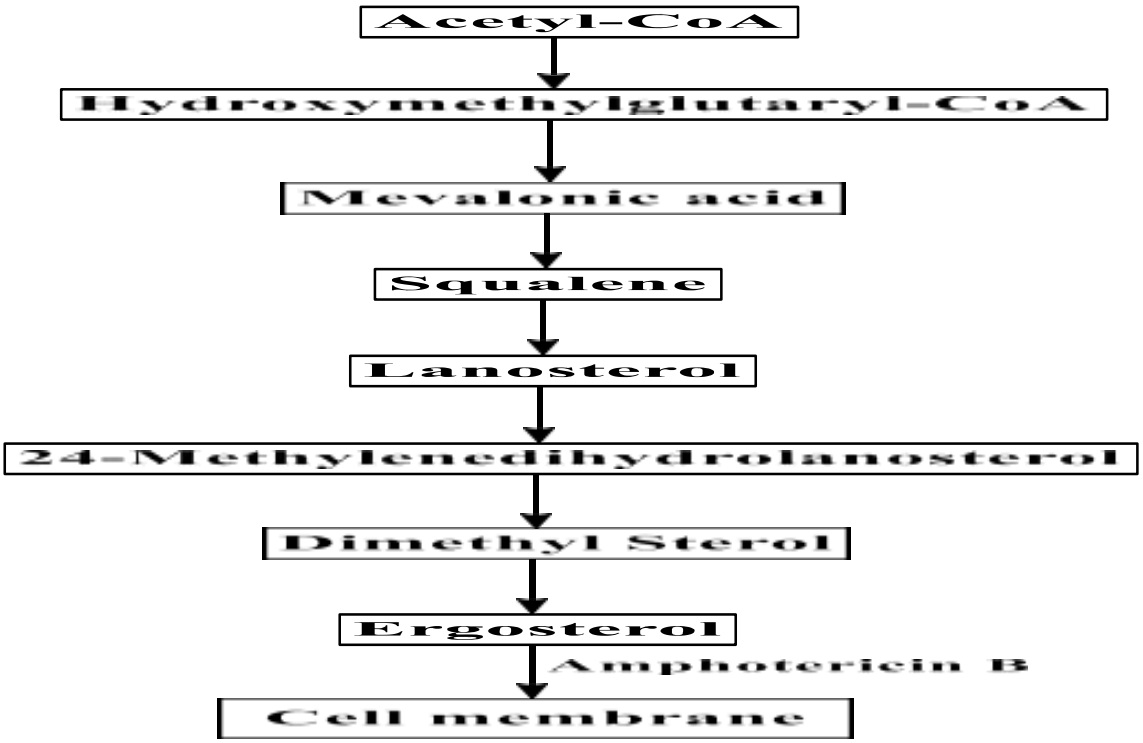

Fig. 8: Clotrimazole mechanism of action

Clotrimazole and other azoles inhibit 24-methylene-dihydro lanosterol demethylations, they get accumulated, this additional points to feedback command of the entire pathway. Depletion of ergosterol concentration in cytoplasm modifies the structure of membrane and leads to the lethal efflux

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of materials of the cytoplasm ions.

Clotrimazole is an OTC drug but its blended combination may need a prescription.

Dosage and administration:

Table 3: Several dosages of clotrimazole in various treatment

S.No.	Dosage form	limit range of clotrimazole	Diseases
1	Cream, Solutons, Spray, lotion	1%	Skin infections
2	Pessaries	100mg, 200mg and 500mg	vulvovaginal candiasis
3	cream	1%,2% and 10%	vaginal areas
4	Longenges	10mg	oropharyngeal candidiasis,

PREFORMULATION STUDIES

Pre-formulation studies

First of All, any formulation, it is needed a prior study for pre-formulation. It introduces essential knowledge regarding the medication and other related components. With the help of pre-formulation, we can make a durable formulation. Pre-formulation reports regarding compatibility with the additional excipients applied. It supports to discover more suitable excipients, additives to extend the formulation strength and support in offering medication in the practice. Clotrimazole was acquired from TCI Chemicals Pvt. Ltd that utilized as an ongoing medication in this formulation..

Physical characteristics

Table 4: Physical properties of clotrimazole

S. No	Drug	Physical appearance and color	Melting point	Solubility
1.	Clotrimazole	White crystalline powder	150.7°C	Soluble inmethanol, acetone

Melting Point Determination of CLOT

At the time at which the compound turns from one form to another i.e. from stable form to its fluid form. The melting time of the clotrimazole obtained estimated utilizing a slender pipe with an end sealed by the reflection of the melting point apparatus. A light volume of simple medication was loaded in the capillary cell and put in the equipment three melting times obtained seen one the initial time of melting, second half melting point and last fully melting time. The average of the all three M.P was calculated and saved.

Calibration arch of CLOT inside Methanol

To build the Calibration arch of clotrimazole we used Methanol. The resultant solution has 100ml of methanol with dissolved 10mg of drug, the whole process undergone

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sonication for 5 minutes. Dilutions done in concentrations of 1, 2, 4, 6, 8 in mcg per ml with the help of methanol, and absorbance of clotrimazole was noted at 221 nm applying UV apparent spectrophotometry. 0.992 was the Verified R^2.

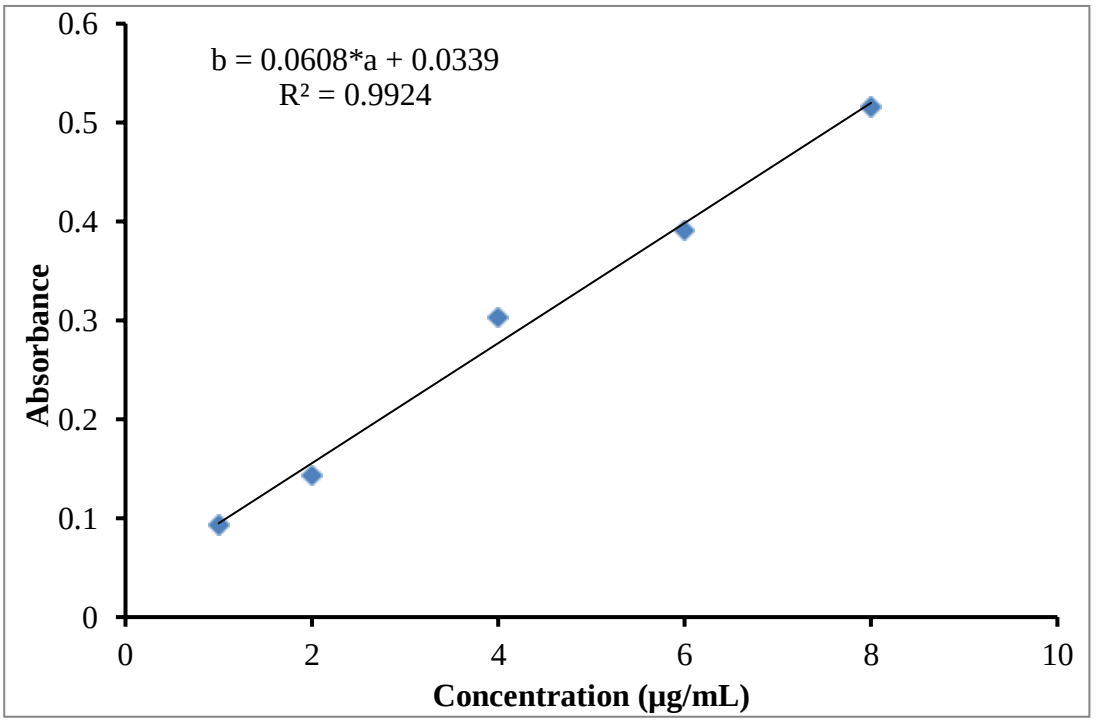

Fig. 9: Clotrimazole calibration arch using methanol

Calibration curve of Clotrimazole in PBS buffer (7.5)

In 10 ml phosphate buffer, 10mg true drug was immersed. 5ml of this solution was taken to make 50 ml (100 µg/ml). Dilutions from this solution were obtained (10-50 µg/ml). This absorption was applied to prepare the absorbance at 221nm.

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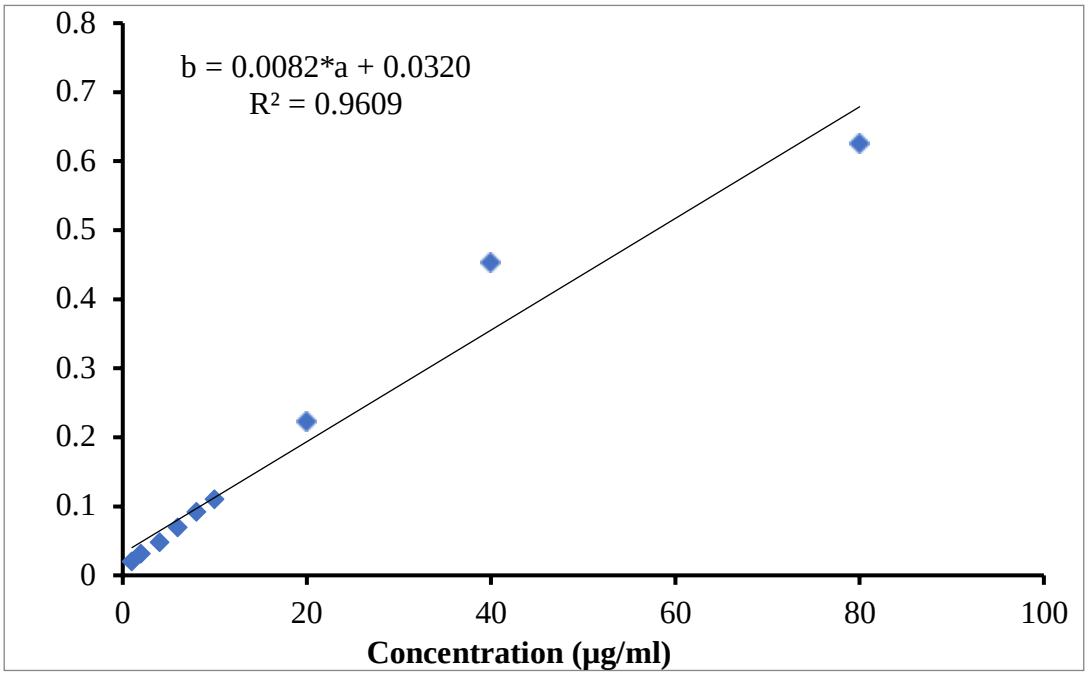

Fig. 10: clotrimazole Calibration arch in PBS buffer (7.4)

Here a, b are respectively x, y coordinate of the curve.

II. MATERIAL AND METHODS

Materials

In this work for developing Nanogel the required chemicals were used from companies SIGMA-Adrich , CDH and Hi-MEDIA, and used as it is not further purified. Table form of the chemical, equipment's and consumables along with its company is given below respectively.

Equipment

Table 5: Equipments list & their details

S. No.	Name of Instrument	Model/Version	Manufacturer
1.	Double Beam UV-Vis Spectrophotometer	LT-2800	Labtronics, India
2.	Benchtop Centrifuge	R-4C DX	REMI Elektrotechnik Ltd, India
3.	Digital Ultrasonic Cleaner	CD 4820	Citizen Scale India Private Limited
4.	Rota evaporator	R-215	BÜCHI Labortechnik, Switzerland
5.	Weighing balance	CX 220	Citizen Scale India Private Limited
6.	Heating/Drying Oven	--------	Jain Scientific Glass Works, India
7.	Digital pH Meter	335 LED Based	SYSTRONICS (India) Limeted
8.	Magnetic Stirrer	2MLH	REMI Elektrotechnik Ltd, India
9.	Melting Point Apparatus	M-560	BÜCHI Labortechnik, Switzerland
10.	Fluorescence microscope	CKXF3	Olympus

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7.1.1. Chemical

Table 6: Chemicals list & their details

S. No	Name of Chemical	Producer
1	Clotimazole	TCI
2	Silver nitrate	CDH
3	Carbopol	CDH
4	pvp	
5	Triethalamine	TCI
6	DCM	
7	Cholesterol	TCI
8	Methanol	HI Media
9	Sodium borohydride	TCI
10.	Disodium hydrogen phosphate	Qualigen Fine chemicals
11.	Potassium dihydrogen phosphate	CDH, New Delhi, India
12	Sodium chloride (NaCl)	
13	Methanol	Molychem
14	Span 80	

Consumable Items

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Table 7: Consumables items & their details

S.No	Consumables	Producer
1.	Dropper	Tarson, India
2.	Storage vial	
3.	Centrifuge tubes	
4.	Dialysis membrane-50	Himedia, India
5.	Gloves	
6.	Syringe filter	Renkem, India
7.	Whattman filter paper	

7.2. Method

7.2.1. Carbopol silver nanoparticles preparation

Synthesis of Carbopol Silver nanoparticles were performed by the process of simple chemical reduction. Carbopol taken in different concentration (0.1-2g/ml) and dissolved in distilled water. To neutralize a carbopol solution few drops of triethylamine was added. secondly Silver nitrate solution of concentration (3.13 g/ml). Then Sodium borohydride solution of mass concentration (0.13 g/ml) was prepared. After that solution of neutral carbopol & silver nitrate both were agitated for half an hour and then for the conversion of Silver into Silver nanoparticles, solution of Sodium Borohydride was dropwise added.

Method

Carbopol silver nanoparticles preparation

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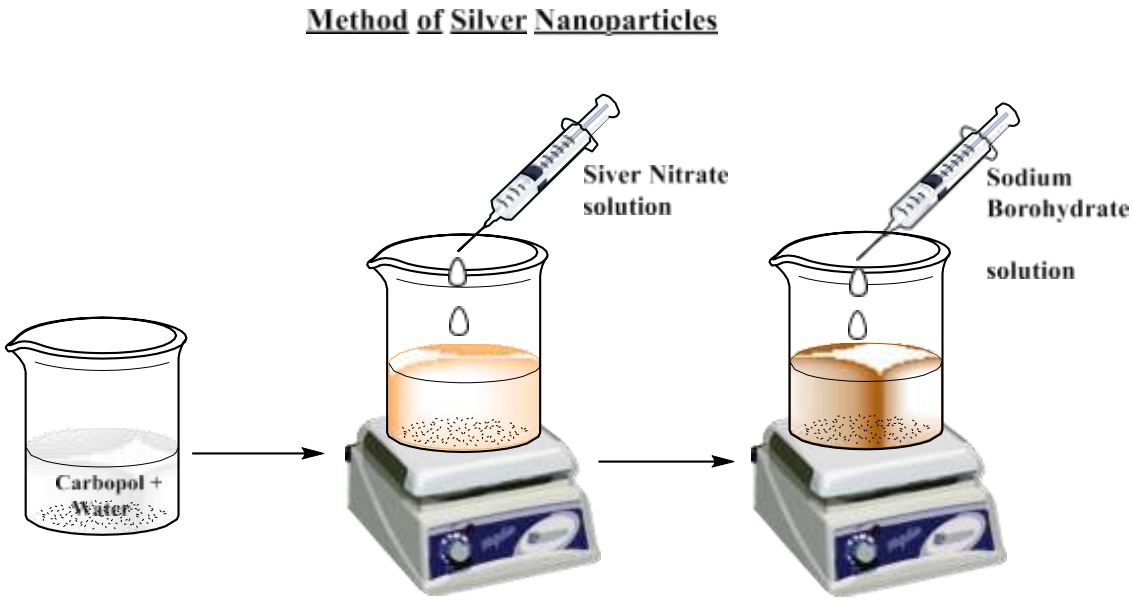

Fig.11: Silver Nanoparticles preparation

Drug loaded niosomes preparation

Thin film hydration technique was used for the preparation of niosomes. Clotrimazole (10mg), cholesterol (10mg) and Span80 (200mg) were dissolved in RBF. Then solvent was evaporated using rotatory evaporator. After that 0.9 % NaCl was added in the RBF for hydration of dry content and shake it well. The RBF was placed on hot water bath to produce dispersion of cloudy niosome.

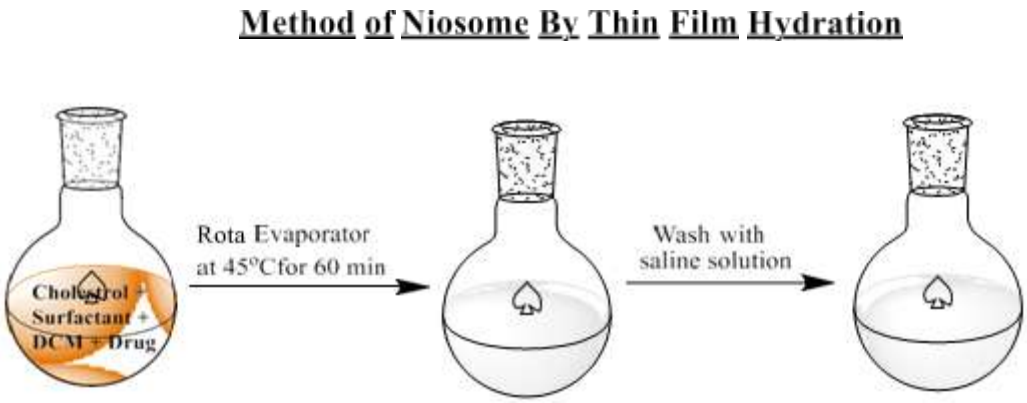

Fig.12: Thin film Hydration method for Niosomes

Ag nanoparticles mixing and drug-loaded niosomes

The components made above were combined gradually with constant stirring for half anhour.

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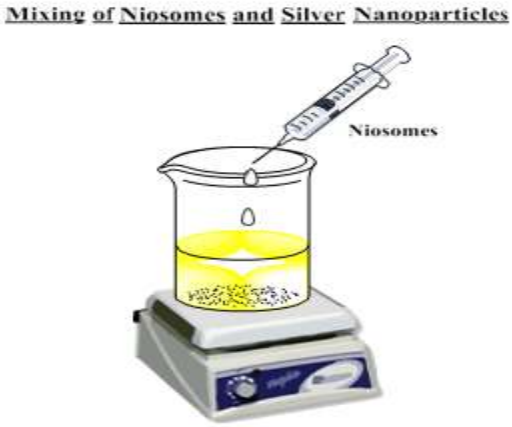

Fig.13: Mixing of Ag Nanoparticles and Niosomes

Mixing of 2 % Carbopol gel with Silver Nanoparticles-Niosomes preparation

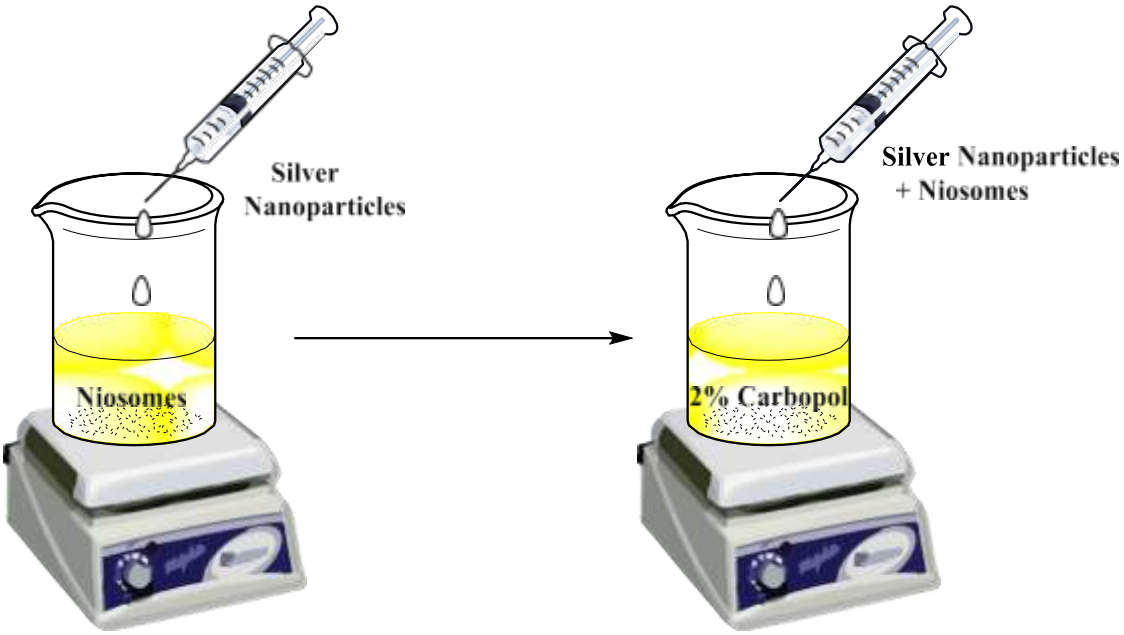

Fig-14: Mixing of drug loaded Niosomes and Silver nanoparticles preparation tocarbopol

CHARACTERIZATION AND IN-VITRO STUDIES

Characterization Studies

Particle size & zeta potential analysis

Five samples of different composition were prepared but could not send for analysis because of covid-19 outbreak.

Silver nano particles color change visualize

Light orange to brown color appearance confirms that silver nanoparticles were formed. Due to aggregation this color may convert into grayish black color.

Drug loading (DL) & Entrapment efficiency (EE):

DL and EE of the prepared nanogel was in Methanol. 1 ml of the nanogel was put in hydrated dialysis membrane bag. This was further dipped in 30 ml of Methanol keeping in on stirring of around 50 rpm at a normal room temperature. After a time interval of two hours a sample of 1ml was pipetted out .The absorbance was determined by UV Visible spectrophotometer at a wavelength of 221 nm. The

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calculation of further calculation is given below.

$$\% \text{ Drug Loading} = \frac{\text{Entrapped Drug}}{\text{Amount of Polymer}} \times 100$$

$$\% \text{ Entrapment efficiency} = \frac{\text{Theoretical drug - unentrapped drug}}{\text{Theoretical drug}}$$

In-Vitro Studies

Release studies

The release study from the Nanogel was performed in Buffer 7.4.The formulation was take in a dialysis membrane bag which was dipped in water for hydration.2ml of the formulation was put in the bag and sealed and dipped in 30ml buffer solution at fifty to Hundred rpm at room temperature. The study went from time (0min to 72hrs).1 ml was pipetted out from the buffer in which the dialysis bag is dipped and 1ml fresh buffer was added to maintain the sink. Absorbance was observed at 221nm by UV-Visible spectroscopy. The percentage of drug released was determined by the formula givenbelow

$$\% \text{ Drug release} = \frac{\text{Amount}}{\text{Dose}} \times 100$$

III. RESULTS & DISCUSSION

Physical characteristic and appearance

The orange to brown color of formulation confirmed that the Silver nano particles were formed. which converts into greyish color after some time due to aggregation. Five batches of different concentration of was prepared and visualized.

Optimization of Silver nanoparticles reactants

Sample No.	Carbapol concentration	Silver nanoparticles concentration	NaBH4 concentration
A1	0.04	0.1550	0.0050
A2	0.05	0.1550	0.0050
A3	0.06	0.1550	0.0050

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A4	0.07	0.1550	0.0050
A5	0.08	0.1550	0.0050

Table 8: Optimization of Silver nanoparticles reactants

On changing stirring speed, pH and time no alteration effect was found so we kept samefor all.

Stirring speed (rpm)	**Reaction Time (Hrs)**	**pH**
200-400	2.5	Neutral

Fig.15: Silver nanoparticles of different concentrations

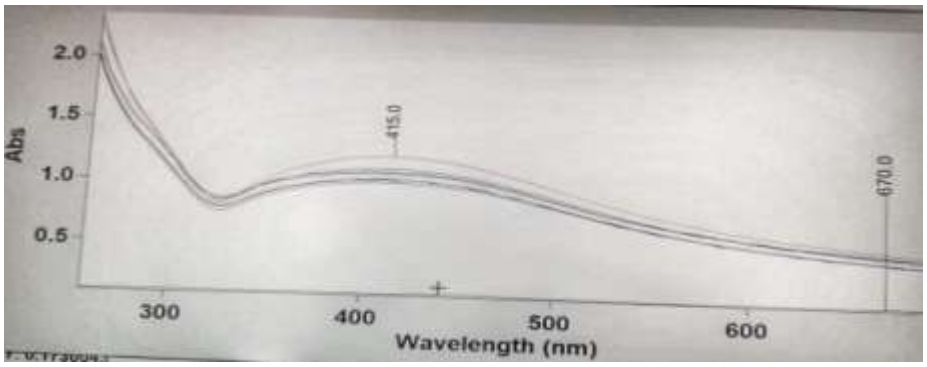

Fig.16: Silver nanoparticles UV visible spectra of different concentration

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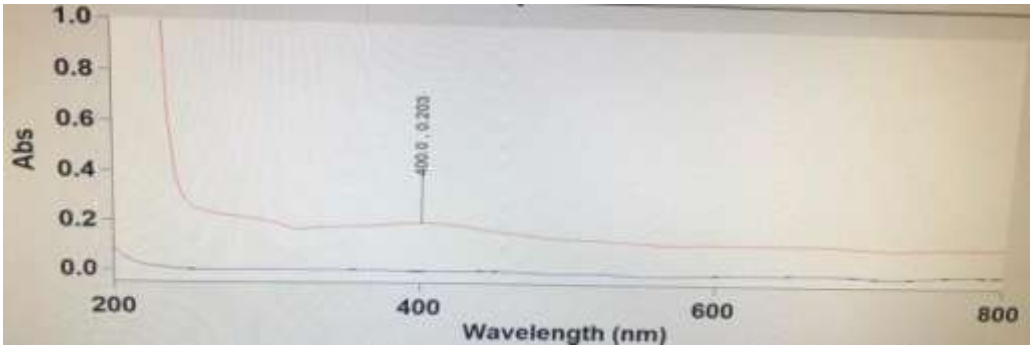

Fig. 17: Final Concentration of Silver nanoparticles UV visible spectra

Sample No.	Carbopol concentration	Silver nanoparticles concentration	$NaBH_4$ concentration	Stirring speed (rpm)	Time of reaction (Hrs.)	pH
A	0.1g	0.1550 g	0.0050	200-400	2	Neutral

Drug loading & entrapment efficiency

Drug loading & entrapment efficiency of formulation was found to be a fairly good.

Name	%DL	%EE
Nanogel	4.86	98.973

Table 10: % Drug loading & entrapment efficiency of nanogel

In-vitro release studies

The release of the Nanogel was done in pH7.4. The formulated Nanogel was put in dialysis membrane bag and dipped in the buffer solution. Readings were taken in different time interval, the developed Nanogel showed release in a controlled and sustained manner.

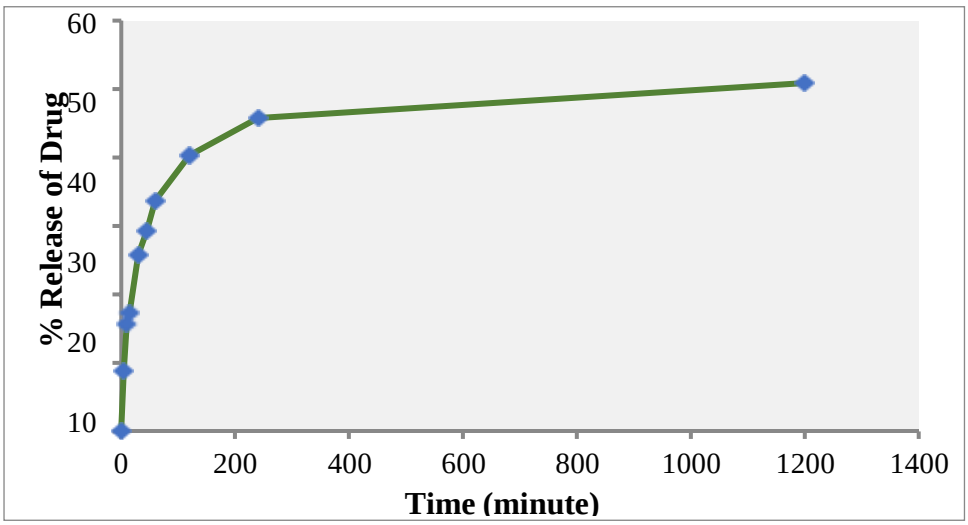

Fig. 18: Graph showing release study of CLOT in 7.4 Ph

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IV. CONCLUSION

Niosomes and Silver nanoparticles combination used in the formulation of a topical antifungal nanogel. Clotrimazole was used topically but because of its poor permeability,the therapeutic effect was delayed. For drug encapsulation niosomes were used which was found to be cheapest and effective vesicular system.

In Imidazole class drugs Clotrimazole is the one of the oldest and potent drug for fungal diseases. It is reported that Silver nanoparticles has antifungal effect which will shows synergistic effect along with clotrimazole, hence potency increases. We prepare the formulation of Silver nanoparticles, niosome & nanogel, The physical feature were determined, drug release and loading data were collected. Silver nanoparticles composition was analysed by UV-Spectroscopy. The release data & entrapment performance was obtained in range.

All of us are hoping our preparation of clotrimazole with Silver nanoparticles with synergistic result enhance the therapeutic effect. Niosomes & nanogel supports the control drug delivery & drug permeability.

Many studies were pending due to the outbreak of Covid19. We prepare the sample for particle size analysis but we are unable to send due to pandemic situation.

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