FORMULATION AND DEVELOPMENT OF NANO STRUCTURED BASED DRUG DELIVERY OF ANTI-FUNGAL DRUG FOR SKIN CARE

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ABSTRACT
Formulation and Development of Nano structured based drug delivery of Anti-fungal drug for skin care. The body's biggest organ, skin, covers the entirety of the outside. The epidermis, dermis, and hypodermis are its three constituent layers, and each has a distinctive architecture and function. The gel formulations exhibited different viscosity levels, ranging from 4156 cp to 6065 cp. Viscosity measures the resistance to flow, and higher viscosity values indicate a thicker and more viscous gel consistency. The viscosity of the gel formulations can be important for determining their ease of application and spreading on the skin. The in vitro diffusion data shows that the gel formulations exhibited increasing diffusion percentages over time. NP-5 consistently had the highest diffusion percentage at each time point. Overall, the diffusion profiles indicate the release of the active substances from the gels and their ability to diffuse through the testing medium over time.

KEYWORDS: Epidermis, Clotrimazole, Fluconazole, Compressibility index, Interparticle friction.

1. INRODUCTION

1.1 Skin

The exterior layer of the human body, or skin, acts as a barrier to protect internal organs from the outside world. It is the biggest organ in the body and essential to many physiological processes. The skin is a multilayered, dynamic structure that contains a variety of cells, tissues, and structures. Each layer has a particular purpose.[1]

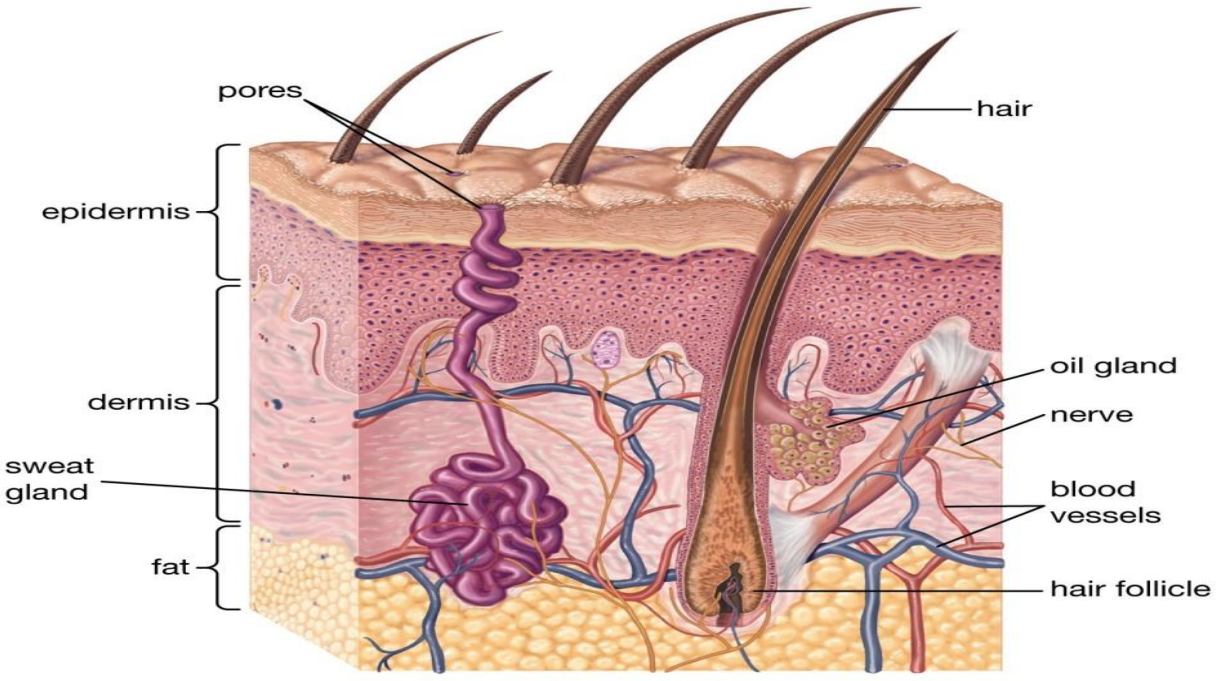


Figure 1.1 Skin

1.2 Functions of Skin

Sensation, thermoregulation, protection, and metabolism are the four primary roles of the skin[2].

- Protection: The skin serves as a physical barrier that guards against diseases, toxic chemicals, and mechanical injury to the interior organs, muscles, and bones. The risk of infections and disorders is decreased because it blocks the entry of bacteria and other particles.
- Body temperature control: The skin aids in controlling body temperature by producing perspiration and shivering. Skin sweat glands release perspiration when

the body becomes too hot, which evaporates and helps to cool the body. Arrector pili, a small group of muscles that contract at cooler temperatures, cause hair to stand on end, trap warm air, and give people goosebumps.

- Sensation: The skin has a variety of nerve endings that may sense touch, pressure, heat, cold, and pain. These nerve endings enable us to perceive our environment.
- Vitamin D is synthesised by the skin when exposed to ultraviolet B (UVB) rays from sunshine and is crucial for keeping strong bones, a robust immune system, and general wellbeing.
- Excretion: Sweating glands in the skin allow for the small-scale elimination of waste materials like salts and urea. This supports preserving the body's chemical ecosystem's delicate equilibrium.
- Absorption: The skin is capable of absorbing some substances, including topical drugs and therapies. Transdermal medication delivery devices and medicinal patches both make use of this characteristic.
- Immunological protection: The skin contributes to the body's immunological protection mechanism. Specialised immune cells found in it aid in defending against infections and other outside invaders.
- UV radiation defence: Melanin, a skin pigment, aids in shielding against the sun's damaging ultraviolet (UV) radiation. It reduces the risk of DNA deterioration and skin cancer by both absorbing and scattering UV radiation.
- Expression and communication: The skin of the face, in particular, plays a crucial role in nonverbal communication and emotional expression. Numerous emotions may be expressed through facial expressions, which are important in interpersonal relationships.

1.3 Nanocarriers as topical drug delivery system

The therapeutic efficacy, bioavailability, and specificity of drugs may all be enhanced by using nanoparticles as drug carriers, which may also boost patient compliance. [3] Additionally, drug retention with controlled release kinetics might be improved by pharmaceutical administration employing nanoparticles at the illness site inside the skin. Nanoparticles, however, find it extremely difficult to pass through skin. It has been established that nanoparticles may penetrate the skin through the transappendageal route, which travels across sweat glands, pilosebaceous, sebaceous, and hair follicles. [5,6] As a result, nanoparticles are able to penetrate the stratum corneum, the skin's top layer of protection. However, the transappendageal route only covers 0.1% of the overall skin surface. The ability of large molecules and nanoparticles to permeate deeper epidermal layers, where the disease is most prominent, is therefore somewhat affected. [7]

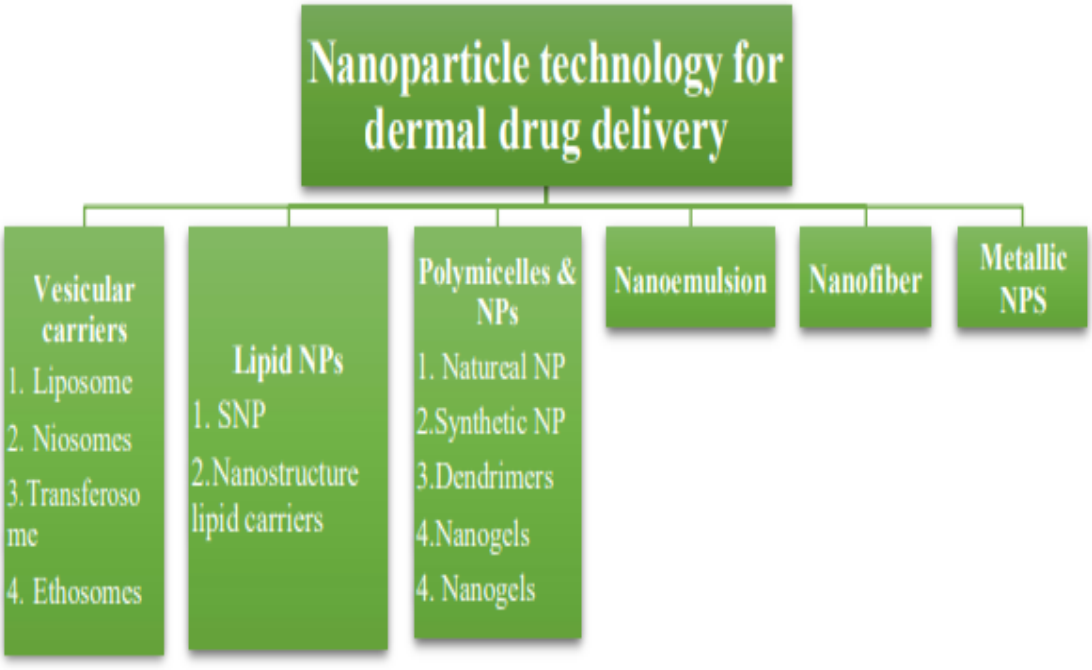


Figure 1.2: Nanoparticle technologies for dermal drug delivery

1.4 Nanostructured Drug Delivery Systems

By providing creative ways to increase therapeutic efficacy, boost patient outcomes, and get around problems with conventional drug delivery techniques, nanostructured drug delivery systems have revolutionised the world of medicine. These systems encapsulate, distribute, and release therapeutic

chemicals in a controlled and targeted way using nanoscale materials and structures.[8]

Nanomaterials are the perfect choice for drug delivery applications due to their special qualities, which include their high surface area-to-volume ratio, customizable surface chemistry, and capacity to overcome biological barriers. Scientists may modify a number of variables, such as particle size, shape, surface characteristics, and drug loading capacity, to optimise drug delivery parameters by creating nanostructured drug delivery systems.[9]

Compared to traditional drug delivery techniques, nanostructured drug delivery systems provide a number of benefits. They can increase a drug's solubility, bioavailability, and stability, allowing it to be delivered even when it isn't highly soluble and lowering the dosage needed. These methods also enable localised medication delivery while reducing systemic adverse effects by specifically targeting particular tissues or cells. It is also possible to develop controlled and sustained drug release patterns, ensuring that therapeutic concentrations are maintained for a long time.[10]

Lipid-based nanostructures, polymeric nanostructures, and inorganic nanostructures are a few of the several kinds of nanostructured drug delivery systems. Liposomes and other lipid-based nanostructures like lipid nanoparticles provide high biocompatibility and flexibility in drug encapsulation. Control over drug release kinetics is made possible by polymeric nanostructures like nanoparticles and micelles, which also provide multifunctional drug delivery platforms. Quantum dots and mesoporous silica nanoparticles are two examples of inorganic nanostructures that have special capabilities for imaging and targeted medication administration.[11]

The creation of nanomaterials with specialised characteristics is required for the engineering of nanostructured drug delivery systems. To create nanostructured drug delivery systems, processes including nanoprecipitation, emulsion/solvent evaporation, and self-assembly are frequently used. PEGylation or ligand conjugation are two surface modification techniques that can improve these systems' stability, biocompatibility, and targeting abilities.[12-13]

1.5 Understanding the Significance of Nanostructures in Drug Delivery

Due to their distinctive characteristics and powers, nanostructures are important in the delivery of drugs. These salient features underline the importance of nanostructures in medication delivery:[15]

1. More Surface Area: Drug loading may be done on a larger surface area thanks to nanostructures' high surface-to-volume ratio. As a result, drug effectiveness is increased thanks to greater drug payloads and better drug dissolution rates.[16]
2. Improved Drug Stability: Drug delivery systems with nanostructures can shield medications from deterioration, enhancing their stability in storage and throughout transit. Drug molecules are protected by nanostructures from the environment and enzymatic deterioration by acting as a barrier.[17]
3. Controlled Release: Drugs may be released gradually and under control thanks to nanostructures. The release rate and duration of drugs may be precisely regulated by adjusting the characteristics of nanostructured carriers like nanoparticles, liposomes, or micelles, resulting in improved therapeutic benefits and fewer adverse effects.[18]
4. Targeted Delivery: To accomplish site-specific medication delivery, nanostructures can be functionalized with targeting ligands or antibodies. The nanostructures' targeting moieties allow them to recognise and attach to certain cells or tissues, boosting medication accumulation there while minimising side effects.[19]
5. Bypassing Biological Barriers: By using various techniques like surface modifications or size optimisation, nanostructures can get past biological barriers like the blood-brain barrier. Drugs may now be delivered to parts of the body that were previously unreachable because of this.[20]
6. Combination Therapies: Nanostructures can be designed to administer many medications or medical agents at once. This enables the use of combination therapy, in which many medications with complementary modes of action are administered together to increase therapeutic effectiveness and prevent the emergence of drug resistance.[221]
7. Personalised Medicine: Nanostructured drug delivery techniques have the potential to support personalised medical strategies. It is feasible to customise drug delivery systems to fit unique patient features by adjusting the composition, size, and surface properties of nanostructures, improving therapeutic effects.[22]

1.6 Types of Nanostructured Drug Delivery Systems

a. Lipid-based Nanostructures[23]

Lipid-based nanostructures are amphiphilic natural or manufactured substances that predominately make up nanoscale structures. These structures are frequently employed in medication delivery systems because of their special qualities and benefits. A description of lipid-based nanostructures is given below:

Liposomes are spherical vesicles with an aqueous core surrounded by one or more lipid bilayers. Hydrophobic and hydrophilic medicines can both be contained within the water core or lipid bilayers of liposomes. Drugs can be effectively encapsulated, protected, and released under regulated conditions thanks to their structure. To improve particular interactions with target cells, tissues, or organs, liposomes can be surface-modified with targeting ligands.[24]

Lipid Nanoparticles (LNPs) are lipid-based colloidal particles that have the ability to encapsulate pharmaceuticals inside of a lipid matrix. LNPs are made up of medicines, stabilising agents, and solid lipids or a combination of solid and liquid lipids. Excellent drug loading capacity, stability, and controlled drug release are all features of LNPs. They can also enhance medication solubility, bioavailability, and tissue penetration while preventing medicines from degrading.[25]

Lipid-Based Micelles: In aqueous solutions, amphiphilic lipids self-assemble to generate lipid-based micelles. The hydrophilic lipid heads of micelles face the surrounding aqueous environment, while the hydrophobic lipid tails constitute the core. Drugs that are hydrophobic can be solubilized by micelles in their hydrophobic core, improving their stability and bioavailability. Additionally, micelle size and surface characteristics can be modified to enhance medication delivery to certain target areas.[26]

b. Polymeric Nanostructures

Nanoscale structures consisting of polymers, which are big molecules made up of repeating monomeric building blocks, are referred to as polymeric nanostructures. These nanostructures have drawn a lot of interest in medication delivery systems because of their distinctive qualities and benefits. The following is a description of polymeric nanostructures:[27]

Nanoparticles: Solid or semi-solid polymeric nanoparticles generally have diameters between 1 and 1000 nanometers. They may be made using a variety of methods, including self-assembly, emulsion/solvent evaporation, and nanoprecipitation. Drugs may be included in polymeric nanoparticles' polymeric matrix or on their surface. Properties such as drug release kinetics, stability, and targeting potential can all be affected by the polymer used.

Nanocapsules: Polymeric nanocapsules have a drug-filled core encased in a polymeric shell. The encapsulated medicine is protected by the polymeric shell, which also controls its release and guards against deterioration. Drugs can be released from nanocapsules in a controlled way by polymer shell diffusion or breakdown.[28]

Dendrimers: Dendrimers are well-defined, highly branching polymer structures that resemble trees. They have an outer shell, internal branches, and a central core. Drugs can be conjugated to dendrimers' surfaces or encapsulated within their interiors. The ability to precisely manage drug loading, release kinetics, and targeting capabilities is made possible by their distinctive design.[29]

Micelles: In aqueous solutions, amphiphilic block copolymers self-assemble to create polymeric micelles. In micelles, the hydrophilic polymer blocks face the aqueous environment while the hydrophobic polymer blocks form the core. Hydrophobic medications can be encapsulated within micelles' hydrophobic cores. Because of their tiny size and stability, micelles allow for effective medication administration and increased hydrophobic drug solubility.

Polymeric hydrogels are three-dimensional crosslinked networks with a high water absorption and retention capacity. Drugs can be added to hydrogels, which can then be employed as sustained-release systems. For the delivery of drugs, they offer a moist and biocompatible environment that enables regulated release over an extended length of time.[30]

c. Inorganic Nanostructures

Nanoscale structures largely made of inorganic substances, such as metals, metal oxides, and semiconductors, are referred to as inorganic nanostructures. Due to their special qualities and possible uses, these nanostructures have attracted considerable interest in a number of sectors, including medicine delivery. An explanation of inorganic nanostructures is provided below:[31]

Particles with diameters generally ranging from 1 to 100 nanometers are known as inorganic nanoparticles. Different techniques, including as chemical synthesis, physical vapour deposition, and template-assisted synthesis, can be used to create them. High surface area, customizable size and shape, and special optical, magnetic, or catalytic capabilities are only a few of the distinguishing qualities of inorganic nanoparticles. To increase stability, biocompatibility, and targeting capabilities for drug delivery applications, they can be functionalized with ligands or coatings.[32]

Quantum Dots (QDs) are semiconductor nanocrystals that have special optical characteristics. Their size-dependent bandgap enables them to precisely control the wavelength of their emission. QDs have the potential to be employed as carriers or vehicles for targeted medication delivery in drug delivery systems as well as imaging probes for diagnostic imaging.[33]

Mesoporous Silica Nanoparticles (MSNs) are silica-based porous nanostructures with pores arranged in a predictable pattern. High drug-loading capabilities are made possible by MSNs' enormous pore volume and high surface area. MSNs' pore sizes and surface characteristics can be modified to regulate medication release rates and boost stability. MSNs can also be functionalized with targeting ligands to target particular cells or tissues.[34]

Gold Nanoparticles: Due to their distinctive optical and electrical characteristics, gold nanoparticles (AuNPs) are often employed in biological applications. To increase stability and enable targeted medication administration, AuNPs can be functionalized with thiolated ligands or biomolecules. They are ideal for

regulated medication release, photothermal treatment, and imaging since they also display localised surface plasmon resonance.[35]

Iron oxide nanoparticles are a type of magnetic nanoparticle that display superparamagnetic characteristics. Magnetic resonance imaging (MRI) contrast enhancement and targeted medication administration are both made possible by the ability to modify them using external magnetic fields. To improve stability and cellular absorption, magnetic nanoparticles can be functionalized with targeted ligands or coated with polymers.[36]

2. LITERATURE REVIEW

Patra et. al., (2018) reported that "Nanomedicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nanoscale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific, and target-oriented delivery of precise medicines. Recently, there are a number of outstanding applications of the nanomedicine (chemotherapeutic agents, biological agents, immunotherapeutic agents etc.) in the treatment of various diseases. The current review, presents an updated summary of recent advances in the field of nanomedicines and nano based drug delivery systems through comprehensive scrutiny of the discovery and application of nanomaterials in improving both the efficacy of novel and old drugs (e.g., natural products) and selective diagnosis through disease marker molecules."[37]

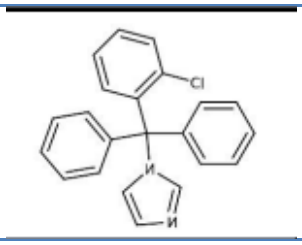
Goldberg et. al., (2007) reported that "The development of nanotechnology provides opportunities to characterize, manipulate and organize matter systematically at the nanometer scale. Biomaterials with nano-scale organizations have been used as controlled release reservoirs for drug delivery and artificial matrices for tissue engineering. Drug-delivery systems can be synthesized with controlled composition, shape, size and morphology. Their surface properties can be manipulated to increase solubility, immunocompatibility and cellular uptake. The limitations of current drug delivery systems include suboptimal bioavailability, limited effective targeting and potential cytotoxicity. Promising and versatile nano-scale drug-delivery systems include nanoparticles, nanocapsules, nanotubes, nanogels and dendrimers. They can be used to deliver both small-molecule drugs and various classes of biomacromolecules, such as peptides, proteins, plasmid DNA and synthetic oligodeoxynucleotides. Whereas traditional tissue-engineering scaffolds were based on hydrolytically degradable macroporous materials, current approaches emphasize the control over cell behaviors and tissue formation by nano-scale topography that closely mimics the natural extracellular matrix (ECM). The understanding that the natural ECM is a multifunctional nanocomposite motivated researchers to develop nanofibrous scaffolds through electrospinning or self-assembly. Nanocomposites containing nanocrystals have been shown to elicit active bone growth. Drug delivery and tissue engineering are closely related fields. In fact, tissue engineering can be viewed as a special case of drug delivery where the goal is to accomplish controlled delivery of mammalian cells. Controlled release of therapeutic factors in turn will enhance the efficacy of tissue engineering. From a materials point of view, both the drug-delivery vehicles and tissue-engineering scaffolds need to be biocompatible and biodegradable."[38]

Shaikh et. al., (2023) reported that "An overview of the use of nanoparticles for topical drug delivery will be given in this review paper. Several experiments have been conducted in the past 25 years to remove some of the obstacles to skin delivery. These investigations have led to a rather modest progress in technology. A more recent method involved increasing the medication's concentration in the carrier to increase drug flow into and through the skin. Hydrophobic and hydrophilic medications can be delivered using nanoparticles, which have the ability to release drugs under regulated conditions over an extended period of time. It also increases patient compliance. Liposomes and solid lipid nanoparticles have the potential to be useful as topical medication delivery methods."[39]

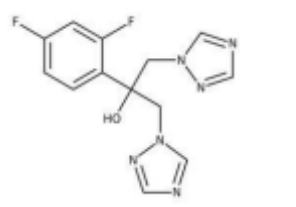
Benson et. al., (2012) reported that "Practical drug development approaches presented by leading experts. Designed to support the development of new, effective therapeutics, Topical and Transdermal Drug Delivery: Principles and Practice explains the principles underlying the field and then demonstrates how these principles are put into practice in the design and development of new drug products. Drawing together and reviewing the latest research findings, the book focuses on practical, tested, and proven approaches that are backed by industry case studies and the authors' firsthand experience."[40]

3. DRUG PROFILE (CLOTRIMAZOLE AND FLUCONAZOLE)

3.1 Clotrimazole (Table 3.1)

Drug	Clotrimazole
Generic Name	Clotrimazole
Structure	
Type	Antifungal
Molecular Weight	344.8
Chemical Formula	C22H17ClN2
Physical Description	White or almost white crystalline powder
Melting Point	Approximately 147-149°C (297-300°F)
Chemical Safety	Generally considered safe when used as directed
Mechanism of Action	A crucial element of the fungal cell membrane, ergosterol, is produced less often when clotrimazole is present. The fungus dies as a result of this disturbance, which damages cell membranes. A frequent treatment for fungal illnesses including athlete's foot, jock itch, and yeast infections, clotrimazole primarily targets fungus.

3.2 Fluconazole (Table 3.2)

Drug	Fluconazole
Generic Name	Fluconazole
Structure	

Type	Antifungal
Molecular Weight	306.27
Chemical Formula	C13H12F2N6O
Physical Description	White or almost white crystalline powder
Melting Point	138-140 °C
Chemical Safety	Health hazard, Irritant
Mechanism of Action	Fluconazole works by preventing the production of ergosterol, a crucial element of the fungal cell membrane. The integrity and functionality of the fungal cell membrane depend on ergosterol. Fluconazole prevents the formation of ergosterol in fungi by blocking the enzyme lanosterol 14-alpha-demethylase, which transforms lanosterol into ergosterol.

4 MATERIAL AND METHODS

4.1 List of Materials (Table 4.1)

S.No	Materials Name	Manufacturer Name
1.	Clotrimazole	S d fine – Chem Limited, Mumbai.
2.	Clotrimazole	S d fine – Chem Limited, Mumbai.
3.	Cholesterol	S d fine – Chem Limited, Mumbai.
4.	Chloroform	S d fine – Chem Limited, Mumbai.
5.	Methanol	S d fine – Chem Limited, Mumbai.
6.	Ethanol	S d fine – Chem Limited, Mumbai.
7.	Hydrochloric Acid	College Lab

8.	HPMC	College Lab
9.	Propylene glycol 400	S d fine – Chem Limited, Mumbai.
10.	Methyl paraben	S d fine – Chem Limited, Mumbai.
11.	Coconut Oil	College Lab
12.	Purified water q.s .to	College Lab

4.2 List of Instruments (Table 4.2)

S.NO	INSTRUMENT	PROVIDER
1.	Rotary flash evaporator	Remi Equipment. Mumbai, India
2.	Electronic digital Balance	Remi Equipment. Mumbai, India
3.	Probe sonicator	College laboratory
4.	Magnetic stirrer	College laboratory
5.	Electronic microscope	Remi Equipment. Mumbai, India
6.	Bath sonicator	College laboratory
7.	Dissolution test Apparatus	College laboratory
8.	Refrigerator	College laboratory
9.	Desiccator	College laboratory
10.	Vacuum pump	College laboratory
11.	Electric heater	College laboratory

12.	Volumetric pipette	College laboratory
13.	Test tubes	College laboratory
14.	Volumetric pipette	College laboratory

4.1 Preparation of powder

The active pharmaceutical ingredients (APIs) and excipients must be precisely weighed and measured in accordance with the prescribed formula as the first step. The primary medicinal ingredients are the APIs, whereas excipients are added to help with formulation and enhance the properties of the finished product.

To achieve equal dispersion, the APIs and excipients are then carefully combined and blended. Uneven distribution might result in variable doses, therefore this step is essential to ensuring the homogeneity of the finished product.

Some drugs may need grinding to reduce particle size and enhance solubility properties, depending on the formulation needs. This procedure increases the drug's efficacy and bioavailability.

Depending on the intended final product shape, the powder combination is then either compacted into tablets or put into capsules after assuring the proper mix. To create well-formed and stable dose units, compression and filling processes are carefully applied.

To guarantee that the finished product satisfies the necessary requirements for safety and efficacy, rigorous quality control inspections are carried out at every stage of the production process. To find and stop any possible flaws or contaminants, quality control techniques are crucial.

Following extensive quality testing and preparation, the powder formulation is ultimately packaged into appropriate containers to guarantee the product's stability and integrity during storage and distribution.

Figure 4.1: Preparation of powder

4.2 Evaluation of Parameters

4.2.1 Angle of Repose

Start by setting the tray or flat surface on a solid, level surface. In order to prevent any influence with the test findings, make sure the surface is clean and dry. The funnel's height or the distance from the hole to the base may be measured with a ruler and noted. Fill the funnel or container to the top with the granular or powdered substance, carefully pouring it in. Allow the material to freely flow through the opening so that it can accumulate in the shape of a cone on the flat surface. Gently touch the funnel or container once the substance has stopped flowing to make sure that it has taken on a stable cone form. The angle of repose is represented by the slope angle of the cone. Take note of the measured angles and make any required comparisons or computations. The possibility for material segregation or instability can be significant insights into the flow qualities provided by the angle of repose.

"The angle of repose was calculated by using the following equation."

$$\tan(\theta) = h/r$$

4.2.2 Important considerations:

- Moisture content: Depending on the material's moisture content, the angle of repose may change. Control the moisture content during the test for consistent results.
- Environmental factors: It's important to maintain a regulated testing environment since variables like temperature and humidity might affect the material's flow characteristics.
- Material-specific characteristics: Due to differences in particle size, shape, and cohesiveness, various materials may have different angles of repose. As a result, it's crucial to take into account the particular characteristics of the substance being examined.

4.2.3 Bulk Density

Make sure the powdery or granular substance is an accurate representation of the whole batch. Consider using a sieve to reduce the aggregates and produce a consistent particle size if the material contains big particles or aggregates. In the graduated cylinder or container, carefully pour the prepared sample of the granular or powdered substance until it reaches the required volume. If a funnel is required to prevent spills, do so. Utilising a scale or weighing balance, weigh the container containing the sample. Make careful to precisely enter the weight. Calculate the average bulk density after doing the process numerous times with the same material to assure accuracy. Multiple trials increase the dependability of the results and lessen the influence of probable mistakes.

"LBD= Weight of the powder/volume of the packing"

4.2.4 Determination of tapped bulk density

Make sure the powdery or granular substance is an accurate representation of the whole batch. Consider using a sieve to reduce the aggregates and produce a consistent particle size if the material contains big particles or aggregates. To calibrate the graduated cylinder or container for precise measurements, fill it with a predetermined amount of water, weigh it to ascertain the water's density, and then repeat. In the graduated cylinder or container, carefully pour the prepared sample of the granular or powdered substance until it reaches the required volume. If a funnel is required to prevent spills, do so. Utilising a scale or weighing balance, weigh the container containing the sample. Record the weight and use the same procedure to determine the initial bulk density:

"TBD= Weight of the powder/tapped volume of the packing"

4.2.5 Compressibility Index

The Compressibility Index is a parameter used to assess the compressibility and flowability of a powdered material. It quantifies how much a material decreases in volume or increases in bulk density when subjected to compression. The Compressibility Index is typically determined using the tapped bulk density and the bulk density of a powdered material:

"Carr's index (%) = [(TBD-LBD)×100]/TBD"

• If the material has a Compressibility Index of 0, it does not compress at all and keeps its original volume after tapping.
• If the material's compressibility index is close to 100%, it likely possesses high compressibility, which would result in a considerable volume decrease or rise in bulk density after tapping. When handled or processed, these materials may have poor flowability properties and a propensity to form cohesive masses or arches, creating flow problems.

• Variable levels of compressibility and flowability are indicated by a compressibility index between 0% and 100%. Higher numbers denote worse flow characteristics, whereas lower values denote better flow characteristics.

4.2.6 Hausner's Ratio

Another factor used to assess the compressibility and flowability of powdered materials is the Hausner's Ratio. Similar to the Compressibility Index, it is determined by taking into account both the material's and the tap's bulk densities. When a powder is tapped or compressed, Hausner's Ratio gives a numerical number indicating how likely it is to experience volume decrease or an increase in bulk density:

Hausner's ratio = DF/DO
where DF is Tapped bulk density and DO is Loose bulk density.

- If the Hausner's Ratio is 1, tapping has no effect on the volume or bulk density. To put it another way, following tapping, the material does not compress or exhibit any inclination to form cohesive masses. These materials are regarded as free-flowing and usually have excellent flow characteristics.
- If the Hausner's Ratio is larger than 1, it means that after tapping, the material either experiences volume decrease or an increase in bulk density. Greater compression and less flowability are indicated by higher values. Hausner's Ratios much higher than 1 may cause materials to flow poorly, produce bridges or arches, or display other undesirable flow characteristics.
- Hausner's Ratio tends to be greater for powders with poor flow characteristics, which indicates increased compressibility and less flowability.

4.3 Preparation of nanoparticles

Clotrimazole and Fluconazole were added to the alcohol-cholesterol combination at a specified drug-to-lipid molar ratio, as indicated in the context. We successfully integrated the reverse phase evaporation technique into liposomal formulations. After the

solution had formed a lipid layer on the flask's circular bottom and been evaporated under vacuum to remove the solvent, aliquots of 10% (w/v) sucrose were added to the flask for hydration. Large multilamellar nanoparticles were suspended for 10 minutes before being subjected to an ultrasonic procedure to create smaller unilamellar nanoparticles. Nanoparticles containing the medications Clotrimazole and Fluconazole were filtered across a 0.2 m cellulose acetate membrane in order to get rid of any possible precipitates and ensure sterilise. The level of retention of Clotrimazole and Fluconazole in the filtered nanoparticles relative to the initial drug addition is known as drug incorporation efficiency. The nanoparticles were maintained in a nitrogen-filled sealed vial for a subsequent shelf stability test.

4.4 Formulation of nanoparticles (Table 4.3)

Composition % (w/v)	FL -1	FL-2	FL-3	FL-4	FL-5
Clotrimazole and Fluconazole	2	2	2	2	2
Propylene glycol 400	-	-	-	0.6	0.5
Methyl paraben	0.5	0.5	0.5	0.5	0.5
Coconut Oil	0.25	0.26	0.27	0.28	0.29
HPMC	1.5	1	1.5	2	1.5
Purified water q.s .to	100	100	100	100	100

4.5 In vitro evaluation of gel

4.5.1 Percentage Yield

Chemistry uses the notion of percentage yield to describe how well a chemical reaction or process works. It is the actual yield of a desired product divided by the theoretical yield, multiplied by 100 to get a percentage value. The theoretical yield is the most product that can be produced using stoichiometric calculations, assuming a 100% efficiency for the process. The container was empty The container containing the gel formulation was first weighed before being reweighed with the gel formulation inside. The practical yield is then obtained by subtracting the weight of the empty container from that of the container containing the gel formulation. The formula was then used to compute the percentage yield.

"Percentage Yield = (Practical Yield / Theoretical Yield) X 100"

4.5.2 Extrudability

Extrudability describes a material's capacity to be extruded using a certain technique or piece of machinery, generally a die or an aperture with a given form. In the industrial process known as extrusion, a material is pushed or forced through a small opening to produce continuous forms or profiles with a constant cross-section. To test a formulation's extrudability, a closed, collapsible tube with a crimped end was aggressively pressed.

4.5.3 pH

1.0 g of gel was properly weighed and spread throughout 100 ml of sterile water. The pH of the dispersion was determined using a digital pH metre that was calibrated with standard buffer solution at pH values of 4.0, 7.0, and 9.0 before to use. The average values of the three pH measurements were calculated.

The pH of the formulation was evaluated to make sure it could be used without running the risk of causing skin irritation. The formulation may be used without being concerned that it would irritate the skin because the gel's pH was found to be 6.6 0.5, which is incredibly near to the neutral pH. This further proved that the formulation's components of choice did not alter pH.

Figure 4.2: Digital pH meter

4.5.4 Viscosity

The resistance of a gel to flowing is referred to as its viscosity. Gels are semi-solid substances with characteristics similar to both solids and liquids. They have a distinct rheological behaviour as a result of the three-dimensional network structure that traps liquid or solvent within their matrix. Viscosity is a crucial rheological characteristic of gels since it affects how readily the gel flows when applied with external pressures.

The kind and concentration of the gelling agent, the makeup of the solvent or liquid phase, the temperature, and other variables all affect viscosity. From low viscosity, where the gel flows freely, to high viscosity, where the gel opposes flow and behaves more like a solid, gels can display a wide range of viscosities.

"The viscosity of gels was determined using a Brookfield viscometer (Spindle type S-24 at 30 rpm). The reading was acquired after the spindle had been immersed in 200 g of gel for approximately 5 minutes."

Figure 4.3: Brookfield Viscometer

4.5.5 Spreadability

The term "spreadability" describes a substance's capacity to evenly and quickly cover a surface with little effort or resistance, such as a cream, lotion, or gel. Spreadability is a crucial element that influences product performance and user experience across a variety of sectors, including food, medicines, and the cosmetics and beauty industries. One of the prerequisites for a topical formulation to meet the ideal standards is the ability to disperse properly. When a formulation is applied to skin or another afflicted area, it can quickly spread over a large area, which is referred to as the "region of easy spread." A formulation's ability to spread has an impact on how successful it is as medicine. On a glass slide that was 7.5 cm long, a circle with a 1 cm diameter had already been pre-marked. The spreadability of the formulation was then examined by placing a second glass slide on top of the first. To measure the speed at which a 20 g weight may be drawn away from the bottom after being put over the top to a distance of 7.5 cm:

S = M.L / T

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other.

4.5.6 Stability studies of topical gel formulation

To evaluate the product's long-term physical, chemical, and microbiological stability, stability studies of topical gel formulations are crucial. These tests are done to make sure the gel is high-quality, safe, and effective for the duration of its shelf life. To imitate real-world circumstances and assess the gel's performance under various environmental parameters, stability testing is often conducted under varied storage conditions.

4. RESULT AND DISCUSSION

Two frequently prescribed antifungal drugs with distinct modes of action and uses are fluconazole and clotrimazole. Fluconazole, an azole antifungal medication, acts by preventing the creation of ergosterol, a crucial element of the membranes of fungal cells. It is generally used to treat diseases brought on by Candida species, including vaginal yeast infections, oral thrush, and systemic fungal infections. It comes in oral and intravenous versions. Additionally, fluconazole may be used as prophylactic to people with weakened immune systems. However, pregnant women should typically avoid taking it and individuals with liver or renal problems should use it with caution.

Contrarily, the antifungal drug clotrimazole, an imidazole, works by impairing the integrity of the fungal cell membrane and the production of ergosterol. For the topical treatment of fungal skin diseases such athlete's foot, jock itch, and ringworm, clotrimazole is frequently offered in creams, powders, and oral lozenges. For the treatment of vaginal yeast infections, it is also offered as a cream or suppository. The majority of the time, clotrimazole is safe to use during pregnancy, but you should follow the directions carefully and avoid getting it in your eyes.

Both fluconazole and clotrimazole are efficient antifungal medications, but the dosage required will depend on the kind of illness, the application location, and the particular patient. To guarantee the best possible therapeutic results and reduce the risk of side effects, it is essential to adhere to the recommended dose and course of therapy as directed by a healthcare practitioner.

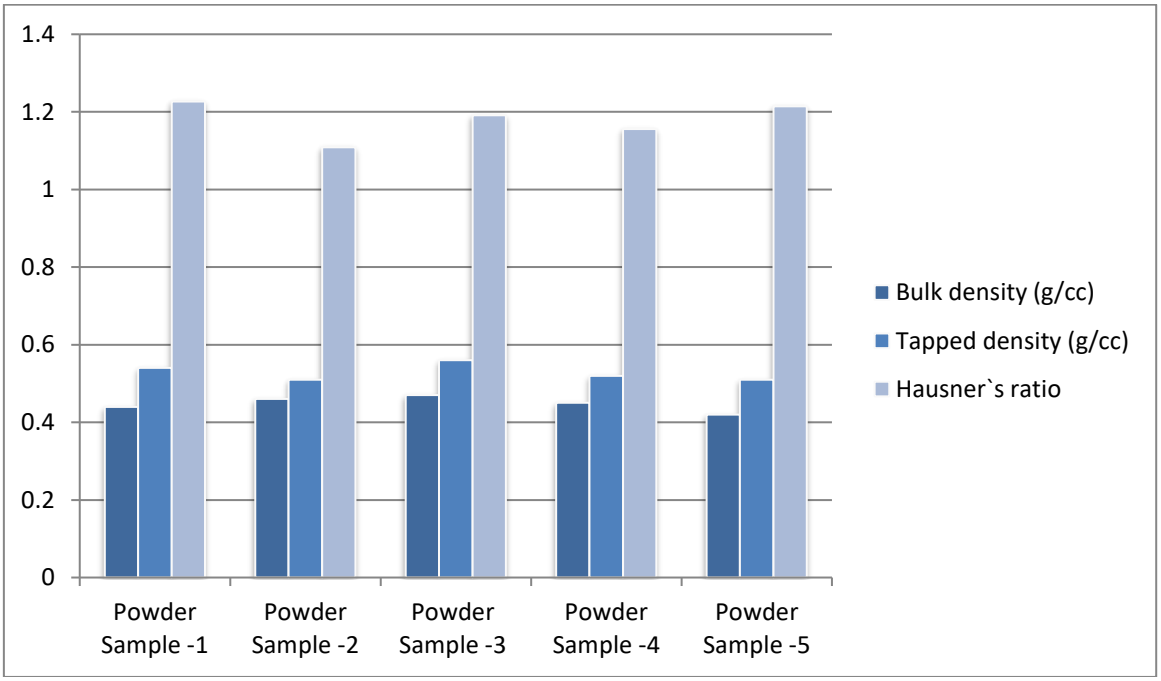
5.1 Preformulation results (Table 5.1)

Both Fluconazole and Clotrimazole are crystalline powders that disintegrate in less than five minutes. They are both white to off-white in colour. While Clotrimazole has a slightly bitter taste, Fluconazole is odourless. Fluconazole has a melting temperature of 138–140°C, whereas Clotrimazole has a melting point of 147–149°C. Fluconazole is just marginally soluble in water while Clotrimazole is virtually insoluble.

S.No	Parameter	Fluconazole	Clotrimazole
1.	Appearance	White to off-white crystalline powder	White to off-white crystalline powder
2.	Taste	Odourless	Slightly bitter
6.	Disintegration Time	Time Less than 5 minutes	Time Less than 5 minutes
7.	Melting Point	138-140°C	147-149°C
8.	Solubility	Sparingly soluble in water	Practically insoluble in water

5.2 Evaluation of micrometric properties (Table 5.2)
The Hausner's ratio values vary from 1.109 to 1.227, the bulk density values from 0.42 g/cc to 0.47 g/cc, and the tapped density values from 0.51 g/cc to 0.56 g/cc. These variables reveal details on the flow and compaction characteristics of the powder samples.

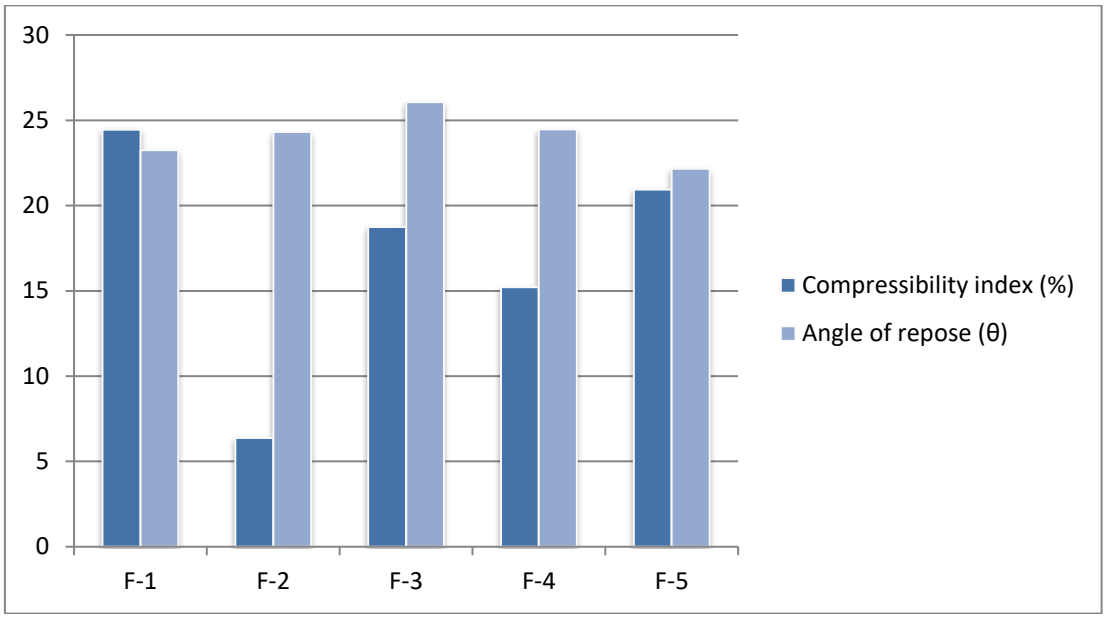
Evaluation Parameters	Bulk density (g/cc)	Tapped density (g/cc)	Hausner`s ratio
Powder Sample -1	0.44	0.54	1.227
Powder Sample -2	0.46	0.51	1.109
Powder Sample -3	0.47	0.56	1.191
Powder Sample -4	0.45	0.52	1.156
Powder Sample -5	0.42	0.51	1.214



Graph of Evaluation of micrometric properties

5.3 Evaluation of Micromeritic studies (Table 5.3)

Evaluation Parameters	Compressibility index (%)	Angle of repose (θ)
Powder Sample -1	18.52	22.25
Powder Sample -2	9.80	20.31
Powder Sample -3	16.07	20.07
Powder Sample -4	13.46	26.40
Powder Sample -5	17.65	23.17

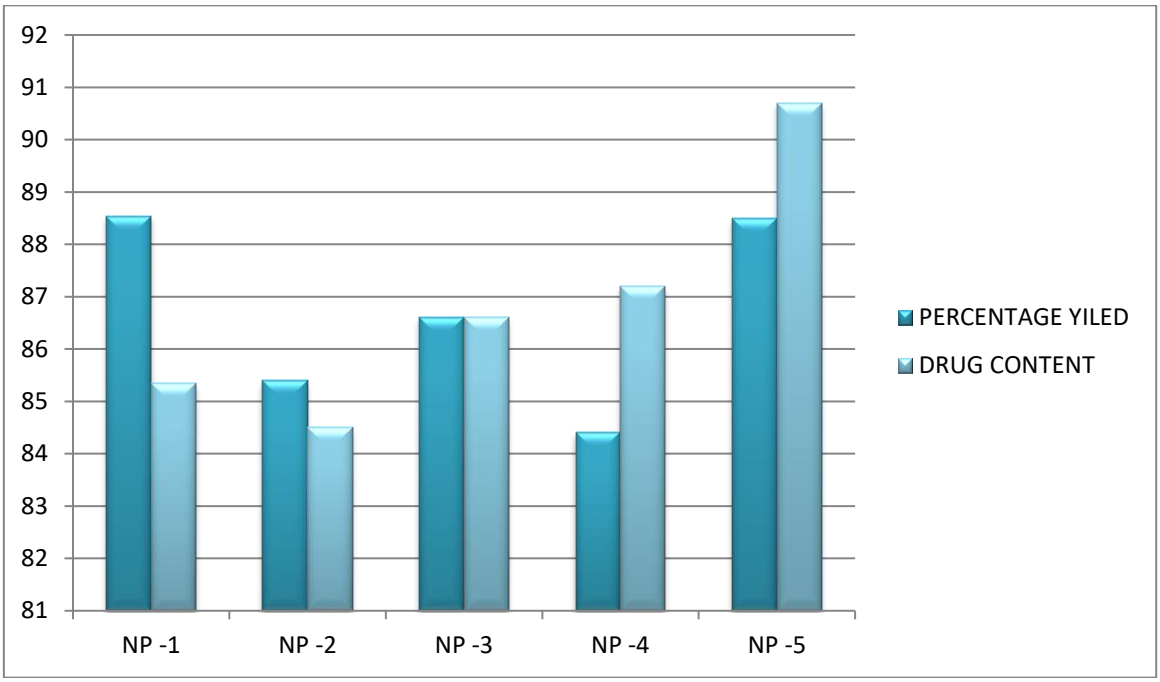


Graph of Evaluation of Micromeritic studies

5.4 Percentage Yield And Drug Content of Gel Formulation (Table 5.4)

The percentage yields for the gel formulations ranged from 84.40% to 88.54%. Additionally, the drug content ranged from 84.50% to 90.70%. It's crucial to remember that a greater drug content translates to a formulation that has more of the active component, which in some circumstances may be preferable.

S.No	FORMULATION	PERCENTAGE YILED	DRUG CONTENT
1.	NP -1	88.54	85.34
2.	NP -2	85.40	84.50
3.	NP -3	86.60	86.60
4.	NP -4	84.40	87.20
5.	NP -5	88.50	90.70

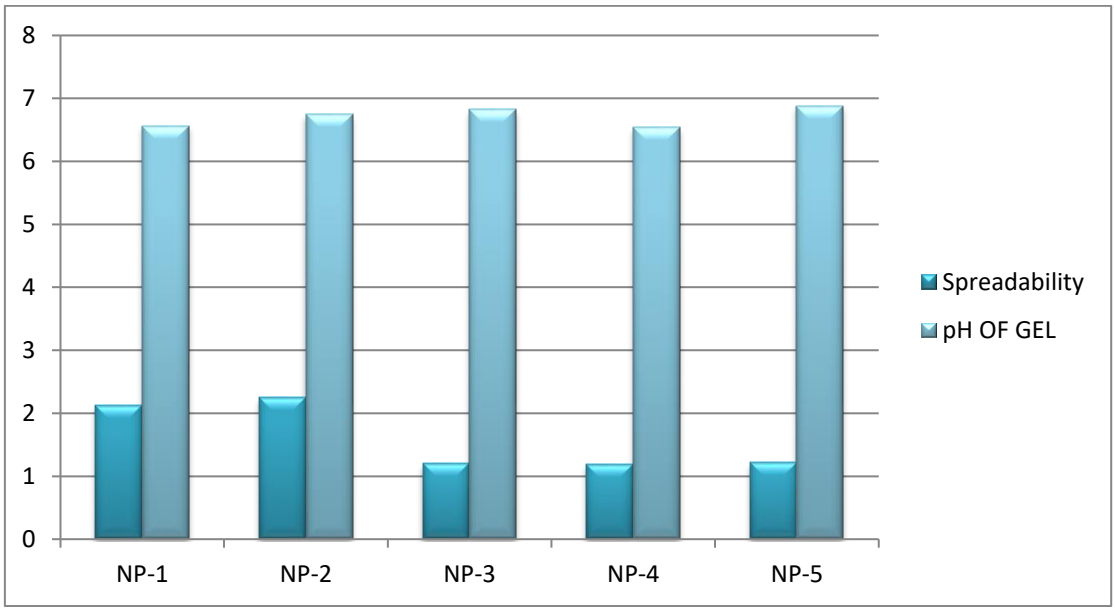


Graph of Percentage Yield and Drug Content of Gel Formulation

5.5 Spreadability of gel formulations and pH of gel formulations (Table 5.5)

The spreadability of the gel compositions varied, ranging from 1.19 to 2.25. Greater spreadability ratings suggest that the gel may be applied to the skin without difficulty. The compositions' pH values, which varied from 6.54 to 6.88, indicated a pH range between neutral and mildly acidic. The durability of the gel formulation and skin compatibility depend on maintaining an adequate pH.

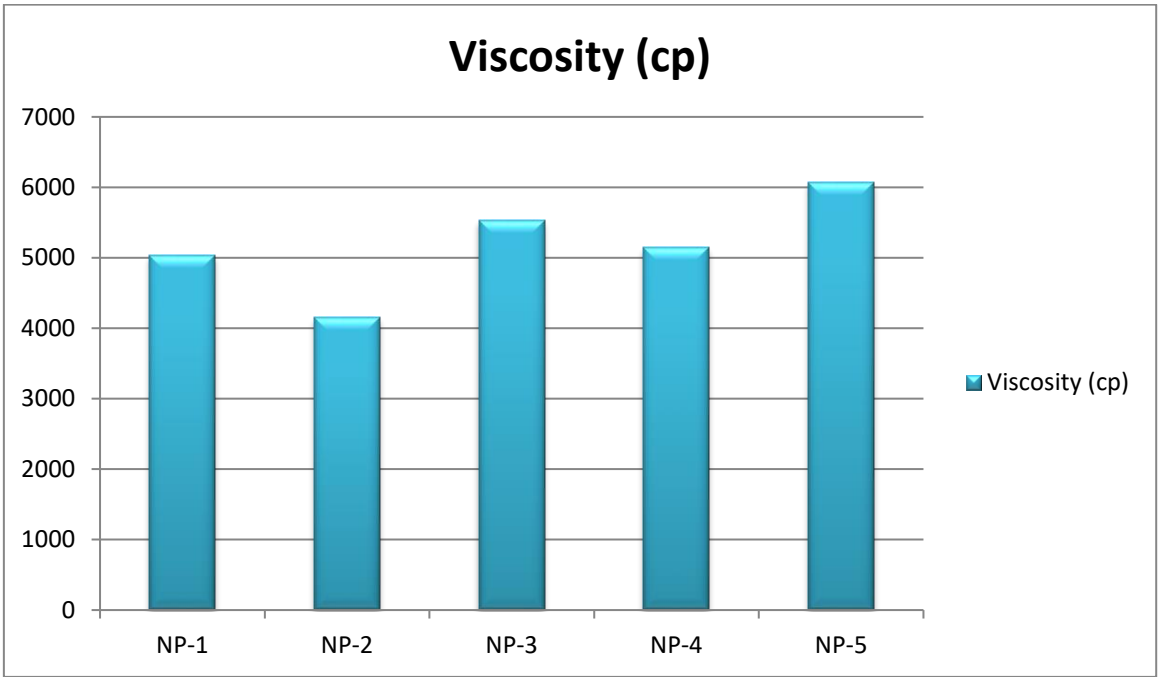
S.no	Formulation	Spreadability	pH OF GEL
1.	**NP-1**	**2.12**	**6.56**
2.	**NP-2**	**2.25**	**6.74**
3.	**NP-3**	**1.20**	**6.82**
4.	**NP-4**	**1.19**	**6.54**
5.	**NP-5**	**1.22**	**6.88**



Graph of Spreadability of gel formulations and pH of gel formulations

5.6 Viscosity of gel formulations (Table 5.6)
The viscosity ranges of the gel compositions ranged from 4156 cp to 6065 cp. Higher viscosity readings suggest a thicker and more viscous gel consistency. Viscosity quantifies the resistance to flow. For defining the gel compositions' ease of use and spreading on the skin, their viscosity might be crucial.

S.No	FORMULATION	Viscosity (cp)
1.	**NP-1**	**5034**
2.	**NP-2**	**4156**
3.	**NP-3**	**5530**
4.	**NP-4**	**5150**
5.	**NP-5**	**6065**



Graph of viscosity of gel formulations

5.7 Extrudability of gel formulations (Table 5.7)
The extrudability of the gel compositions varied. Excellent extrudability was shown by NP-2, NP-4, and NP-5, demonstrating their ibility to be smoothly and readily pushed out of the container. The extrudability of NP-1 and NP-3 was good, indicating that they may also be dispensed without too much difficulty. The user experience and ease during application may be impacted by the gel compositions' extrudability.

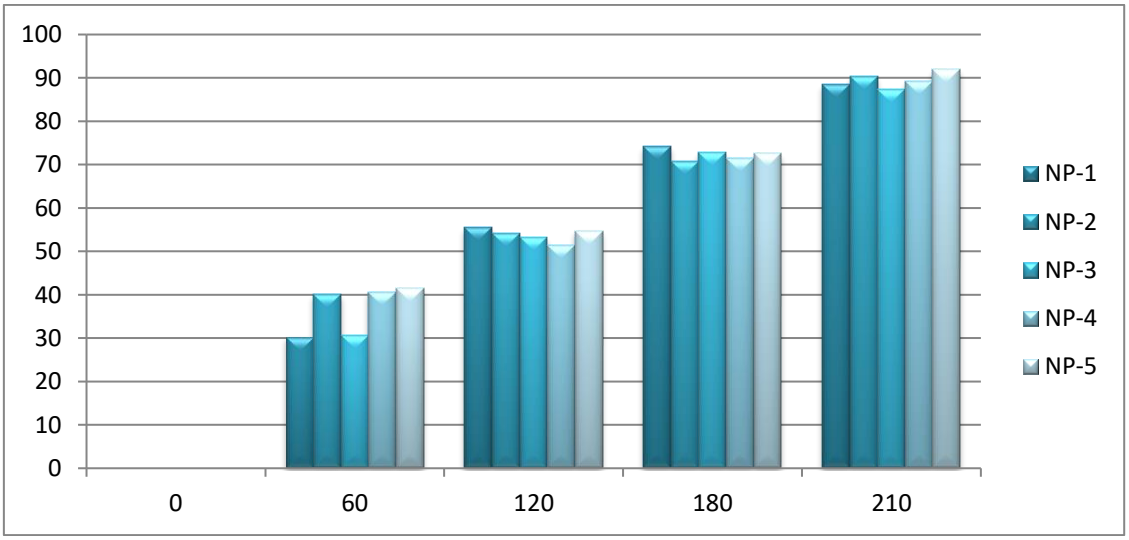
S.No	**FORMULATION**	**EXTRUDABILITY**
1.	**NP-1**	**Good**
2.	**NP-2**	**Excellent**

3.	**NP-3**	**Good**
4.	**NP-4**	**Excellent**
5.	**NP-5**	**Excellent**

5.8 In vitro diffusion chart (Table 5.8)
The results on in vitro diffusion reveals that the gel formulations had percentages of diffusion that increased with time. At each time point, NP-5 consistently had the greatest diffusion percentage. Overall, the diffusion profiles show the active ingredients' capacity to release from the gels and disperse across the testing medium over time.

In vitro diffusion chart

S.No	Time	NP-1	NP-2	NP-3	NP-4	NP-5
1.	**0**	**0**	**0**	**0**	**0**	**0**
2.	**60**	**30.25**	**40.15**	**30.66**	**40.65**	**41.46**
3.	**120**	**55.60**	**54.20**	**53.30**	**51.40**	**54.70**
4.	**180**	**74.12**	**70.90**	**72.80**	**71.50**	**72.50**
5.	**210**	**88.55**	**90.30**	**87.45**	**89.11**	**91.90**



Graph of In vitro diffusion

5. SUMMARY AND CONCLUSION

Both Fluconazole and Clotrimazole are crystalline powders that disintegrate in less than five minutes. They are both white to off-white in colour. While Clotrimazole has a slightly bitter taste, Fluconazole is odourless. Fluconazole has a melting temperature of 138–140°C, whereas Clotrimazole has a melting point of 147–149°C. Fluconazole is just marginally soluble in water while Clotrimazole is virtually insoluble.

The bulk density values range from 0.42 g/cc to 0.47 g/cc, the tapped density values range from 0.51 g/cc to 0.56 g/cc, and the Hausner's ratio values range from 1.109 to 1.227. These parameters provide information about the compaction and flow properties of the powder samples.

The gel formulations showed varying percentage yields ranging from 84.40% to 88.54%. The drug content also varied between 84.50% and 90.70%. It is important to note that higher drug content indicates a higher concentration of the active ingredient in the formulation, which can be desirable in some cases.

The gel formulations showed different levels of spreadability, ranging from 1.19 to 2.25. Higher spreadability values indicate that the gel can be easily spread on the skin. The pH values of the formulations ranged from 6.54 to 6.88, indicating a slightly acidic to neutral pH range. Maintaining an appropriate pH is important to ensure skin compatibility and stability of the gel formulation.

The gel formulations exhibited different viscosity levels, ranging from 4156 cp to 6065 cp. Viscosity measures the resistance to flow, and higher viscosity values indicate a thicker and more viscous gel consistency. The viscosity of the gel formulations can be important for determining their ease of application and spreading on the skin.

The gel formulations showed varying levels of extrudability. NP-2, NP-4, and NP-5 exhibited excellent extrudability, indicating that they can be easily and smoothly squeezed or dispensed from the container. NP-1 and NP-3 demonstrated good extrudability, suggesting that they can also be dispensed without significant difficulty. The extrudability of the gel formulations can impact user experience and convenience during application.

The in vitro diffusion data shows that the gel formulations exhibited increasing diffusion percentages over time. NP-5 consistently had the highest diffusion percentage at each time point. Overall, the diffusion profiles indicate the release of the active substances from the gels and their ability to diffuse through the testing medium over time.

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