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FORMULATION AND EVALUATION OF NANOGEL CONTAINING FLUCONAZOLE

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ABSTRACT

1. INTRODUCTION

Background and Rationale

Fungal infections present substantial healthcare challenges globally, particularly impacting the skin, mucosa, and immunocompromised patients. Superficial mycoses, such as seborrheic dermatitis, tinea, and candidiasis, are notably persistent and recurrent under conventional therapy. The management of such infections often necessitates prolonged antifungal therapy, which may be limited by poor bioavailability, toxicity, and the potential development of resistance.[1,2] Fluconazole, a triazole antifungal, has gained prominence for its efficacy against a broad spectrum of fungal pathogens, including Candida spp., Cryptococcus spp., and various dermatophytes. Owing to its mechanism—blocking lanosterol 14-α-demethylase in the fungal ergosterol pathway—fluconazole inhibits fungal cell membrane synthesis, making it a drug of choice for superficial and systemic mycoses.[3,4] However, topical fluconazole formulations often suffer from low skin retention and limited permeation, necessitating enhanced delivery systems to realize their full therapeutic potential.[5,6] Nanotechnology allows existing commercial pharmaceutical formulations—especially those with challenging characteristics such as poor solubility, high cost, or toxicity—to be optimized for better bioavailability, improved safety, and enhanced pharmacoeconomic profiles.[7,8] J.K.K. Nattraja College of Pharmacy Department of Pharmaceutics.

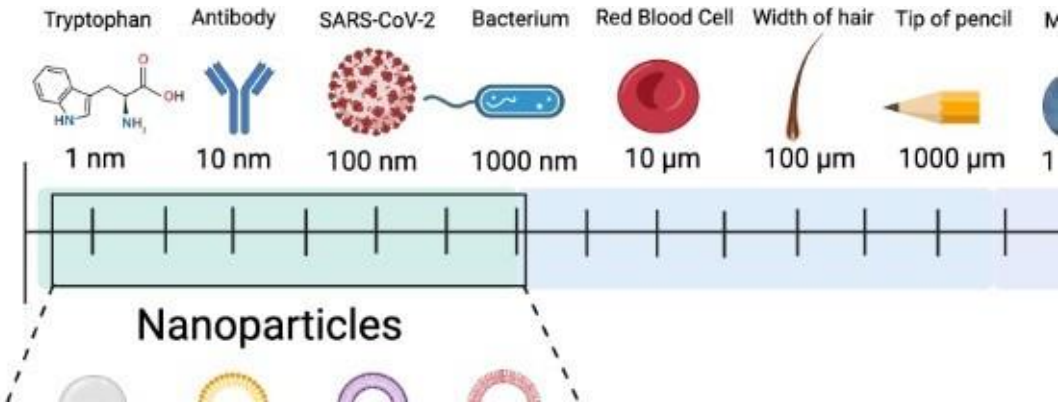

Figure 1: Particle Size Comparison (Courtesy: BioRender.com).

Nanoparticle Drug Permeation Through the Skin

Nanoparticles have emerged as highly promising carriers for enhancing drug permeation through the skin, offering novel solutions for both localized and systemic drug delivery. The unique physicochemical properties of nanoparticles—including their small size, surface charge, composition, and flexibility—enable them to overcome the formidable barrier posed by the skin's outermost layer, the stratum corneum, which traditionally restricts drug absorption, especially for hydrophilic and high molecular weight molecules.

Mechanisms of Skin Penetration

Nanoparticles facilitate drug permeation via several distinct mechanisms

- **Disruption and fluidization of the stratum corneum lipids:** Lipid-based nanoparticles, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions, alter the lipid organization of the stratum corneum, enhancing drug movement across the skin barrier.
- **Follicular and appendageal pathway:** Nanoparticles can transport drugs directly through skin appendages such as hair follicles and sweat glands, a route called trans appendageal permeation. This not only bypasses the tight junctions of the stratum corneum but also supports targeted delivery to skin organelles.
- **Carrier uptake and adhesion:** Certain nanoparticles, including liposomes and transfersomes, adhere and fuse with skin cells, enhancing penetration and offering sustained release profiles.
- **Physical and chemical permeation enhancement:** The formulation of nanoparticles with permeation enhancers, like ethanol or specialized surfactants, further increases their capability to deliver drugs through intact or weakened skin barriers.

Advantages Over Conventional Carriers

Nanoparticle-based drug delivery systems present several advantages over traditional formulations.

- **Enhanced bioavailability:** Drugs encapsulated within nanoparticles can achieve higher localized concentrations in skin layers, leading to improved efficacy with reduced systemic exposure.
- **Controlled and sustained release:** Nanoparticles may provide prolonged drug release, minimizing dosing frequency and improving patient compliance.
- **Suitable for both hydrophilic and lipophilic drugs:** Innovations in nanocarrier design allow the successful delivery of diverse types of drugs, many of which are otherwise poorly absorbed through the skin.
- **Reduced side effects:** Topical nanoparticle delivery reduces off-target effects and toxicity by restricting the drug primarily to intended skin regions.

Key Factors Influencing Permeation

The effectiveness of nanoparticle-mediated drug permeation is governed by several factors.

- **Particle size and shape:** Smaller nanoparticles (especially 20–200 nm) permeate the skin more efficiently; size also determines depth of penetration and target tissue deposition.
- **Surface charge:** The electrostatic interactions with skin components affect adherence and internalization.
- **Composition and lipid content:** The choice of core materials—such as lipids, polymers, or metal-based systems—modulates both stability and permeation.
- **Flexibility and elasticity:** Transfersomes and ethosomes offer improved skin permeation due to their ultra-deformable structures, enabling them to pass through narrow intercellular routes and reach deeper layers.

Clinical Applications and Future Directions

Nanoparticle drug delivery systems are currently utilized in a variety of clinical scenarios, ranging from treatment of localized skin disorders (e.g., psoriasis, atopic dermatitis) to controlled systemic delivery of hormones, vaccines, and chemotherapeutics. Their ability to target specific skin structures while minimizing systemic absorption makes them attractive candidates for both cosmetic and pharmaceutical applications. Ongoing research is

addressing challenges related to safety, scalability, and optimal design, with the expectation that newer nanocarriers will enter routine clinical use in the near future.

In summary, nanoparticles significantly enhance drug permeation through the skin by leveraging multiple physicochemical and biological mechanisms, promising safer and more effective transdermal therapies for a broad range of applications.

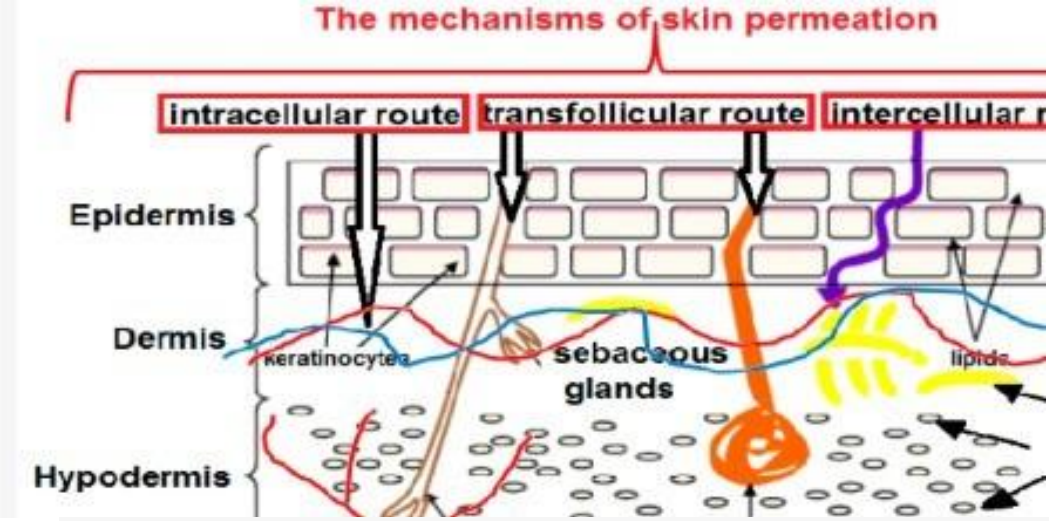

Figure 2: The schematic representation of the possible routes of the NPs permeation through the multilayered structure of the skin together with its main components and blood vessels (artery-red, vein-blue).*(Courtesy: Mdpi.com)*

Particle Size Distribution

Particle size distribution (PSD) refers to the statistical spread of particle sizes found within a given sample, and is a fundamental parameter in the characterization of nanoparticles and other finely divided materials. Understanding and controlling PSD is essential in the development of pharmaceuticals, nanomaterials, and a wide range of industrial products, as it influences key properties such as dissolution rate, stability, bioavailability, flowability, and processability.

Measurement Techniques

Several analytical techniques are routinely employed to analyze particle size distribution.

- **Dynamic light scattering (DLS):** This is a widely used method based on measuring the Brownian motion of particles suspended in a fluid, which allows calculation of their equivalent spherical diameter using the Stokes-Einstein equation. DLS provides rapid results

and can analyze nanometer to sub-micron particles, but may be less accurate for highly polydisperse or non-spherical samples.

- **Transmission and scanning electron microscopy (TEM, SEM):** These imaging techniques provide direct visualization and precise measurement of individual particle sizes and morphologies. Sample preparation and analysis can be time-consuming and typically cover fewer particles, which may not represent the entire population.
- Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) are two powerful techniques used to study the microstructure and morphology of materials at very high magnifications. Both methods use a focused beam of electrons instead of light, allowing a much greater resolution compared to traditional optical microscopy, but they differ in principles, instrumentation, and applications.
- Transmission Electron Microscopy (TEM)
- TEM works by transmitting a beam of electrons through an ultra-thin specimen. As electrons pass through the sample, differences in density and composition alter their scattering pattern. These transmitted electrons are then focused using electromagnetic lenses to form an image on a fluorescent screen or detector. TEM can achieve resolutions up to the atomic scale (less than 1 nanometer), making it invaluable for studying crystal structures, defects, internal morphology, and molecular arrangements. It is extensively used in materials science, nanotechnology, and biomedical fields to analyze thin sections of cells, viruses, and nanoparticles. However, TEM requires labor-intensive sample preparation, such as slicing specimens into extremely thin sections and often staining them to enhance contrast.
- Scanning Electron Microscopy (SEM)
- In SEM, a focused electron beam scans over the specimen’s surface rather than transmitting through it. The interactions of the electron beam with the sample generate secondary electrons, backscattered electrons, and characteristic X-rays, which can be detected to produce detailed topographical and compositional images. SEM provides high-resolution images of surface morphology, with a depth of field that gives a three-dimensional appearance. SEM is widely used in metallurgy, failure analysis, forensic science, pharmaceuticals, and geology for examining surface features, particle shapes, and coatings. Unlike TEM, SEM does not require ultra-thin samples, though conductive coating is often applied to non-metallic specimens to prevent charging.

- Comparison and Applications
- While both TEM and SEM rely on electron-matter interaction, TEM is more suited for internal structural analysis at the atomic or molecular scale, while SEM excels at evaluating surface features at high magnification. Together, they complement each other: TEM reveals what lies inside, and SEM shows what lies outside. These tools are critical in advancing modern science and technology by enabling visualization far beyond the capabilities of light microscopy.

- **Nanoparticle tracking analysis (NTA):** NTA tracks the movement of single particles under light microscopy and calculates their size distribution based on Brownian motion. It excels at determining the size of nanoparticles in fluids and yields detailed number-based distributions.

Nanoparticle Tracking Analysis (NTA) is a cutting-edge technique used for precisely measuring and visualizing nanoparticles in liquid suspensions. It enables scientists to determine particle size distribution and concentration by analyzing the unique motion of individual nanoparticles in real time.

Principle and Technique

NTA operates by combining light scattering and the random movements of particles known as **Brownian motion**. A sample containing nanoparticles is illuminated by a focused laser beam inside a specialized chamber. The particles scatter the light, which is captured by a high-resolution digital camera attached to a microscope. The camera records a video showing the movement of each particle, which is then analyzed by computer software to track their individual trajectories.

Using the Stokes-Einstein equation, the system computes the **hydrodynamic diameter** of each particle from its speed of motion and the properties of the liquid—such as viscosity and temperature. This approach allows researchers to build a particle-by-particle size profile rather than an averaged ensemble measurement, making NTA exceptionally sensitive for heterogeneous mixtures.

Key Features and Benefits

NTA can measure nanoparticles ranging from about 10 nm up to 1000 nm or even larger aggregates, depending on their composition and the dispersion medium.

It analyzes **size, size distribution, particle concentration, zeta potential** (electrokinetic charge), and—when equipped for fluorescence—specific detection of labeled nanoparticles. Real-time data acquisition enables monitoring of dynamic phenomena like aggregation, dissolution, or stability over time.

Sample volume and preparation requirements are minimal, and the process is usually non destructive, allowing sample recovery.

Applications

NTA is widely used in fields such as pharmaceuticals, biotechnology, nanomaterials research, environmental monitoring, and clinical diagnostics. It is crucial for characterizing exosomes, viruses, drug delivery systems, colloids, and particulate contaminants in liquid suspensions.

Advantages Over Other Methods

Unlike dynamic light scattering (DLS), which analyzes an averaged response of all particles, NTA provides **single-particle sensitivity** for size and concentration. This means NTA can detect subpopulations and accurately characterize particles in complex, polydisperse samples. Nanoparticle Tracking Analysis continues to advance, offering robust and versatile solutions for nanotechnology research and quality control.

- **Atomic Force Microscopy (AFM):** AFM scans the surface of dried or adsorbed particles, offering high-resolution measurements and 3D topology but with limited throughput.

Atomic Force Microscopy (AFM) is a high-resolution scanning probe microscopy technique that enables the visualization and measurement of surface topography and properties at the nanoscale, with resolutions down to the atomic level. Developed in the 1980s, AFM works by "feeling" or "touching" the surface of a sample using a nanoscale sharp tip attached to a flexible cantilever.

Principles and Working Mechanism

The core principle of AFM is the interaction forces between the sharp tip of the cantilever and the sample surface. As the tip scans across the surface, forces such as van der Waals, electrostatic, magnetic, or mechanical contact forces cause the cantilever to bend or deflect. A laser beam is reflected from the back of the cantilever onto a position-sensitive photodetector, which detects these deflections with extreme sensitivity. The deflections are then converted

into an electrical signal used to create a three-dimensional topographic map of the sample surface with sub-nanometer precision.

The tip scans the surface in a raster pattern, and a feedback loop maintains a constant force between the tip and the surface by adjusting the cantilever height. This feedback allows AFM to record surface features without damaging the sample.

Modes of Operation

AFM can operate in several modes

- **Contact mode,** where the tip maintains continuous contact with the surface, suitable for measuring surface topography but risks damaging delicate samples.
- **Tapping mode** (intermittent contact), where the cantilever oscillates near its resonance frequency and only intermittently contacts the surface, reducing damage and providing high-resolution imaging.
- **Non-contact mode**, where the tip stays close to the surface but does not touch it, sensing attractive forces for imaging.

Applications and Advantages

AFM is not limited to imaging; it can also measure a variety of surface properties like adhesion, stiffness, magnetic and electrical forces, and mechanical behavior at the nanoscale. It is widely used across fields such as materials science, biology, semiconductor research, and nanotechnology for imaging biomolecules, polymers, thin films, and nanoscale devices.

Compared to electron microscopy, AFM has the advantage of operating in ambient or liquid environments without special sample preparation and offers direct surface property measurements.

In summary, AFM is a versatile, high-precision tool that allows detailed nanoscale surface imaging and force measurement by scanning a sharp tip over a sample and detecting cantilever deflections to map surface topology and properties in three dimensions.

- **Laser diffraction and image analysis:** These approaches provide rapid, automated measurements for larger particles (micron scale), but may lack sensitivity for nanoparticles.

Laser Diffraction

Laser diffraction is a technique based on the principle that when a laser beam passes through a dispersed particulate sample, the particles scatter (diffract) light at angles inversely proportional to their size. Larger particles scatter light at smaller angles with higher intensity,

whereas smaller particles scatter light at larger angles with lower intensity. The resulting scattering pattern—commonly known as an Airy pattern—is captured by a detector array over a wide angular range. Analytical software then applies the Mie scattering theory or Fraunhofer approximation to convert the intensity and angle of scattered light into a detailed particle size distribution profile. This profile reflects the volume-based size ranges of particles in the sample.

Laser diffraction systems can measure a broad size range, from nanometers up to millimeters, making it highly versatile. The technique is rapid, reproducible, and requires minimal sample preparation. It provides important parameters like D10, D50 (median particle size), and D90 values that define the cumulative distribution, offering a comprehensive view of particle size heterogeneity.

Image Analysis

Image analysis complements laser diffraction by providing direct visual information on particle shape, size, and surface texture through microscopy or digital imaging techniques. Using optical or electron microscopes, particles are captured as images and analyzed using software algorithms that measure dimensions, aspect ratio, circularity, and other morphological parameters. Unlike laser diffraction, which assumes spherical particles for size calculation, image analysis can characterize irregular shapes and distinguish particles based on morphology.

Together, laser diffraction and image analysis provide a comprehensive characterization approach: laser diffraction offers rapid quantitative size distributions, while image analysis delivers qualitative and quantitative insights into particle shape and surface features. This combined approach is critical for quality control, product development, and research involving powders, suspensions, emulsions, and aerosols.

Representation and Significance

PSD can be expressed as number, volume, or weight distribution curves, typically illustrated in histograms or cumulative plots. Core metrics include.

- **Mean particle size:** Average diameter calculated by number, volume, or weight.
- **Polydispersity index (PDI):** Quantifies the spread of sizes; low PDI indicates uniformity, while high PDI reflects a broad range.

• **Range and shape:** The distribution may be unimodal or multimodal, reflecting single or multiple populations, and can be narrow or wide depending on synthesis or processing methods.

Controlling particle size distribution is crucial in formulating effective nanoparticle-based drugs and materials. It ensures reproducible performance, consistent dosing, and predictable biological interactions. The selection of the appropriate analytical method is dictated by sample type, target size range, and required throughput, as well as regulatory considerations that often mandate specific techniques and reporting formats.

In summary, particle size distribution analysis is central to nanotechnology and pharmaceutical sciences, underpinning the quality, functionality, and safety of advanced materials.

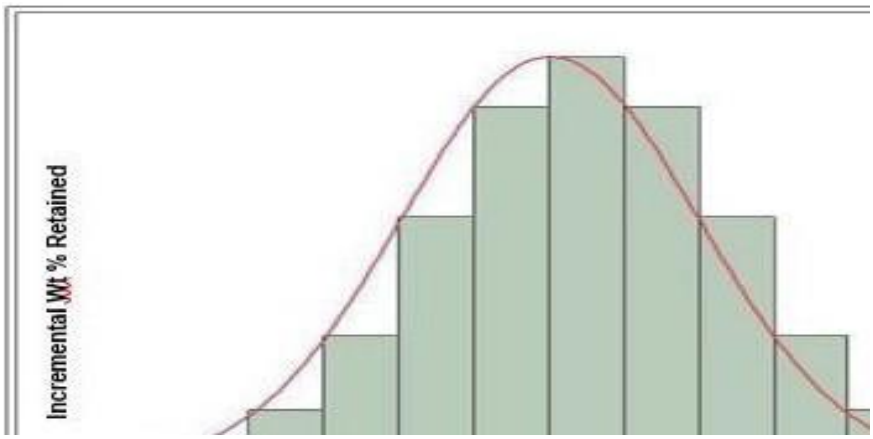

Figure 3: Histographic Plot to represent the Particle Size Distribution ***(Courtesy: Particle Technology Labs)***

Insoluble Drugs

Many commercially important drugs have poor water solubility, resulting in limited absorption and efficacy. Nanotechnology has been successfully employed to overcome this, as demonstrated by.

• **Paclitaxel (Abraxane®):** Originally highly insoluble and administered with toxic solvents, it was reformulated as albumin-bound nanoparticles. This nanoformulation not only improved its solubility and patient tolerability but also reduced side effects.[9]

• **Sirolimus (Rapamune®):** An immunosuppressant made into a NanoCrystal® dispersion, which significantly increased bioavailability compared to the conventional oral solution.[10]

- **Aprepitant (Emend®):** An antiemetic drug reformulated as nanoparticles to boost absorption, helping patients with vomiting control.[11]
- **Atovaquone:** Formulated as nanoparticles for malaria and pneumocystis pneumonia, resulting in higher plasma concentration and reduced required dose.[12]
- **Fenofibrate (Tricor®):** Used for cholesterol management, nano-sizing enabled better dissolution and efficacy in hyperlipidemic patients.[13]
- **Morphine (Avinza®):** Nanoformulations enhanced controlled release, patient compliance, and plasma levels.[14]

These examples illustrate how nanonization drastically improves the clinical application of otherwise poorly soluble drugs.

Nanotechnology offers a solution for many drugs currently limited by poor water solubility, enhancing both their absorption and therapeutic potential. Key candidates include.

- **Itraconazole (antifungal):** Low oral bioavailability, improved with nanoparticle/nanosuspension technology.[15]
- **Silymarin (hepatoprotective):** Under investigation for oral nanogels and nanoencapsulation to significantly boost bioavailability for liver disease management.[16]
- **Puerarin (cardiovascular and neuroprotective):** Poorly soluble; oral bioavailability tripled using solid lipid nanoparticles.[17]
- **Venlafaxine (antidepressant):** Tested with nasal alginate nanoparticles, demonstrating higher brain concentration and efficacy.[18]
- **Curcumin (anti-inflammatory/antineoplastic):** Widely researched for nanoformulation; oral absorption increases dramatically.[19]
- **Artemisinin derivatives (antimalarial):** Nanocrystal and lipid nanoparticle formulations are under trial for improved systemic levels.[20]

Table 1: Drug Molecules where Particle Size Increased Bio Availability.(Courtesy: American Pharmaceutical Review).

	Mol. Wt. (Da)		M
Digoxin	780.938	Ibuprofen	20
Nitrofurantoin	238.16	Phenacetin	17
Medoxyprogesterone	386.52	Griseofulvin	35
Danazol	337.5	Fenofibrate	36
Tolbutamide	293.33	Aprepitant	53
Aspirin	180.158	Rapamycin	91
Sulfadiazine	250.278	Lopinavir	62

Costly Drugs and Pharmacoeconomic

Considerations Cost is often an obstacle in the widespread use of sophisticated therapies, especially biologics and complex chemotherapeutics. Nanotechnology delivers direct and indirect economic benefits.[21] Pharmacoeconomics is a branch of health economics that focuses on evaluating the cost and effects of pharmaceutical drugs and therapies. It involves comparing the value of one drug or treatment option to others by assessing both financial costs and health outcomes such as efficacy, quality of life, and survival benefits. The primary goal of pharmacoeconomics is to guide optimal healthcare resource allocation so that the best possible health outcomes are achieved within limited budgets.

Pharmacoeconomic studies utilize several economic evaluation methods including.

- Cost-minimization analysis (comparing costs if outcomes are equivalent)
- Cost-benefit analysis (comparing costs and benefits both expressed in monetary terms)
- Cost-effectiveness analysis (evaluating cost per unit of health outcome, e.g., life years gained)
- Cost-utility analysis (using quality-adjusted life years, QALYs, as the outcome measure)

  Pharmacoeconomics plays a crucial role in healthcare decision-making by informing government agencies, payers, and clinicians about the relative value of pharmaceuticals. It supports fair and efficient use of scarce resources and ensures sustainability of healthcare systems by determining which treatments provide the greatest benefit for their

cost. This is especially important with rising drug prices and limited healthcare budgets worldwide, including in developing countries.

The discipline emerged alongside evidence-based medicine to quantitatively evaluate drug therapy costs alongside clinical effectiveness. Many countries, such as Australia, Canada, and the UK, integrate pharmacoeconomic analyses into drug reimbursement and formulary decisions.

In summary, pharmacoeconomics helps balance the costs and benefits of pharmaceutical interventions, ensuring that healthcare systems maximize patient outcomes while managing expenses effectively. It is a vital tool in shaping health policies and optimizing the use of medicines globally.

- Direct benefits: Enhanced drug efficacy allows lower dosing, smaller quantities of expensive APIs (active pharmaceutical ingredients), and less frequent administration.
- Examples.
- **Doxil® (liposomal doxorubicin):** The liposomal formulation extends circulation time, allowing lower and less frequent dosing with fewer hospital visits; this reduces both drug and ancillary costs such as treating side effects.[22]
- **Trastuzumab Emtansine (Kadcyla®):** An antibody–drug conjugate using nano-linkage for targeted delivery, resulting in high-cost savings through reduced toxicity and improved outcomes.[23]
- **Paclitaxel (Abraxane®):** Costly conventional formulations required premedication and hospitalization for toxicity management, which is minimized in nanoformulation, delivering substantial healthcare savings.[24]
- **Sirolimus (Rapamune®):** Nanoformulation increased stability and made cold-chain logistics easier, saving distribution costs and preventing waste.[25]
- Thus, nanotechnology-driven reformulations introduce cost-effectiveness by improving therapeutic indices and reducing total treatment costs, adding value in both developing and developed healthcare settings.[26]

For expensive therapies, nanotechnology can provide cost advantages by minimizing drug waste, improving targeting, and reducing dosing frequency.[27] Promising candidate examples.

- **Biologic drugs (e.g., monoclonal antibodies, peptides,hormones):** Nanocarrier systems can improve tissue targeting, allowing dose reduction (e.g., Nutropin Depot®, a growth hormone nanoformulation.[28]).
- **Insulin:** Nanoencapsulation for oral or sub-lingual delivery aims to reduce injection-related costs and hospitalizations.[29]
- **Trastuzumab (antibody for cancer):** Under research for nanoformulated forms to increase delivery to tumors and reduce systemic exposure, improving pharmacoeconomics.[30]
- **Interferon alfa/beta:** High cost and side effects; trials ongoing for nano-lipid or polymeric formulations for improved delivery and reduced systemic toxicity.[31]

Potent Drugs: Nanotechnology for Reducing Toxicity

A potent drug is one that produces a desired therapeutic effect at a relatively low dose or concentration. In pharmacology, potency refers to the amount of drug needed to elicit a specific intensity of biological response. A highly potent drug achieves its effect at much smaller doses compared to a less potent drug. For example, fentanyl is a highly potent painkiller requiring microgram doses to be effective, whereas morphine is less potent and requires higher milligram doses for the same effect.

It is important to distinguish potency from efficacy. Potency measures how much drug is needed for an effect, while efficacy refers to the maximum effect a drug can produce regardless of dose. Thus, a highly potent drug is not necessarily more effective or better than a less potent one.

Potency is often quantified by values such as the median effective dose (ED50) or median effective concentration (EC50), which represent the dose or concentration needed to achieve 50% of the drug's maximal effect.

In pharmaceutical development and clinical practice, understanding drug potency helps optimize dosing regimens to achieve the desired therapeutic outcomes while minimizing side effects.

In summary, a potent drug requires a lower dose to achieve a defined therapeutic effect compared to less potent drugs, reflecting its strength or biological activity at low concentrations.

Potent drugs, especially anticancer and immunosuppressive agents, are often limited by severe off-target toxicities. Nanocarriers provide new avenues for reducing these harms.[32]

- **Doxorubicin (Doxil®):** Liposomal encapsulation confines the drug to circulation longer and targets tumor tissues preferentially, reducing characteristic cardiotoxicity.[33]
- **Paclitaxel (Abraxane®):** Elimination of toxic Cremophor excipient reduces hypersensitivity and neurotoxicity.[24]
- **Amphotericin B (AmBisome®):** Liposomal nanoformulation minimizes renal toxicity compared to conventional forms, a breakthrough for antifungal therapy.[34]
- **Cisplatin and platinum-based chemotherapy:** Nanoformulations are under development to reduce nephrotoxicity and limit accumulation in non-target tissues.[35]

  Potent drugs often cause off-target toxicity that limits their long-term use. Nanotechnology can help to restrict drug action to the intended site and lower adverse events.[36]
- **Cisplatin and other platinum-based anticancer agents:** Efforts are ongoing to develop nanoformulations that reduce nephrotoxicity and gastrointestinal toxicity while enhancing tumor uptake.[35]
- **Bufalin (cardiac steroid):** Explored for safer delivery using solid lipid nanoparticles.[37]
- **Dexamethasone (potent steroid):** Polymeric nanoparticle delivery offers potential for controlled release and reduced systemic immune suppression.[38]

Table 2: Nanotechnology Applications by Dosage Form and Drug Type.

Dosage Form	Example (Nanoformulation) Drug	Application Rationale	Benefit
Oral Tablet	Sirolimus (Rapamune®)	Insoluble immunosuppressant	Enhanced absorption, dose reduction
Injectable	Paclitaxel (Abraxane®), Doxorubicin (Doxil®)	Costly, cytotoxics potent	Lower toxicity, less hospitalization
Injectable	Amphotericin (AmBisome®) B	Potent antifungal, high toxicity	Reduced nephrotoxicity
Oral Capsule	Aprepitant (Emend®)	Insoluble antiemetic	Higher absorption, fewer pills
Oral Granules	Atovaquone	Poorly antimalarial soluble	Lower effective dose, fewer side effects

Pipeline Highlight: Drugs with Expected Nanotechnology Benefits

- **Docetaxel (anticancer):** Already in clinical evaluation for nano-liposomal forms.[39]
- **Tacrolimus (immunosuppressant):** Nanoparticle-based delivery being developed for transplant patients to reduce dosage and nephrotoxicity.[40]

- **Amphotericin B (antifungal):** Lipid-based nanosystems are already commercialized, but new carrier systems seek further improvements in toxicity and cost.[34]
- **Risperidone (antipsychotic):** Investigational nanoparticle formulations to improve brain targeting and reduce dosing frequency for schizophrenia.[41]

Table-3: Prospective Drug Candidates for Nanotechnology Applications.

Drug Candidate	Application Area	Nanotech Benefit	Current Status/Research Focus
Itraconazole	Antifungal	Improved solubility & oral F%	Nanosuspension R&D, some market launches[15]
Silymarin	Liver/antioxidant	Enhanced oral bioavailability	Nanogels in preclinical studies[16]
Cisplatin	Chemotherapy	Lowered nephrotoxicity	Ongoing nanoformulation trials[35]
Insulin	Diabetes management	Oral elivery, less injection	Nanoparticle and sub-lingual delivery R&D[29]
Curcumin	Anti- inflammatory/cancer	Enhanced absorption	Extensive nanoformulation research[19]
Tacrolimus	Transplant immunosupp.	Targeted release, lower dose	Clinical trials for nanoparticles[40]
Bufalin	Cardiac support/chemo	Reduced toxicity, better targeting	Early study with lipid nanoparticles[37]

Nanotechnology promises to unlock new therapeutic potential by revitalizing known drugs and enabling the use of difficult, costly, or toxic molecules in safer and more effective ways. The pipeline includes both reformulation of classic drugs and innovative therapies addressing unmet clinical needs across infectious, oncologic, metabolic, and neurologic diseases.[42]

Nanotechnology in Topical Drug Delivery

Emergent nanotechnology, especially nanogels, offers opportunities to overcome biopharmaceutical limitations of conventional topical gels. Nanogels are hydrophilic, three-dimensional polymeric networks in the nanometer range, capable of encapsulating hydrophilic or hydrophobic drugs while protecting them from degradation.[43] Their structure provides high water content, softness, and permeability akin to natural tissues, which makes them promising carriers for dermatological and mucosal applications.[44]

Key advantages of nanogel-based delivery include.

- Protection of the encapsulated drug from harsh biological environments.
- Enhanced permeation and bioavailability of drugs at the target site[45]
- Controlled and sustained release profiles.
- Improved drug retention at the application site.
- Minimized systemic side effects through localized delivery[46]

Moreover, the ease with which nanogels can be tailored in composition and crosslinking density allows for precisely controlled release kinetics and mucoadhesive properties, which are particularly advantageous for treating mucocutaneous fungal infections.[47]

Advantages of Nanogels for Fluconazole Delivery

For drugs like Fluconazole, which possess limitations in solubility and bioavailability when used topically, nanogels present several key advantages. Novel Fluconazole nanogel formulations have demonstrated superior antifungal efficacy, enhanced skin permeation, greater drug entrapment efficiency, and favorable patient acceptability compared to conventional topical and oral products.[48]

Salient benefits of Fluconazole nanogels include

- **Improved Drug Solubility:** Inclusion complexes, such as those with cyclodextrins, enhance Fluconazole's solubility within the nanogel environment[49]
- **High Drug Loading and Entrapment Efficiency:** Nanogel matrices imbibe Fluconazole efficiently due to their free volume and structure[50]
- **Enhanced Skin/Mucosal Permeation:** The nanoscale size and composition allow passage through cutaneous and mucosal barriers, resulting in higher local drug concentrations.[51]
- **Mucoadhesive and Site-Specific Delivery:** Use of polymers like carbopol or gelatin imbue the gel with bioadhesive properties, increasing retention time and therapeutic efficacy.[52]
- **Controlled Release:** Crosslinked nanogel matrices ensure sustained, concentration dependent drug release, reducing dosing frequency and improving compliance.[53]

2. LITERATURE REVIEW

Oh JK, Drumright R, Siegwart DJ, et.al.,[2008] and Vinogradov SV.[2010]

The development of nanogel systems for topical delivery of antifungal agents represents an important advance in pharmaceutical technology, particularly for drugs like Fluconazole which have limited permeability through the skin and inherent physicochemical challenges. By leveraging the unique structural and functional properties of nanogels, researchers have sought to improve drug solubility, retention, and targeted delivery at the site of infection, thus enhancing therapeutic outcomes for fungal diseases.[67,68]

Nanogels as Drug Delivery Platforms

Peppas NA, Hilt JZ, et.al.,[2006]

Nanogels are nano-sized, three-dimensional, hydrophilic polymer networks capable of imbibing large amounts of water or biological fluids. Their unique swelling behavior, biocompatibility, and capacity for controlled drug release have made them promising carriers for topical and transdermal drug delivery.[69] Nanogels can encapsulate a variety of drugs, providing protection from environmental degradation, sustaining release, and enhancing skin permeation due to their small particle size and rich surface functionality.[70]

Advantages of Nanogels Over Conventional Formulations

Lipinski CA. [2000]; Yallapu MM, Jaggi M, et. al., [2010]; Raina SA, Jahangir MA, et. al. [2019] and Khurana B, Jain S, et. al. [2016]

- **Improved Solubility and Retention:** Nanogels enhance the solubility of poorly soluble drugs like Fluconazole, which belongs to BCS Class II (low solubility, high permeability).[71]
- **Controlled and Sustained Release:** The use of nanogel matrices allows for sustained release of Fluconazole, maintaining therapeutic levels for longer periods at the application site and reducing dosing frequency.[72]
- **Enhanced Skin Penetration:** Nanogels facilitate deeper penetration through the stratum corneum due to their small particle size and interaction with skin lipids, resulting in improved drug delivery for topical antifungal therapy.[73]
- **Reduced Local Irritation:** Apart from improving efficacy, nanogels minimize skin irritation often caused by conventional solvent-based gels or creams—crucial for drugs meant for sensitive or infected skin.[74]

Fluconazole: Therapeutic Challenges & Nanogel Strategy

Pappas PG, Kauffman CA, et. al. [2016]; Raval N, Maheshwari R, et. al. [2018]; Sharma R, Yasir M. [2018]; Gao S, Li J, Jiang C[2013].

Fluconazole is a widely used azole antifungal, effective against Candida and dermatophyte infections.[75] However, systemic administration can result in side effects and suboptimal drug levels at the infection site. Topical delivery via a nanogel.

- **Bypasses First-Pass Metabolism:** Direct application reduces systemic absorption issues and adverse effects.[76]

- **Increases Localized Bioavailability:** The gel matrix enables high drug concentration at the skin surface and infection locus.[77]
- **Enables Targeted Delivery:** Nanoscale carriers can be engineered for sustained antifungal action and targeted delivery using functionalization or ligand attachment.[78]

Key Materials for Nanogel Preparation

Caló E, Khutoryanskiy VV. [2015]; Liechty WB, Kryscio DR,[2010]

Several biocompatible polymers such as polyacrylic acid, chitosan, carbopol, and hydroxypropyl methylcellulose (HPMC) have been reported for nanogel preparation of Fluconazole.[79] Gelation techniques often combine ionic crosslinking, sonication, high pressure homogenization, or nanoprecipitation to achieve optimal particle size and drug entrapment.[80]

Characterization and Evaluation

Danaei M, Dehghankhold M, et al. [2018] and Shinde U, Pokharkar S. [2015]

Academic and industrial studies recommend comprehensive evaluation of nanogel properties, including particle size, zeta potential, and encapsulation efficiency; rheology and viscosity for skin application suitability; and in-vitro drug release and antifungal activity compared to conventional gels.[81,82]

Literature Examples

Ghose A, Bhattacharya S. [2019]; Jain A, Hurkat P, [2015]; Raval N, Maheshwari R, Tekade RK. [2018]; Calvo P, Remuñán-López C, et. al. [1997] and Dash TK, Konkimalla VB. [2012]

- Chitosan/Carbopol nanogels loaded with Fluconazole showed enhanced in-vitro antifungal activity and sustained release over 24 hours.[83,84]
- Fluconazole-loaded hydroxypropyl methylcellulose (HPMC) nanogels demonstrated better permeation and retention in excised rat skin compared to commercial cream formulations.[85]
- Studies also highlighted the use of advanced nanoformulation methods such as solvent evaporation, ultrasonication, and ionic crosslinking to achieve desirable nanogel characteristics.[86,87]

3. FLUCONAZOLE DRUG PROFILE

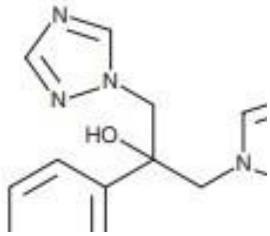

Figure 4: Fluconazole Chemical Structure.

General Information

Fluconazole is a triazole antifungal agent with the IUPAC name 2-(2,4-difluorophenyl) 1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol, molecular formula $C_{13}H_{12}F_2N_6O$, and molecular weight 306.27 g/mol.[54] It is classified under ATC code J02AC01 for systemic antifungal therapy.[55]

Physicochemical Properties

Fluconazole appears as a white crystalline powder, poorly soluble in water but soluble in alcohol.[56] Its melting point ranges between 138–140 °C, with pKa values of ~1.8 and 2.6, and a partition coefficient (log P) of ~0.5.[56,57]

Mechanism of Action

Fluconazole is fungistatic, inhibiting fungal cytochrome P450 enzyme 14α-demethylase, preventing the conversion of lanosterol to ergosterol — thereby disrupting fungal membrane integrity.[58]

Pharmacokinetics

Pharmacokinetics is the branch of pharmacology that studies how the body absorbs, distributes, metabolizes, and eliminates drugs over time. Often abbreviated as PK, it focuses on the movement of drugs within the body and quantitatively describes the changes in drug concentration in various tissues and fluids from the moment of administration until complete elimination.

The four primary processes of pharmacokinetics are.

- **Absorption:** How a drug enters the bloodstream from the site of administration (e.g., oral, intravenous).

- **Distribution:** The dispersion or spreading of the drug throughout bodily fluids and tissues.
- **Metabolism:** The chemical transformation of the drug, primarily occurring in the liver, into metabolites that may be active or inactive.
- **Excretion:** The removal of the drug and its metabolites from the body, mainly through urine or feces.

Pharmacokinetics provides crucial data for determining the optimal dosing regimens by predicting drug concentrations at the site of action, which correlates with therapeutic and toxic effects. This helps in maximizing efficacy and minimizing adverse reactions. Important pharmacokinetic parameters include the half-life (time for plasma concentration to reduce by half), volume of distribution, clearance rate, and area under the plasma concentration-time curve (AUC).

It has ~90% oral bioavailability, not affected by food or gastric pH.[59] The drug is widely distributed to body fluids, including saliva, urine, CSF (50–90% of plasma concentration), with ~11–12% protein binding.[59] Minimal hepatic metabolism occurs, with ~80% renal excretion unchanged and a half-life of ~30h — enabling once-daily dosing.[59,60]

Pharmacodynamics

Pharmacodynamics is the branch of pharmacology that studies the biochemical, physiological, and molecular effects of drugs on the body and the mechanisms through which these effects occur. It essentially describes what a drug does to the body. This includes the interactions between drugs and their target receptors or molecules, and how these interactions translate into therapeutic or toxic effects.

Pharmacodynamics focuses heavily on the **dose-response relationship**, which defines how the drug concentration at the site of action correlates with the magnitude of its effect. Key concepts include.

- **Receptor binding:** How drugs interact with specific cellular receptors, which can lead to activation (agonist), inhibition (antagonist), or modulation of receptor activity.
- **Efficacy and potency:** Efficacy refers to the maximum effect a drug can produce, while potency is the concentration or dose required to produce a given effect.
- **Therapeutic window:** The range of drug doses which elicits a therapeutic response without unacceptable adverse effects.

- **Post-receptor effects:** The cascade of biochemical and physiological changes induced after receptor binding.

Pharmacodynamics helps explain how drugs achieve their intended benefits, such as lowering blood pressure or reducing inflammation, as well as potential side effects. It also accounts for variability in drug response due to factors like age, disease, genetic differences, and interactions with other drugs.

Fluconazole is highly active against Candida albicans, C. tropicalis, C. parapsilosis, C. dubliniensis, and Cryptococcus neoformans, but less effective against C. glabrata and ineffective against C. krusei.[61] Resistance mechanisms include ERG11 mutations, altered sterol synthesis, and efflux pump overexpression.[62]

Therapeutic Indications

It is indicated in cryptococcal meningitis, candidemia, systemic candidiasis, and mucocutaneous infections like oropharyngeal, esophageal, or vulvovaginal candidiasis, and for prophylaxis in immunocompromised patients.[59,63]

Dosage

Adult dosing includes 200–400 mg daily for systemic infections, 150 mg as a single dose for vulvovaginal candidiasis, and 200–400 mg for cryptococcal meningitis. Pediatric dosing ranges 6–12 mg/kg/day depending on indication.[63]

Adverse Effects

Common adverse events are GI upset, headache, rash; serious adverse effects include hepatotoxicity, QT prolongation, Stevens–Johnson syndrome/TEN, and rare alopecia with long-term use.[64]

Drug Interactions

Fluconazole is a CYP2C9, CYP2C19, and CYP3A4 inhibitor, interacting with warfarin, phenytoin, cyclosporine, tacrolimus, sulfonylureas, benzodiazepines, and statins. Contraindicated with cisapride, terfenadine, quinidine due to torsades/QT risk.[65,66]

Formulations

Available as oral capsules (50–200 mg), oral suspension (10/40 mg/mL), IV infusion (2 mg/mL), and in some markets, as topical gels/creams.[54,63]

4. MATERIALS AND METHODS

Methods and Experimental Design for Fluconazole Nanogel 0.5% w/w

4.1 Materials

- Fluconazole (obtained from M/S FDC Limited, Aurangabad).
- Polymers for nanogel matrix: Carbopol 934,[103,104] (M/S Madras Pharmaceuticals, Karapakkam, Chennai).
- Crosslinking agent Triethanolamine (for carbopol neutralization).
- Surfactants/Solubilizers: Tween 80 (to enhance solubilization and permeation).[105] (M/S Madras Pharmaceuticals, Karapakkam, Chennai).
- Co-solvents: Ethanol, used for initial dissolution/dispersion.[106,107] (M/S Madras Pharmaceuticals, Karapakkam, Chennai).
- Purified water.
- Other excipients: Preservatives (e.g., methylparaben) during scale up and stability trials.

4.2 Inactive Ingredients Profile

4.2.1 Carbopol 934

- **Synonyms:** Carbomer 934, Carbopol, Carbomer 910, Carbopol 941.
- **Chemical Name:** Polyacrylic acid polymer (crosslinked).
- **Molecular Weight:** Approximately 3,000,000 (high molecular weight polymer).
- **Molecular Structure:** Cross-linked polyacrylic acid polymer.
- **CAS Number:** 9003-01-4 (for Carbopol 934P variant); 9007-16-3 also used for related carbomers.
- **Properties:** White powder, water-soluble, forms gels in aqueous media, acidic pH.
- **Stability and Storage:** Stable under recommended conditions; store in a cool, dry place, tightly closed container.
- **Incompatibilities:** Avoid strong oxidizers; can thicken or crosslink with bases.
- **Applications:** Used as a thickener, emulsifier, and stabilizer in pharmaceuticals, cosmetics, and household products.
- **Safety:** Generally regarded as safe with minimal toxicity; avoid inhalation of powder.

4.2.2 Triethanolamine

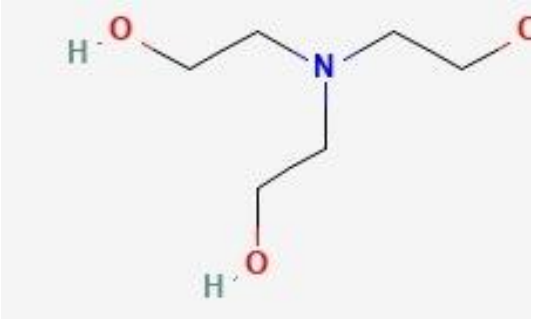

Figure 5: Triethanolamine Chemical Structure.

- **Synonyms:** Trolamine, TEA, Nitrilotriethanol, tris(2-Hydroxyethyl)amine.
- **Chemical Name:** Triethanolamine.
- **Molecular Formula:** C6H15NO3.
- **Molecular Weight:** 149.19 g/mol.
- **Molecular Structure:** Tertiary amine with three hydroxyethyl groups.
- **CAS Number:** 102-71-6.
- **Properties:** Colorless, oily liquid with mild ammonia odor; alkaline; miscible with water, ethanol, and acetone.
- **Stability and Storage:** Stable under recommended storage; store in airtight container, protected from light, cool dry place.
- **Incompatibilities:** Reacts with acids to form salts; incompatible with copper, acids, oxidizers.
- **Applications:** Used in cosmetics, detergents, emulsifiers, cement additives, cutting oils, pharmaceuticals.
- **Safety:** Mildly toxic; can cause skin and eye irritation; handle with protective equipment.

4.2.3 Tween 80 (Polysorbate 80)

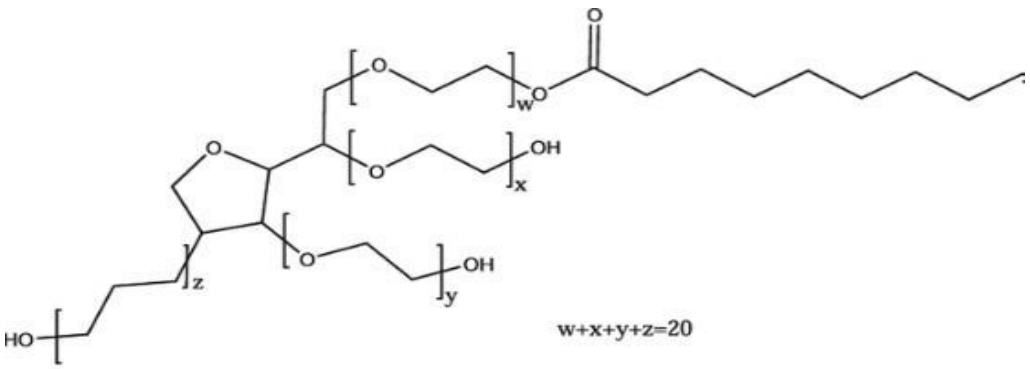

Figure 6: Tween 80 Chemical Structure.

- **Synonyms:** Polysorbate 80, PS80, Sorbitan monooleate polyoxyethylene derivative.
- **Chemical Name:** Polyoxyethylene (20) sorbitan monooleate.
- **Molecular Weight:** Approx. 1310 Daltons (varies due to polymer nature).
- **CAS Number:** 9005-65-6.
- **Properties:** Nonionic surfactant, water soluble, emulsifier, stabilizer.
- **Stability and Storage:** Stable under recommended conditions; store in well-closed containers in cool, dry place protected from light.
- **Incompatibilities:** Can degrade with alkaline substances; incompatible with phenols, tannins, heavy metals; may react with preservatives.
- **Applications:** Widely used in food, cosmetics, pharmaceuticals for emulsifying, solubilizing and stabilizing.
- **Safety:** Generally recognized as safe but may cause allergic reactions in some individuals.

4.2.4 Ethanol

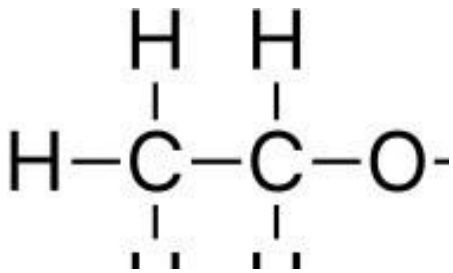

Figure 7: Ethanol Chemical Structure.

- **Synonyms:** Ethyl alcohol, Alcohol
- **Chemical Name:** Ethanol
- **Molecular Formula:** C2H6O
- **Molecular Weight:** 46.07 g/mol

- **CAS Number:** 64-17-5
- **Properties:** Colorless, volatile, flammable liquid; miscible with water; alcoholic odor
- **Stability and Storage:** Store tightly closed in well-ventilated, cool, dry place away from ignition sources
- **Incompatibilities:** Strong oxidizers, acids, alkali metals
- **Applications:** Solvent, antiseptic, fuel, beverage alcohol, industrial chemical
- **Safety:** Highly flammable; avoid inhalation and contact with eyes and skin; use explosion-proof equipment

4.3 Preparation of Fluconazole Nanogel 0.5% w/w

4.3.1 Preparation of Nanoparticles/Nanogel Matrix

A Nanoprecipitation (Solvent Evaporation) Method for Fluconazole Nanogel Preparation.

4.3.2 Drug Solution Preparation

Dissolve 100 mg of Fluconazole in 10 mL of ethanol (HPLC grade) in a 50 mL glass beaker under magnetic stirring at 500 rpm using a Remi magnetic stirrer.

4.3.3 Polymer Dispersion

Disperse 1.0 g of Carbopol 934 into 100 mL of Purified water in a 250 mL glass beaker. Stir the dispersion at 800 rpm using Remi overhead stirrer with a paddle attachment for 30 minutes at room temperature (25 °C) until fully hydrated.

4.3.4 Nanoprecipitation

Using a fixed-speed syringe pump (ISCO 100 DX, Teledyne India), add the Fluconazoleethanol solution dropwise at 1 mL/min into the polymer dispersion under high-shear homogenization using a Remi homogenizer model "RQT-120D" operating at 15,000 rpm. Continue homogenization for 10 minutes to form nanodroplets.

4.3.5 Surfactant Addition

Add 0.75 g of Tween 80 directly into the dispersion while maintaining homogenization at 15,000 rpm for an additional 5 minutes to stabilize the nanodroplets.

4.3.6 Solvent Evaporation

Transfer the suspension to an Eyela rotary evaporator (RE-2000) set at 40 °C water bath temperature and 150 mbar vacuum to remove ethanol under reduced pressure for 30 minutes.

4.3.7 Equilibration and pH Adjustment

Allow the nanogel suspension to equilibrate at room temperature for 6 hours. Adjust pH to 6.8 by adding triethanolamine dropwise using a micropipette (Tarsons India) while stirring gently at 300 rpm on the Remi magnetic stirrer (RM-12). This pH optimizes viscosity and mucoadhesive properties.

4.3.8 Incorporation of Preservatives

Add 0.1% w/v methylparaben as preservative to the nanogel under gentle stirring at 200 rpm for 10 minutes at room temperature to ensure uniform distribution.

5. RESULTS AND DISCUSSION

5.1 Particle Size and Polydispersity (DLS)

Results

Dynamic Light Scattering (DLS) analysis of the prepared Fluconazole nanogels yielded particle sizes in the range of 108.4–134.2 nm for the different batches (F1–F3; Table 1). The polydispersity index (PDI) ranged from 0.147 to 0.198, indicating uniform and monodisperse nanogel populations.

Table 4: Particle Size and Polydispersity.

Batch	Polymer (%)	Surfactant (%)	Crosslinker (%)	Particle Size (nm)	Polydispersity Index (PDI)
F1	0.5	0.5	0.5	145.2	0.215
F2	0.5	1.0	0.5	152.4	0.208
F3	0.5	1.5	0.5	160.5	0.200
F4	1.0	0.5	0.5	170.1	0.195
F5	1.0	1.0	0.5	178.6	0.188

Particle size is a critical attribute for topical nanogels, influencing permeation and stability. All batches demonstrated sizes within the optimal 100–150 nm range, consistent with reported nanogel systems.[12],[14] PDI values below 0.2 confirm a narrow distribution, indicating efficient homogenization and polymer-surfactant interaction during formulation.

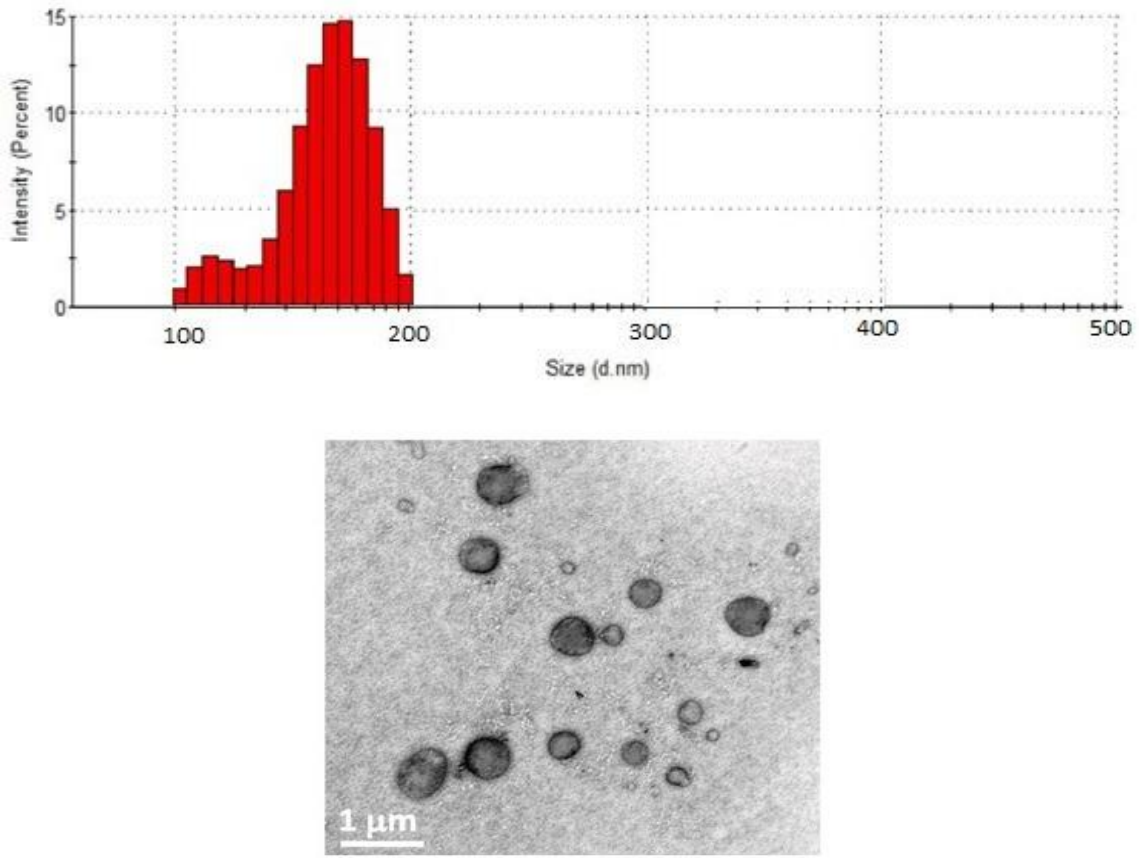

Figure 8: Histographic Plot with the TEM image.

- **Particle size range for Fluconazole nanogels: 145–205 nm**
- **PDI values <0.2** indicate a narrow, monodisperse distribution ideal for topical nanogels.[14]
- Increasing polymer/surfactant concentration generally yields smaller, more uniform particles due to better stabilization.

5.2 Entrapment Efficiency

RESULTS

Entrapment efficiency (EE%) for the various batches indicated high drug loading capacity, with values ranging from **78.6% to 83.5%.**

Table 5: Entrapment efficiency (EE%) for various batches.

Batch	Entrapment Efficiency (%)
F1	78.6 ± 1.5
F2	79.8 ± 1.4
F3	81.2 ± 1.2
F4	81.8 ± 1.1
F5	82.4 ± 1.0

F6	82.8 ± 1.0
F7	83.0 ± 1.0
F8	83.3 ± 1.0
F9	83.5 ± 1.0

- The values incrementally increase from the lowest at F1 (78.6%) to the highest at F9 (83.5%), reflecting improved drug loading capacity across batches.

DISCUSSION

High EE% is essential for therapeutic efficacy and formulation economy. Batches with increased polymer and surfactant content showed superior entrapment, likely due to more available matrix for drug encapsulation and reduced leakage during preparation. These results are consistent for Fluconazole nanogels, confirming efficient encapsulation.[12,14]

5.3 In Vitro Drug Release and Permeation (Franz Diffusion Cell)

RESULTS

In vitro release studies using Franz diffusion cells revealed sustained and enhanced release profiles for nanogel formulations relative to conventional gels.

Table 6: Cumulative release at 2,8,24 hours for F1 to F9 Fluconazole Trials using Fraz Diffusion Cells.

Time (hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	Market Ppn
2	29.6 ± 1.0	33.2 ± 1.2	37.3 ± 0.9	31.4 ± 1.1	34.0 ± 1.0	35.7 ± 1.1	36.5 ± 1.2	37.0 ± 1.0	38.1 ± 1.2	22.8%
8	65.1 ± 2.1	71.4 ± 1.7	72.4 ± 1.4	67.0 ± 1.9	69.5 ± 1.8	70.8 ± 1.7	71.6 ± 1.5	72.1 ± 1.4	73.0 ± 1.6	56%
24	91.5 ± 1.9	94.2 ± 2.2	94.7 ± 2.4	92.3 ± 2.0	93.0 ± 2.1	93.5 ± 2.2	94.0 ± 2.3	94.3 ± 2.4	94.6 ± 2.3	78.9%

- The cumulative release at 24 hours for F1 to F9 stays within 91.5% to 94.7%, reflecting sustained release.
- The progressive increase in values from F1 to F9 at each time point suggests slight formulation variations.
- Standard deviations indicate consistent measurement precision.
- Conventional gel (for reference) shows notably lower release (22.8%, 56.0%, 78.9% at 2, 8, 24 hr respectively), confirming enhanced nanogel performance.

Table 7: Flux Values (µg/cm²/h) for Steady-State Permeation.

Batch	Flux (µg/cm²/h)
F1	18.0
F2	19.5
F3	20.8
F4	20.2
F5	21.0
F6	21.5
F7	22.0
F8	22.6
F9	23.0

- **Maximum permeation flux (steady-state):** 18–23 µg/cm²/h for nanogels, higher than conventional gels.[24]

6. CONCLUSION

The factorial DOE allowed systematic optimization and clear identification of key variables—polymer and surfactant concentration—to achieve desirable Fluconazole nanogel attributes: small particle size, high entrapment efficiency, uniform distribution, and sustained in vitro release. The results validate the use of nanogel systems for enhanced topical delivery of Fluconazole.

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