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An Overview: Nanoparticles as Promising Drug Delivery through Skin

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ABSTRACT

Stratum corneum is an outer most layer of skin tissue acts as a barrier between the human body and the outside world. Drugs can be effectively delivered topically through the skin to treat or prevent illnesses, including systemic and dermatological conditions. skin disease globally is fungal infection, Fungi typically attack the skin's surface during the early stages of an infection before moving into the deeper layer through desquamation. the topical medication is applied at the right doses, side effects are minimized, bioavailability is increased, and patient compliance is increased. Nanoparticles (NPs) have attracted enormous interest in the field of medication delivery. Particulate dispersions or solid particles with a size range of 10–1000nm are referred to as nanoparticles. In which the drug is dissolve, entrap, encapsulate, or bind the medication. These nanoparticles improve the effectiveness, safety, and tolerance of integrated medications. The advantages of using nanoparticles as a Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

INTRODUCTION

TOPICAL DRUG DELIVERY SYSTEM:

The human skin is the largest organ. Drugs can be effectively delivered topically or transdermally through the skin to treat or prevent illnesses, including systemic and dermatological conditions. The outer most layer of skin tissue, known as the stratum corneum (SC), acts as a barrier between the human body and the outside world. The SC is the main barrier preventing cosmetics and medications used topically from penetrating.[1]

The development of a topical delivery system is a challenging project that necessitates careful selection of both the active principle and the vehicle in which the medication is to be given, as the barriers associated with these routes may limit drug access to effective sites.[2]

However, because hydrophilic medications have a low water content, they are challenging to transfer to the stratum corneum. These molecules enter the skin through "pores," or gaps, in sebaceous glands and hair follicles, which restrict the drug's absorption. Medication applied topically via the skin needs to have a molecular weight of less than 500 Da and the proper lipophilicity. When the topical medication is applied at the right doses, side effects are minimized, bioavailability is increased, and patient compliance is increased. [3]

One of the main causes of skin disease globally is fungal infection, which is estimated to affect 40 million people in developing and underdeveloped nations. Fungi typically attack the skin's surface during the early stages of an infection before moving into the deeper layer through desquamation; one of the most common types of superficial cutaneous infections is Candida species. Fungal infections that express themselves in the deeper layer of skin are known as cutaneous mycoses. A popular term for cutaneous fungal diseases is "Dermatophytes." A fungal infection that reaches deeper into the skin tissue is referred to as "subcutaneous mycosis." Both superficial and deep fungal infections can be treated with antifungal chemotherapy. Many fungal infections are caused by opportunistic pathogens that are either endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections).[4]

Topical delivery consists of two types: [5]

External topicals are applied topically to the cutaneous tissues in order to cover the afflicted area. They might be sprayed, smeared, or otherwise distributed. Internal topicals are given to

the mucous membrane orally, vaginally, or to anorectal tissues for local action Topical preparations are typically used to produce localized effects at the application site by virtue of the drug's penetration into the skin's underlying layers or mucous membranes. While some unintentional drug absorption may happen, it usually happens in little amounts and is not very concerning.

Advantages:[6]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoid of risk.
- Inconveniences of intravenous therapy and of the varied conditions of absorption like pH changes presence of enzymes gastric emptying time etc.
- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoid fluctuation of drug levels inter-and intrapatent variations.

Disadvantages:

- Skin irritation of contact dermatitis may occur due to the drug and / excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergic reactions.
- Can be used only for drugs which require very small plasma concentration for action.
- Enzyme in epidermis may denature the drugs.
- Drugs of larger particle size not easy to absorb through the skin.[6]

ANATOMY OF SKIN:[7]

Skin is the largest organ in the body. It is composed of three laps. The outer flap is called epidermis, the middle is dermis and the inner most layer is hypodermis.

1. Epidermis: Consists of epithelial cells. Among these cells, both vital cells and dead cells are extant. These new cells at the bottom of epidermis divide fast and push the older cells upward. The epidermis does not have any direct source of blood veins to provide nutrition for it. It takes its nutrients from the diffusion of necessary molecules from a rich vascular network in the basal dermis.

Epidermis composed of five layers, from inside to outside;

1. stratum germinativum (basal layer),
2. stratum spinosum,
3. stratum granulosum,
4. stratum lucidum and
5. stratum corneum

Stratum cornea is the outer most layer of epidermis and has a girth of 10-20µm when it is dry and 40µm when it is hydrated and becomes swollen. Stratum cornea has a structure of "bricks and mortar" arrangement. Stratum cornea consists of 70% proteins, 15% lipids and only 15% water. Molecules can permeate through skin by two altered pathways. The first pathway is called the transappendegeal route. In this route, the molecules should steep through skin by permeation through sweat glands and across the hair follicles. The number of molecules, which can penetrate through this pathway, is very limited. The second pathway of penetration through skin is the Trans epidermal pathway. In this pathway, molecules should pass through stratum corneum as multi-layered barrier. This pathway has two micro pathways; the intracellular micro pathway and the Trans late micro pathway.

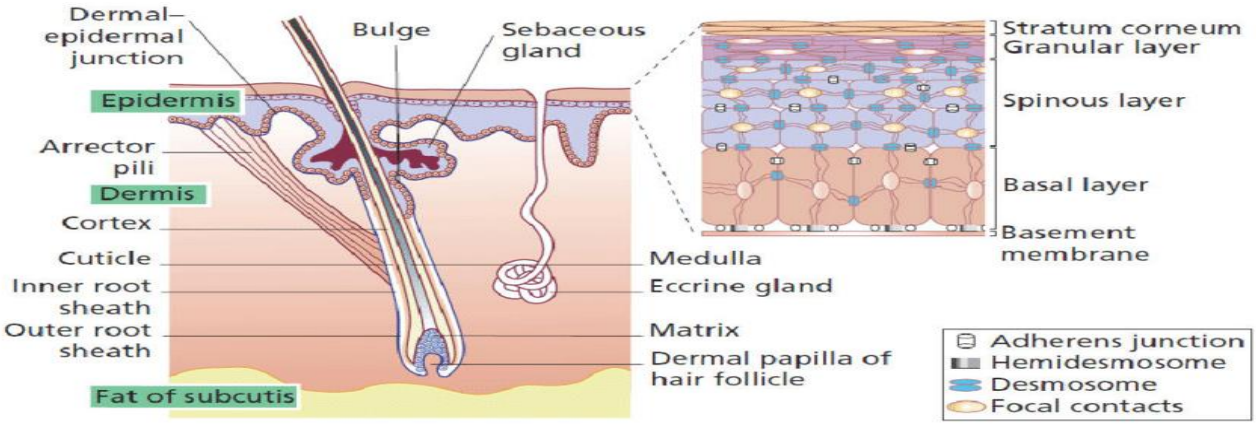

Figure 1: **A diagrammatical representation of a cross-section through human skin showing the different cell layers and appendages.**

2. Dermis:[8] The next layer of the dermis skin is a thick layer of fibrous and elastic tissue that gives it flexibility and strength. This layer is primarily composed of collagen, elastin, and fibrillin. The dermis contains nerve endings, sweat glands, oil glands, hair follicles, and blood vessels. The dermis is a vascularized collagen rich connective tissue that contains mucopolysaccharides (also known as the ground material).

3. Hypodermis:[9] The hypodermis is the skin's deepest layer. It is the skin layer that comes into contact with the body's deeper tissues, including the bones and muscles. Though they are covered by the epidermis, sweat glands, sebaceous glands, and hair follicles are all made in the dermis. Sweat glands apply a thin layer of salt solution to the skin's surface. Skin temperature is regulated by the evaporation of this fluid, which cools the skin. There are pleasant glands all across the body. The amounts of sweat dilutions produced is dependent on the surrounding temperature, the degree of heat-producing skeletal muscle activity, and a range of emotional factors. Sebum is secreted by the sebaceous glands. Oily material called sebum is secreted by hair follicles onto the skin.

NANOPARTICLE DRUG DELIVERY SYSTEMS:

Nanoparticles (NPs) have attracted enormous interest in the field of medication delivery during the last few decades. Particulate dispersions or solid particles with a size range of 10–1000 nm are referred to as nanoparticles. A nanoparticle matrix is used to dissolve, entrap, encapsulate, or bind the medication.[10]

Polymeric nanoparticles have attracted significant attention in the study of drug delivery systems as they offer a means for localized or targeted delivery systems of a drug to a specific tissue/organ site of interest with an optimal release rate.[11]

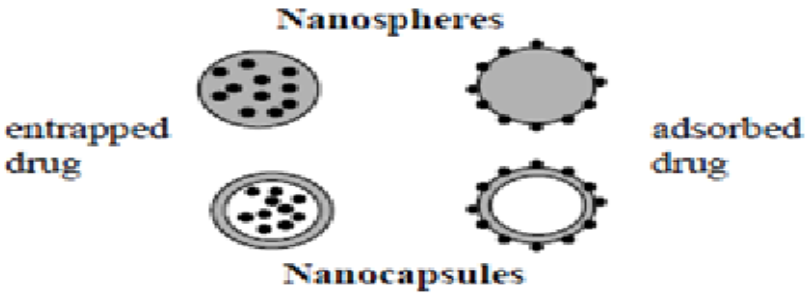

Figure 2: Various types of drug loaded nanoparticles.

Some properties of Nanoparticle drug delivery systems[12]

- Simple and inexpensive to manufacture and scale-up.
- No heat, high shear forces or organic solvents involved in their preparation process.
- Reproducible and stable.
- Applicable to a broad category of drugs; small molecules, proteins and polynucleotides.
- Ability to lyophilize.

- Stable after administration.
- Non-toxic.

Advantages of nanoparticles: [13]

Nanoparticles offers numerous advantages in drug delivery system.

- Nanoparticles have many significant advantages over conventional and traditional drug delivery system.
- Nanoparticles can be administered by various routes including oral, nasal, parenteral, intra-ocular etc.
- In the tiny areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a particular cell type or receptor.
- Due to small particle size nanoparticles overcome resistance by physiological barriers in the body and easily penetrates to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
- Nanoparticle enhance the aqueous solubility of poorly soluble drug, which improves bioavailability of drug.
- As a targeted drug carrier nanoparticles reduce drug toxicity and enhance efficient drug distribution.
- By using polymers drug release form nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.
- Useful to diagnose various diseases.
- Enhanced stability of ingredients.
- Prolonged shelf life.
- Used in dental surgery also as filling the tiny holes in teeth.
- Change the method of drug delivery to improve customer acceptance or reduce manufacturing costs.

Limitations of nanoparticle:[14]

Despite these advantages, nanoparticles present limitations, such as.

- Altered physical properties leading to particle-to-particle aggregation, making physical handling of liquid and dry nanoparticles difficult due to their smaller size and their largest surface difficult.
- The smaller the particle size, the greater the surface area, and this property makes nanoparticles very reactive in the cellular environment.
- The small particle size results in limited drug load in and pulse delivery. These practical problems must be solved before nanoparticles can be used clinically or commercially.
- The small size and large surface area can lead to aggregation of nanoparticles, making physical manipulation of nanoparticles in liquid and dry form difficult.
- In addition, the small particle size and high surface area of easily result in limited drug loading and burst release. These practical problems must be overcome before nanoparticles can be used clinically or commercially.

NEED FOR DEVELOPING NANOPARTICLES: [15]

In order to obtain site-specific effect of the drug at the optimal rate and dose, the main objectives in designing nanoparticles as a delivery system are to manage the particle size, surface characteristics, and release of pharmacologically active substances. Polymeric nanoparticles have certain special advantages over liposome, such as helping to enhance the stability of drugs| proteins and possessing helpful controlled release features.

Criteria for ideal polymeric carriers for nanoparticles & nanoparticle delivery systems Polymeric carriers:[12]

- Easy to synthesize and characterize.
- Inexpensive.
- Biocompatible.
- Biodegradable.
- Non-immunogenic.
- Non-toxic.
- Water soluble.

PREPARATION OF NANOPARTICLES:[16]

For the preparation of nanoparticles, the selection of the appropriate method is based on the drug to be loaded and the physicochemical properties of the polymer. The most widely used methods are,

A. Emulsion-Solvent Evaporation Method
B. Solvent Displacement/Precipitation method
C. Polymerization method
D. Coacervation or ionic gelation method
E. Salting out method
F. Emulsions - Diffusion method

1. Emulsion-Solvent Evaporation Method: The nanoparticles are usually prepared by using this method. Two steps are mainly involved in this method shown in Fig 3. In an aqueous phase, emulsification of the polymer solution is required in the first step. While in the second step, evaporation of polymer Solution occurs and nanospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by ultracentrifugation and to eliminate free drug or residue, washed with distilled water and for storage these are lyophilized. This method is also known as the solvent evaporation method and high-pressure emulsification.

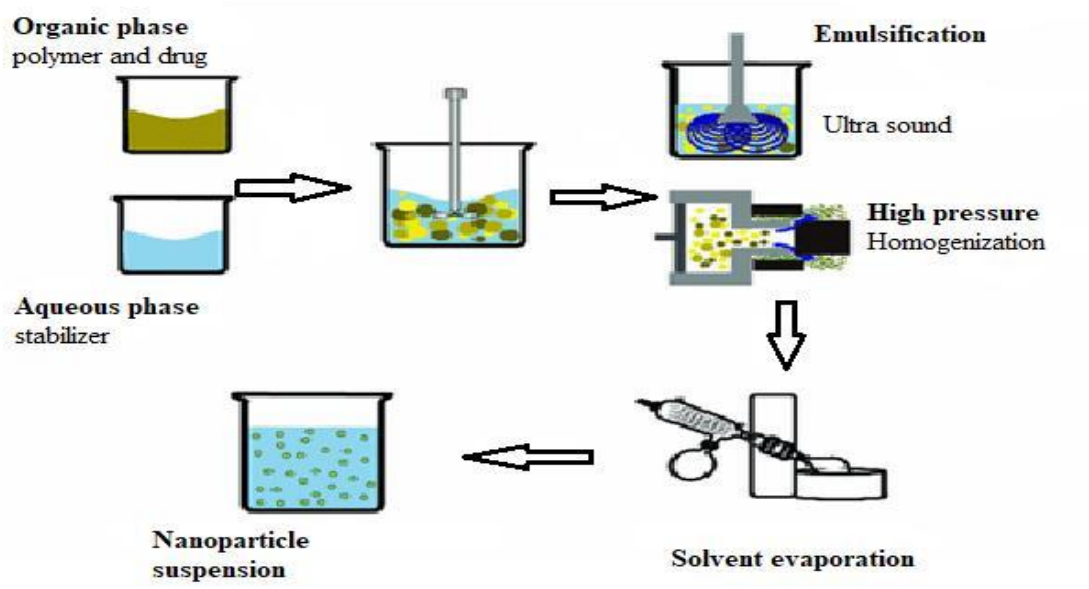

Figure 3: Emulsion-Solvent Evaporation Method

2. Solvent Displacement/Precipitation Method: Solvent displacement involves from an organic solution, the precipitation of a preformed polymer, and in the aqueous medium the diffusion of the organic solvent in the presence or absence of surfactant. In semi-polar water-miscible solvents like acetone or ethanol, polymers, drug, and lipophilic surfactant are dissolved. Then the solution is injected using magnetic stirring, into a stabilizer containing an aqueous solution. By the rapid solvent diffusion, Nanoparticles are formed. Then under reduced pressure solvent is removed from the suspension. The particles size is also affected by the rate of addition of the organic phase into the aqueous phase. It was observed that by increasing the rate of mixing, both particles size and drug entrapment decrease. For most of the poorly soluble drugs, the nanoprecipitation method is well suited.

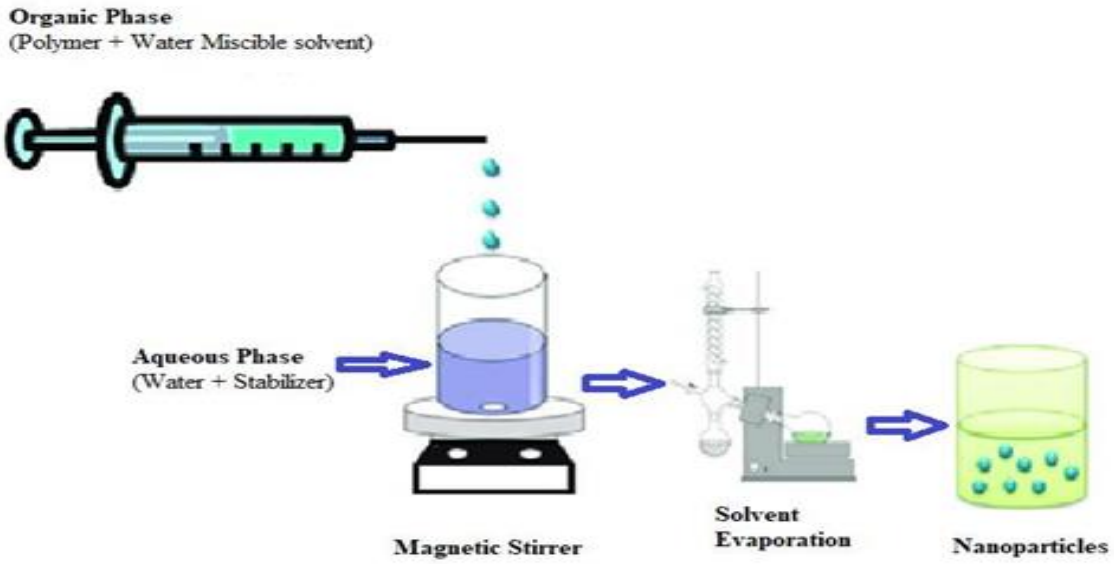

Figure 4: Nanoparticle preparation using the solvent displacement method

3. Polymerization Method: In this method, monomers are polymerized to form nanoparticles in an aqueous Solution. The drug is included either by being liquefied in the polymerization medium or by adsorption onto the nanoparticles after polymerization is completed. The Nanoparticle suspension is then filtered to eliminate Various stabilizers and surfactants employed for Polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been described for making poly butyl cyanoacrylate or poly (alkyl cyanoacrylate) nanoparticles. Nanocapsule development and their particle size depending on the concentration of the surfactants and stabilizers used.

4. Coacervation Or Ionic Gelation Method: The preparation of nanoparticles utilizes biodegradable hydrophilic polymers such as chitosan, gelatin, and sodium alginate. This method includes a mixture of two aqueous phases, of which one is the polymer chitosan, di-block copolymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly anion sodium tripolyphosphate. In this method, positively charged chitosan links with negatively charged to form coacervates with a size in the range of nanometre. Coacervates are developed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation includes the material undergoing a transition from liquid to gel due to ionic interaction due to ionic interaction conditions at room temperature.

5. Salting Out Method: This technique is based on the separation of water-miscible solvent from an aqueous solution by the salting-out effect. In this method, toxic solvents are not utilized. Polymer and drug dissolved in a solvent which emulsified into an aqueous solution containing salting-out agent but salting out can also be produced by saturation of the aqueous phase using colloidal stabilizer / emulsion stabilizer/viscosity increasing agent such as polyvinyl pyrrolidine or hydroxyethyl cellulose, PVA, PLGA, and poly(trimethylene carbonate). After preparation of o/w emulsion diluted with the addition of sufficient water to allow the complete diffusion of acetone into the aqueous phase, thus inducing the formation of no spheres. This technique does not require an increase in temperature and stirring energy required for lower particle size. The disadvantage of this technique is its entire application to lipophilic drugs and the extensive nanoparticle washing steps. Solvent and salting-out agents are then eliminated by cross-flow filtration.

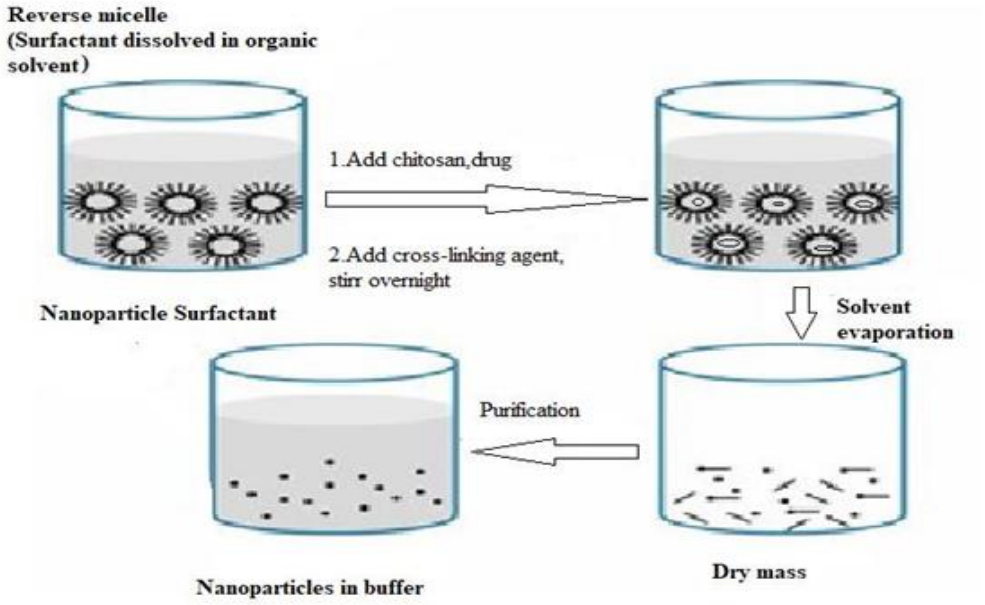

Figure 5: Nanoparticle preparations using salting-out method.

6. Emulsions - Diffusion Method: In this method, the polymer is liquefied in water-miscible solvent and saturated with water. Polymer water-soaked solvent phase is emulsified in an aqueous solution containing a stabilizer. Then the solvent is eliminated by evaporation or filtration.

Mechanisms of drug release:[17]

The drug from the polymeric drug carriers deliver at the site of the tissue by anyone of the three general physico-chemical mechanisms which are explained below:

- By hydration which causes the swelling of the polymer nanoparticles followed by release through diffusion.

- By an enzymatic reaction that leads to rupture or degradation or cleavage of the polymer at the site of delivery and results in the release of the drug from the entrapped inner core.

- Dissociation of the drug from the polymer and it does de-adsorption/release from the swelled nanoparticles.

EVALUATION OF NANOPARTICLES:

1. Zeta potential:[18]

Zeta potential was measured by the zetasizer. For this purpose, the colloidal suspensions were diluted with distilled water and placed in the zetasizer chamber.

2. Particle size: [19] Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, and toxicity and targeting ability of nanoparticle system. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

3. *In-vitro* drug release studies:[20] In vitro drug release profile was performed by using dialysis bag method with the help of dialysis membrane molecular weight cut off 12000-14000 Da. The release rate of drug from formulation depends on various factors like polymer ratio, polymer degradation or erosion, solubility. In the present study nanoparticles dispersion was filled in the dialysis tube and immersed in Phosphate saline buffer (pH 7.4) under continuous magnetic stirring and the temperature should be maintained at 37±1ºC throughout the procedure. At specific time intervals, the samples were taken and diluted to determine the concentration UV spectrophotometer at 307nm.

4. *In-vitro* release kinetics study: [21]

In order to analyze the drug release mechanism, in vitro release data were fitted into a zero-order, first order, Higuchi, and Korsmeyer-peppas model.

Zero order kinetics: The zero order rate equation describes the systems where the drug release rate is independent of its concentration.

$$Q_1 = Q_0 + K_0\, t$$

First order kinetics: The first order equation describes the release from a system where the release rate is concentration dependent. Kinetic equation for the first order release is as follows:

$$\text{Log } Q_t = \log Q_0 + K_1\, t/2.303$$

Higuchi model: describes drug release as a diffusion process based in the Fick's law, square root time dependent.

$$Q_t = KH\ t_{1/2}.$$

5. Stability of nanoparticles:[22] Stability studies of prepared nanoparticles determined by storing optimized formulation at 4°C ±1°C and 30°C ± 2°C in stability chamber for 90 days. The samples were analyzed after a time period like at 0, 1, 2, and 3 months for their drug content, drug release rate (t50%) as well as any changes in their physical appearance.

6. Drug entrapment efficiency:[23] The encapsulation efficiency and loading capacity of the nanoparticles were determined by the separation of nanoparticles from the aqueous medium containing non-associated fluconazole by cold centrifugation (Eppendorf Centrifuge) at 11000 rpm for 30 minutes. The amount of free fluconazole in the supernatant was measured by Shimadzu 1800 UV-Visible Spectrophotometer at 261 nm. The entrapment efficiency (%) of drug was calculated by the following equation;

$$Entrapment\ efficiency\ (\%) = \frac{\text{Initial amount of drug added} - \text{Amount of drug actually present} \times 100}{\text{Initial amount of drug Added}}$$

7. Drug-excipient compatibility studies: [24]The drug excipient compatibility studies were performed by using FT-IR spectrophotometer. The FT-IR spectra of drug, polymers, and formulations were analyzed separately and then correlated for incompatibility.

APPLICATIONS OF NANOPARTICLE DELIVERY SYSTEMS[25]

Targeting drug delivery by encapsulation

Nano encapsulation of drugs. They have many advantages in the protection of premature degradation and interaction with the biological environment, enhancement of absorption into a selected tissue, bioavailability, retention time and improvement of intracellular penetration. Several disease related drugs or bioactive molecules are successfully encapsulated to improve bioavailability, bioactivity and control delivery. Nanomedicine formulation depends on the choice of suitable polymeric system having maximum encapsulation (higher encapsulation efficiency), improvement of bioavailability and retention time. Different drugs with various polymeric (PLA, PLGA, PCL, chitosan, gelatin) nanoparticles show impact upon surface modification, bioavailability and drug release mechanisms.

Nanoparticles for oral delivery of peptides and proteins

Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation.

Nanoparticles for drug delivery into the brain

The blood-brain barrier (BBB) is the most important limiting factor for the development of new drugs for the central nervous system due to its relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. BBB is impermeable for the water-soluble drugs from blood circulation to CNS and it is selectively permeable for lipophilic and small size molecules.

Nanoparticles for ophthalmic delivery

To overcome the poorly soluble drugs in lachrymal secretions of eye these Nano formulations play a vital role and could prove. Nano suspension of nanoparticles offers most advantage of prolong residence time in cull- de-sac, which is most important for the ocular diseases for effective treatment and also maintain tonicity with respective to the eye. The dissolution rate and intrinsic solubility is depending on the lachrymal fluid the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. The intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids.

Topical formulations

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin. Micellar nanoparticle is a technology applicable for topical applications. This technology allows high concentrations of drug to penetrate the skin and functionally create a drug depot in the stratum corneum and epidermis. This route of delivery provides similar advantages of patch technology in avoiding both contact with the gastrointestinal tract and hepatic first-pass effects, and is cosmetically more acceptable to many patients.

Nanoparticles for diagnostic applications

The nanoparticles are used to diagnose cancer and treated. Magnetic Nanoparticles being a sub-family of nanomaterials show remarkable new phenomena such as superparamagnetism, high saturation field, extra anisotropy contributions or shifted loops after field cooling. These phenomena arise from finite size and surface effects that dominate the magnetic behavior of individual nanoparticles. Small size gives effective surface area, low sedimentation rate,diffusion and reduces dipole-dipole moment. The magnetic property of nanoparticles (MNP) offers an advantage that it provide selective attachment to a functional molecule, confer magnetic properties to the target, and allow manipulation and transportation to a desired location through the control of a magnetic field produced by an electromagnet or permanent magnet. MNPs can be easily controlled by external magnetic field gradients. This helps to transport the MNPs into human tissue and be directed and concentrated within the target tissue by means of external magnetic field, especially in cancer tumor.

Cosmetic applications

Solid lipid nanoparticles are one type of nanoparticle formulated from physiological lipids. These lipids have some inherent properties such as Occlusive nature and Ultraviolet ray protection which allows their use in cosmetics. The enhanced permeability of the lipid nanoparticles through horny dead layers and allows skin hydration due to occlusive property.

Solid lipid nanoparticles give physical protection due to their particulate matter. Physical sunscreens act by reflecting and scattering UV rays. This effect of physical sunscreens depends upon the particles refractive index, the size of the particles and thickness of formulation films on skin. The solid lipid nanoparticles are better a scattering light than liquid emulsion droplets.

Nanoparticles for gene delivery

Nanoparticles loaded with plasmid DNA, Vaccines could also serve an effective sustain delivery by escaping from the Endolysosomal compartment to cytoplasmic compartment and it was reported that following their intracellular uptake and endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting in sustained gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein.

Pulmonary delivery It means drugs administered for their local or systemic effect through bronchial tree or through lungs. Alveoli are the functional units of lungs which have high surface area, high epithelial permeability and rich vasculature make this route popular for rapid absorption and free from the first pass metabolism. The unique size of nanoparticles not only increases its absorption but also enhances and controls the release and transport of drugs. The preferable drugs for this route of delivery are antiallergic bronchodilators and steroidal anti-inflammatory agents such as betamethasone.

RECENTLY REPORTED NANOPARTICLE FORMULATION[26-39]

SL.NO	AUTHOR NAME	METHOD	DRUG	COMPONENTS	REPORT
1	Mourya *et al*., (2020),	Ionic gelation method	Miconazole nitrate	Chitosan, sodium tripolyphosphate, acetic acid Carbopol 934.	The optimized formulation with better bioadhesive property may improve the bioavailability of topical administration.
2	Kong *et al.*, **(**2021),	Inotropic gelation method	Proanthocyan-idin.	Chitosan, Sodium tripolyphosphate,	Supported the use of chitosan nanoparticles to encapsulate PC and improve its bioactivity in food products.
3	Shende *et al., (*2020),	Inotropic gelation method	Curcumin	Chitosan, Poly Lactic Glycolic Acid and carboxy methyl cellulose	Curcumin-loaded nanoparticles are showed significant enhancement in wound healing action due to synergistically use of chitosan.
4	Luo *et al., (*2020),	Inotropic gelation method	Astaxanthin.	Chitosan, Stearic acid (SA) and dextran.	The prepared Astaxanthin nanoparticles are shows promising features as an oral delivery vehicle for lipophilic bio

					actives.
5	Guo *et al*., (2021),	Inotropic gelation method	Adriamycin	Chitosan, Sodium Tripolyphosphate	The nanoparticles with enhanced biological activity, reduced cytotoxicity, and pH-sensitive release could be served as potential drug carrier in drug delivery system.
6	Qian *et al*., (2019),	Inotropic gelation method	Chitosan	Chitosan, Sodium Tripolyphosphate,	The antimicrobial activity of nanoparticles was significant better than that of chitosan with the same molecular weight.
7	Sharma *et al*., (2019),	Ionic gelation technique	Carvediol.	Chitosan, Sodium tripolyphosphate, (TPP)	The optimized chitosan nanoparticles formulation have higher bioavailability than marketed tablet formulation.
8	Adlin *et al*.,(2009),	ionic gelation technique	Flutamide.	Chitosan, Tri poly phosphate (TPP), tween 80.	Thus, nanoparticles of Flutamide (F4) with core: coat ratio 1:4 was found to be free flowing and able to sustain the drug release effectively.

9	Farid *et al.*, (2020),	ionic gelation technique	ofloxacin.	Chitosan, Sodium tripolyphosphate, (TPP)	An ofloxacin loaded chitosan nanoparticles against *E.coli* and *S.aureus* showed Minimum Inhibitory Concentration nanoparticles could be applied as carrier for decreasing the dose of antibacterial agents in the infection.
10	Akbari *et al*., (2021),	ionic gelation technique	salicylic acid	Chitosan, Sodium tripolyphosphate (TPP)	The Salicylic acid Nano particles were more cytotoxic than salicylic acid. These data demonstrated that the drug release. mechanism governed by Korsmeyer-Peppas model.
11	Sadozai *et al*., (2022),	emulsion/ solvent evaporation method	ketoconazole	. Poly(lactase-co-glycolide) (PLGA), Polyvinyl alcohol (PVA), Carbopol 934P-NF	Our gel formulation could strongly reduce drug permeation through the skin, and more than 60% of the drug was retained on the upper surface of the skin in contrast to 38.42% of the commercial cream.
12	Akther *et al*., (2021),	emulsion–diffusion–evaporation technique	α-mangostin	e poly (D, L-lactic-co-glycolic acid) (PLGA), Polyvinyl alcohol,	. The formulated Poly Lactic Glycolic Acid Nano Particels were converted

					into a preformed carbopol gel base it had a significant cytotoxic effect and antioxidant effect
13	Sachith *et al., (*2022),	ionic gelation technique	ezetimibe	Chitosan ,Sodium tripolyphosphate (TPP)	This chitosan-based delivery system opens new and interesting perspectives as drug carriers. because There was a steady decrease in the entrapment efficiency on increasing the polymer concentration in the formulations.
14	U. M. Dhana Lekshmi *et al.*,(2012),	solvent evaporation method	Metformin hydrochloride	Poly (lactide-co-glycolide) [PLGA] Poly (methyl methacrylate) (PMMA) and Poly (Vinyl Alcohol) (PVA)	All formulations showed haemolytic effect less than 5%. The study revealed that Metformin loaded PMMA and PLGA polymeric nanoparticle did not produce any toxicity.

FUTURE OPPORTUNITIES AND CHALLENGES:[40]

Nanoparticles provide massive advantages regarding drug targeting, delivery and release and with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of

nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.

CONCLUSION

Fungal infections are becoming a global burden and cause significant morbidity and mortality. While there are several effective antifungal agents their therapeutic benefits are limited by high toxicity or unfavorable physicochemical properties. Nano particles have the potential to over come many of these limitations. Nanoparticles are a promising drug carrier for various drug delivery systems. nanoparticulate systems have great promise for converting unstable, ineffectively soluble, and ineffectively absorbed physiologically active chemicals into potentially deliverable pharmaceuticals.

Many other nanoparticles formulations have shown promising results in terms of enhancing antifungal drug aqueous solubility, improving its antifungal efficacy, enhancing stability and targeting to infected tissues. Therefore, research in the field of antifungal drug delivery should focus on overcoming the obstacles that prevent clinical translation of nanoparticle-based formulation.

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