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Nanoparticulate Gel for Topical Delivery: A Critical Review

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Thejaswini H B[1], Chandrashekar S M[2]

[1]*Research scholar Sunrise University, Alwar, Rajasthan, India*

[2]*Research Guide Sunrise University, Alwar, Rajasthan, India*

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ABSTRACT

Nanosized drug carriers have attracted much attention in the past decade as options in formulations for topical therapy. Nanotechnology takes part in several technology fields from electrics to cosmetics. According to the National Nanotechnology Initiative (NNI), nanoparticles have a diameter ranging from 1 to 100 nm. In this size range, it is possible to achieve control of matter at the atomic and molecular scale. Nanotechnology offers possible solutions to many current problems using smaller, lighter, faster, and better-performing materials, components, and systems compared to the bigger scale. However, nanotechnology refers to technologies in which the conscious use of nanoscale structures to create new properties. Material properties change completely when the material consists of nanosized particles. Then the particle surface area relative to volume and mass is very large and causes physical, chemical, and biological properties of a radical change in the substance.[5] Nano-sized carriers such as polymeric nanoparticles (nanospheres, nanocapsules), solid lipid nanoparticles, liposomes, and nano-emulsions have been widely applied as topical formulations to enhance cutaneous drug delivery. The chemical and physical features of these nanosized carriers can effectively protect unstable drugs from degradation/ denaturation, thereby decreasing the side effects of toxic drugs by producing controlled release, and enhancing the cutaneous penetration of the drugs across the skin barrier by increasing the concentration gradient.

INTRODUCTION:

The development of successful topical drug delivery systems has been limited in scope due to the significant penetration barrier provided by the stratum corneum (SC), the topmost skin layer.[1] Stratum corneum comprises a multi-layered “brick and mortar” like structure, where mortar is an intercellular matrix of a unique composition of lipids and the bricks are composed of keratin-rich corneocytes.[2] To overcome this barrier, numerous passive and active penetration enhancement methods have been evaluated. Chemical penetration enhancers have been intensively investigated over the years, but the concentrations required for improved penetration often lead to sensitization or irritation.[3]

Nanosized drug carriers have attracted much attention in the past decade as options in formulations for topical therapy. Nanotechnology takes part in several technology fields from electrics to cosmetics. According to the National Nanotechnology Initiative (NNI), nanoparticles have a diameter ranging from 1 to 100 nm. In this size range, it is possible to achieve control of matter at the atomic and molecular scale. Nanotechnology offers possible solutions to many current problems using smaller, lighter, faster, and better-performing materials, components, and systems compared to the bigger scale.[4,5]

However, nanotechnology refers to technologies in which the conscious use of nanoscale structures to create new properties. Material properties change completely when the material consists of nanosized particles. Then the particle surface area relative to volume and mass is very large and causes physical, chemical, and biological properties of a radical change in the substance.[5] Nano-sized carriers such as polymeric nanoparticles (nanospheres, nanocapsules), solid lipid nanoparticles, liposomes, and nano-emulsions have been widely applied as topical formulations to enhance cutaneous drug delivery. The chemical and physical features of these nanosized carriers can effectively protect unstable drugs from degradation/ denaturation, thereby decreasing the side effects of toxic drugs by producing controlled release, and enhancing the cutaneous penetration of the drugs across the skin barrier by increasing the concentration gradient.

Nowadays nanotechnology has been applied to improve drug delivery in many ways, and the nanosystems provide several advantages. The reason is that nanostructured materials have shown promise as drug delivery systems because of their controlled- and sustained-release properties, subcellular size, and biocompatibility with tissue and cells. Especially, nanotechnology is adapted for non-soluble and hydrophobic drugs for improving solubility.[6,7]

Various nanostructured materials were produced and applied to drug delivery such as nanoparticles, nanocapsules, nanotubes, micelles, nano-, microemulsions, and liposomes.[8] In this thesis, the focus was on nanoparticles.

Nanoparticles are one type of nanomaterial. Nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Several materials such as metal (copper, zinc, gold, silver), carbon nanotubes, polymers (chitosan), or other materials can be used for the preparation of nanoparticles in a variety of medical applications. Recent advancement in nanotechnology has proven that nanoparticles can be used as drug carriers. The small size of particles (ranging from 10 nm to 1000 nm) has several benefits. Various advantages of nanosizing are decreased fed/fasted variability and patient-to-patient variability, increased oral bioavailability, rate of dissolution, and surface area. In addition, nanosize applications offer less amount of dose required, enhanced solubility, and a more rapid onset of therapeutic action.[9] A variety of nanoparticles can be designed by considering the aim of the application. Figure 1 shows different types of nanoparticles.

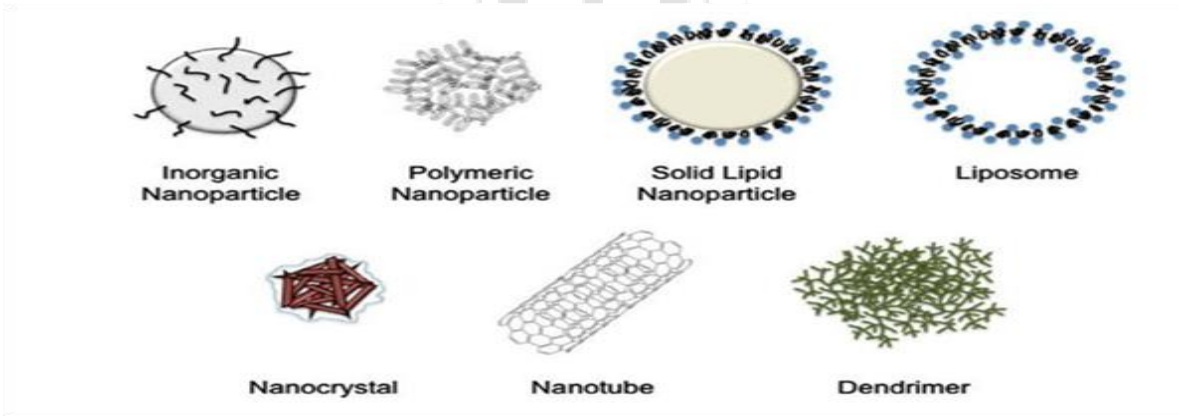


Figure No 1. Some types of nanoparticles: inorganic, polymeric, solid lipid, liposome, nanocrystal, nanotube, and dendrimer.

Most polymeric nanoparticles are biodegradable, biocompatible, and non-toxic and degrade to produce readily cleared degradation by-products. They have been adopted as a preferred method for nanomaterial drug delivery.[10] PNPs have been extensively studied as particulate carriers in the pharmaceutical and medical fields.[11] Encapsulation strategies include polymers with absorbed drugs, dendritic molecules or coordination compounds with drugs bonded covalently or weakly attached, and artificial or natural micelles or liposome vesicles containing nano doses of insoluble or toxic drugs which can be selectively released on

targets.[6] It is possible to prepare polymeric nanoparticles with different polymers, and in this thesis, chitosan polymer was used for the preparation of nanoparticles.

Most of the polymeric nanoparticles with surfactants offer the stability of various forms of active drugs and have useful smart-release properties. There are numerous biological applications have been reported for the nano-scale to micro-scale sized particles, such as site-targeted, controlled, and enhanced bioavailability of hydrophobic drugs.[12-15] Due to the size of the nanoparticle the drugs have been targeted into various applications, such as various cancers targeting is promising.[16] Moreover, polymeric particles proved their effectiveness in stabilizing and protecting the drug molecules such as proteins, peptides, or DNA molecules from various environmental hazards degradation.[13-15,17,18] So these polymers are affording the potential for various protein and gene delivery.

Numerous methods had been available to fabricate nanoparticles; it depends on the physical and chemical properties of the polymer and active ingredients. Most of the formulation techniques involve different mechanisms such as using organic solvents, temperature, ultra-sonication, and mechanical agitation which can degrade the pharmaceutically active ingredients. So the nano-particulate system can be developed to consider the formulation methodology should not damage the active pharmaceutical ingredients. There are numerous biodegradable and biocompatible polymers with different physicochemical characteristics are offered to prepare smart nanoparticles, those polymeric nanocarriers can be natural or semi-synthetic, or synthetic. Those nanoparticles can enhance the systemic circulation half-life and minimize unwanted internalization and prevent the denaturation of the therapeutically active moiety and could use to deliver the target agents.

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a widely prescribed group of analgesic and anti-inflammatory agents used to treat a variety of acute and chronic painful conditions. The use of NSAIDs in a topical formulation may be beneficial in reducing the likelihood of a patient experiencing adverse effects associated with systemic therapy. Medications applied directly to the skin are either intended for local action or systemic effects. Topically applied medications (e.g., topical patches, creams, gels, ointments, solutions, etc.) are intended to reach local tissue to achieve the desired therapeutic effect[19]. They are Cyclooxygenase-2 (Cox-2) inhibitors that inhibit prostaglandin synthesis responsible for inflammation.

The majority of NSAIDs are administered orally due to the adverse effects associated with the orally administered NSAIDs, such as gastric and duodenal irritation. The use of NSAIDs topically prevents dose-related adverse effects such as acute renal insufficiency and prostaglandin inhibition. Numerous other advantages of topically administered NSAIDs include higher concentration at the desired site that blood levels, increased permeation of drugs through the stratum corneum, absence of gastric degradation and hepatic first-pass effect, and lastly as it is administered topically it does not require any professional supervision and nor does it have the stigma associated needles as compared to the parental dosage form.[20]

Ketoprofen is a therapeutic agent with anti-inflammatory, antipyretic, and analgesic activity that has been selected in this paper as a model compound for the preparation of controlled delivery systems for topical applications. The physicochemical characteristics of this molecule regarding lipophilicity (log P = 2.8) and molecular weight are adequate for penetration through the human stratum corneum. Ketoprofen is highly permeable through the stomach, its poor water solubility limits its entry into the systemic circulation. During gastric emptying, ketoprofen enters the small intestine, where it cannot permeate through the membrane despite being solubilized. Ketoprofen is classified in the Biopharmaceutics Classification Scheme as a class II drug. Since dissolution is the rate-limiting step during drug absorption, the poor water solubility in oral forms of ketoprofen results in low bioavailability due to incomplete absorption. In addition to absorption difficulties, oral formulations of ketoprofen can cause gastric mucosal damage, which may result in ulceration and bleeding.[21-23]

Chitosan

Chitin is the second most important natural polymer after cellulose in the world, and chitosan (CHT) is the most important derivative of chitin. When the degree of deacetylation of chitin reaches about 50%, it becomes soluble in aqueous acidic media and is called chitosan. Figure 2 presents the structure of chitin and chitosan. Chitosan, N-acetyl- d-glucosamine, and β-(1,4)-linked d-glucosamine, are one of the most commonly used natural biomaterials. It is a hydrophilic polymer and a natural linear biopolyaminosaccharide. Chitosan is largely used in different applications as solutions, gels, or films and fibers because it is soluble in aqueous solutions. This polymer presents excellent bio-compatibility, biodegradability, and antimicrobial activity.[24-26]

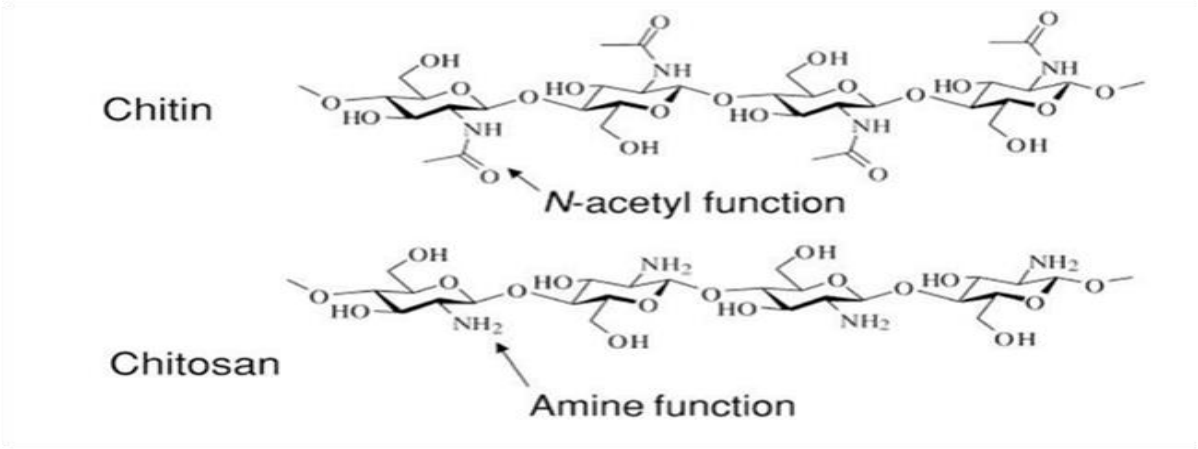


Figure no 2. Structure of chitin and chitosan. Chitosan is delivered by deacetylation of chitin.

Generally, drugs have problems such as poor stability, water insolubility, low selectivity, high toxicity, insensitiveness side effects, poor biodistribution, and lack of selectivity. Drug carriers play a significant role in resolving these problems. In this thesis, chitosan nanoparticles were prepared and employed as drug carriers. Chitosan nanoparticles as drug carriers have the advantage of providing controlled drug release, they can also aid to improve drug solubility and stability, enhance efficacy and reduce toxicity.[27]

The properties of chitosan are shown in Figure 3. Chitosan nanoparticles are capable of passing through biological barriers in vivo because of their small size. In addition, chitosan nanoparticles can deliver drugs to the lesion site to enhance efficacy, and modified nanoparticles also have other properties such as improved drug targeting. Being a natural product and having other good features such as low immunogenicity and low toxicity, chitosan is a renewable pharmaceutic adjuvant with good biocompatibility.[27,28]

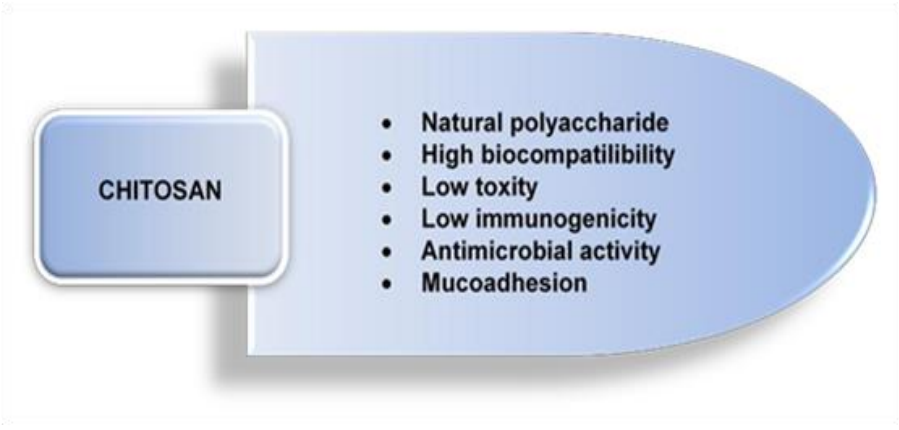


Figure no 3. Properties of chitosan.

The properties of chitosan allow it to be used in local anesthetic drug delivery in the skin, because chitosan is mucoadhesive, reactive (it can be produced in many different forms), and most importantly, it has a positive charge under acidic conditions. Earlier studies show that chitosan hydrogels are non-cytotoxic and potential for extended drug release, making them promising local anesthetic delivery vehicles.[29]

Ionic gelation method

Several methods for the preparation of polymeric nanoparticles have been developed and one of them is the ionic gelation method. It is also the one that is used in this work. The method is simple and mild and involves the mixture of two aqueous phases at room temperature.

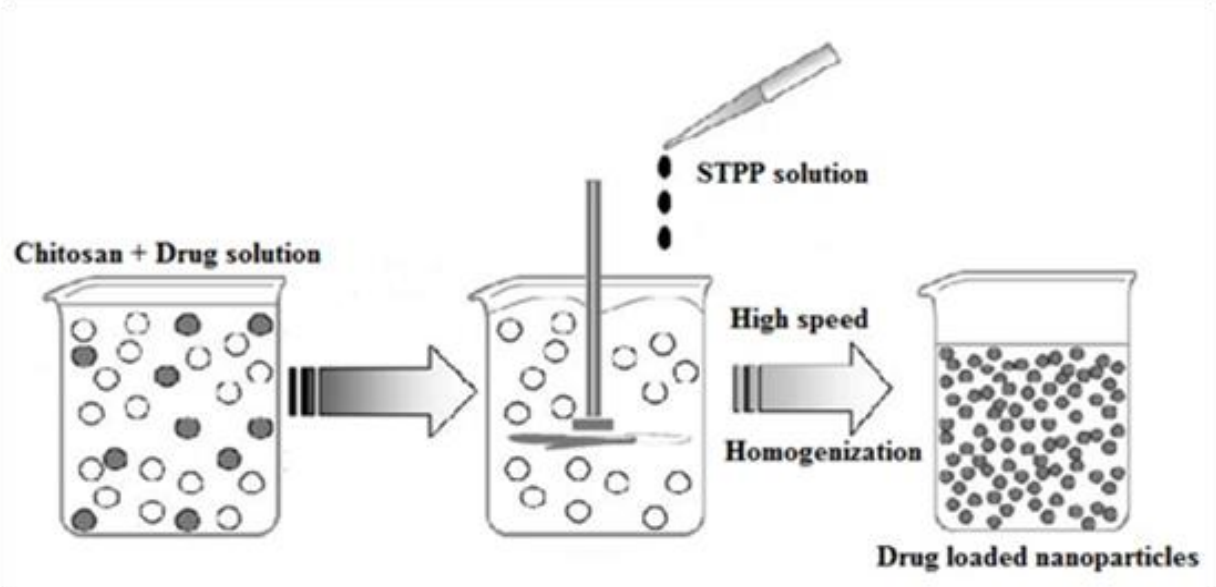


Figure no 4. Schematic representation of the ionic gelation method. Tripolyphosphate is added to chitosan-drug solution dropwise with high-speed mixing for making drug-loaded nanoparticles. TPP works as a cross-linker between chitosan and drug.

In the ionic gelation method (Figure 4), based on the formation of complexation between the positively charged amine group of chitosan and negatively charged polyanion, such as tripolyphosphate (TPP) to form coacervates with a size in the range of nanometer. TPP can be used for preparing chitosan nanoparticles because it is non-toxic, multivalent, and able to form gels through ionic interactions.[11,30]

Nanoemulsions are nanosized emulsions, which are manufactured for improving the de-livery of active pharmaceutical ingredients. A typical nanoemulsion contains oil, water, and an emulsifier. Nanoemulsions have various advantages; for example, they can improve the

bioavailability of the drug, it is non-toxic and non-irritant as well has im- proven physical stability. The most important benefit is that it helps to solubilize lipophilic drugs, and lidocaine (the drug that is used in this thesis) is a lipophilic molecule.[31]

Due to the unique properties of nanoemulsions, it is an attractive candidate for applications in the food, cosmetic, and pharmaceutical industries and in drug delivery applications. In this chapter, the focus will be on applications of nanoemulsions as building blocks for complex material synthesis to produce, for example, compartmentalized nanoparticles. One of the best-known applications in polymer synthesis is emulsion polymerization. It means synthesis, where hydrophobic monomers contained in droplets are polymerized to create polymeric particles. Nanoemulsions have been utilized extensively in polymer synthesis.[31,32]

Nanoparticles based on biocompatible and biodegradable synthetic or semi-synthetic polymers, including poly (lactide-co-glycolide) (PLGA), poly (ε-caprolactone), chitosan, and a combination of chitosan and poly (gamma-glutamic acid) and (gamma-PGA), have shown promise in dermal drug delivery. These carriers can potentially (i) protect labile compounds from premature degradation, (ii) provide controlled and sustained release via modification of polymer composition,[33-35] (iii) increase localized targeting thereby reducing systemic absorption, and (iv) reduce irritation.[36]

Dispersion of polymer-based nanoparticles in hydrophilic gels can further improve drug delivery to the skin. Gels can aid in creating uniform dispersion of the carriers in the matrix, and increase contact time and deposition of the carriers on the skin resulting in enhanced skin penetration of the payload. It has been reported that these nanoparticles significantly enhance the permeation of highly lipophilic molecules into the lower skin strata, even though the delivery of such compounds is typically restricted to the uppermost layers.[37] These results indicate that nanoparticles can be used as effective skin penetration enhancers.

RATIONALE

To formulate an efficient and effective topical preparation, considerations should be given to the objective. This is directly concerned with the site of action and the desired effect of the formulation. Topical preparations may be used for:

1. Surface effects: cleansing (removal of germs and dirt), cosmetic (improvement of appearance), protective (prevention of moisture loss), antimicrobial (reduction of infection).

2. Stratum corneum effects: protective (sunscreens that penetrate this layer), keratolytic (sloughing of the skin, helpful in the treatment of psoriasis), protective (moisturizing).

3. Viable epidermal and dermal effects: several classes of drugs can penetrate these layers (anti-inflammatory, antihistamine anesthetic, antipruritic). Even though it is tough for drugs to penetrate the stratum corneum, once they are in the dermis, they can diffuse into the systemic circulation. It is difficult to formulate a drug with only a local effect without successive uptake by the blood.

4. Systemic effects: few drugs, such as scopolamine, clonidine, nitroglycerin, and estradiol, have been formulated in a manner to achieve systemic effects.

5. Appendage effects: some classes of drugs are intended to put forth their action in these portions of the skin (depilatory, antimicrobial, exfoliant, and antiperspirant). Infection remains a major reason for morbidity and mortality following the shock period in burnt patients. Measures to lessen the risk of wound infection and subsequent sepsis include early removal where possible. The patient who is suffering from major burns is at risk from both systemic and cutaneous infections.

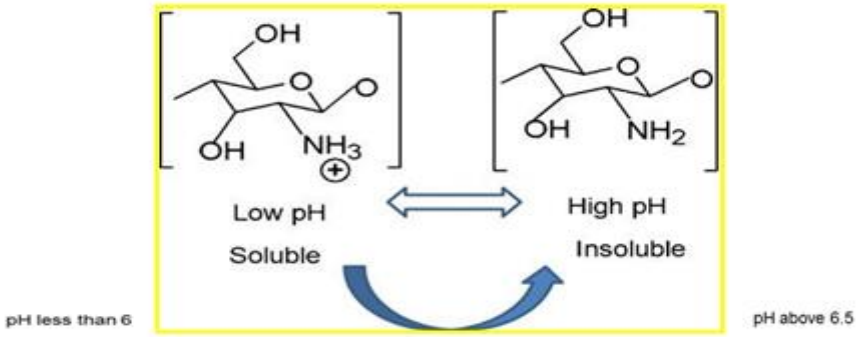
Nanogels are robust nanoparticles that could be used to deliver active drug compounds in controlled drug delivery applications as a sustained release. The design, synthesis, loading, and release of pain relief/pain control / local anesthetics using polymeric nanogel produced via various types of polymerization techniques of high skin permeable API to have a longer duration of action.

- Ketoprofen, a potent NSAID is a preferential inhibitor of cyclooxygenase -2 and has analgesic and anti-inflammatory activity, widely used in the treatment of rheumatoid arthritis, osteoarthritis, and another joint disease.

- Thus there arises a necessity to explore safer routes of administration which shows controlled release, reduction in dosage regimen, improving bioavailability at targeted site in comparison with plain ketoprofen, and eliminating first pass metabolism limiting wastage of drug.

- Thus, the motive is to formulate a biodegradable, non-toxic controlled release from nanoformulation for topical administration of ketoprofen which shows improvement in diffusion profile topical gel in comparison to the topical gel of plain drug.

- Chitosan, being a cationic polysaccharide in neutral or basic pH conditions, contains free amino groups and hence, is insoluble in water. In acidic pH, amino groups can undergo protonation thus, making it soluble in water.



- Among the various types of chitosan-polyanion complexes reported in the literature, the combination of chitosan and poloxamer 188 is considered to be the most interesting for colloidal carrier systems. Hence it was selected as a nanoparticulate carrier in the present study.

Snapshot of work:

- To reduce the size of the nanometer.
- Reduction in dosage regimen
- To modulate the controlled release of short half-life drugs.
- To fabricate polymeric nanoparticles by ionic gelation method.
- To study the effect of polymer concentration in the formulation.
- To formulate gel containing the polymeric nanoformulation.
- To improve *in-vitro* performance.

Introduction to Disease

Inflammation

Inflammation is caused by the release of chemicals from tissues and migrating cells. Most strongly implicate dare the prostaglandins (PGs), leukotrienes (LT_5), histamine, bradykinin, and, more recently, platelet-activating factor (PAF) and interleukin-1. Evidence for their

involvement comes from studies with competitive antagonists for their receptors and inhibitors of their synthesis. Prostaglandin, prostacyclin (PGI_2), and thromboxane A_2 (TXA_2) are produced from arachidonic acid by enzymes cyclooxygenase which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms; the former serves physiological 'house-keeping' functions, while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the site of inflammation generations of PGs locally which mediate many of the inflammatory changes.[38]

Kinin Receptors

The existence of two types of kinin receptors (B_1, and B_2) has been established. Most kinin action sinnon-inflammed tissues are mediated by B_2 receptors which are constitutively present on:

1) Visceral smooth muscle contraction of the intestine, uterus, and airway.

2) Vascular endothelium– NO release, vasodilation, increased permeability.

3) Sensory nerves- acute pain

The B_1 receptor is located on the smooth muscle of large arteries and veins- mediates contraction of these vessels, but is expressed minimally in normal tissues. Inflammation induces the synthesis of B_1 receptors so that they might play a major role at inflamed sites. Bradykinin has a higher affinity for B_2 than for B_1 receptors, while Kalliden is equipotent on both.[39]

Pathophysiological Roles

Mediation of Inflammation

Kinin produces all the signs of inflammation-redness, exudation, pain, and leukocyte mobilization. Tissue injury can cause local kinin production which then sets in motion the above defensive and reparative processes. Activation of B_1 receptors on macrophages induces the production of IL-, TNF-α, and other inflammatory mediators.

Mediation of Pain

By directly stimulating nerve-ending sand by increasing PG production kinins appear to serve as mediators of pain. The B_2 antagonists block acute pain produced by Bradykinin, but induced B_1 receptors appear to mediate chronic inflammation.[39]

Anti-Inflammatory Drugs Oral v/s Topical Delivery

A successful topical NSAID requires not only efficacy at the target site but the ability to reach that site, which may involve delivery via systemic circulation and direct penetration. An important question in determining the potential advantages of Topical NSAIDs is whether any clinical effect is achieved by direct transport to the tissue or by systemic absorption and redistribution.

The skin layers through which any drug must be transported are the stratum corneum (the uppermost layer of dead epidermal cells), the viable epidermis (devoid of blood vessels), the basement membrane, and the dermis(containing blood vessels).[40] Absorption into the systemic circulation or penetration into deeper tissues occurs from this point.[41]

Compared with oral administration, topical application leads to relatively high NSAID concentrations in the dermis. Concentrations achieved in the muscle tissue below the site of application are variable but are at least equivalent to that obtained with oral administration. NSAIDs applied topically do reach the synovial fluid, but the extent and mechanism (topical penetration versus distribution via the systemic circulation) remains to be determined. In addition, marked interindividual variability was noted in all studies; percutaneous absorption may be strongly influenced by individual skin properties. Topically applied NSAIDs have a superior safety profile to oral formulations.[42]

Adverse effects secondary to topical NSAID application occur in approximately 10 to 15% of patients and are primarily cutaneous (rash and pruritus at the site of application). GI adverse drug reactions are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs. In theory, an NSAID applied topically could achieve therapeutic concentrations in the tissues subjacent to the site of application while maintaining low serum concentrations. This could provide numerous potential benefits to patients, including avoidance of gastrointestinal (GI) tract and first-pass metabolism, as well as reduced risk of serious adverse events related to elevated serum NSAID concentrations. Avoidance of the GI tract should mitigate the common direct toxicities of nausea, vomiting, dyspepsia, and

diarrhea which occur secondary to high local concentrations of NSAID in the alimentary tract.[42]

Benefits

NSAID-mediated toxicity is often dose related. Thus, reduction in serum concentrations should also lessen the risk of potentially serious systemic adverse effects secondary to NSAID-induced prostaglandin inhibition: acute renal insufficiency, nephritic syndrome, NSAID gastropathy, prolonged bleeding time, and fluid retention. Finally, the topical application should mitigate the risk of drug-drug interactions, such as NSAID-mediated protein binding displacement of warfarin.

Local Action

Local enhanced topical delivery of topically applied NSAIDs does occur in humans, but the tissue depth at which the systemic circulation takes over the distribution of the drug is highly variable among individuals. Individual variability in subcutaneous vasculature may account for the wide range of tissue depths reported after topical administration, as well as inconsistency in patient response to topical NSAIDs. Few generalizations can be made regarding the best drug or topical dosage form for enhancing cutaneous NSAID penetration and efficacy. Optimizations of vehicle formulation, pH, and occlusion have all been documented to enhance penetration. The transdermal application gives rise to much lower plasma concentrations than oral administration. NSAID concentrations in the synovium subjacent to the site of topical application are at least comparable to those achieved after equivalent oral administration; subcutaneous concentrations after topical administration far exceed that which is normally achieved after oral administration.[43]

Table. No. 1. Available formulations of topical nonsteroidal anti-inflammatory drugs

Ointment	**Indomethacin**
Cream	Diclofenac, ibuprofen, benzydamine, salicylicacid
Spray	Indomethacin
Patch/plaster	Flurbiprofen, diclofenac
Gel	Piroxicam, diclofenac, felbinac, ketoprofen, indomethacin, ibuprofen, salicylicacid,eltenac
Drops	Ketorolac,flurbiprofen, suprofen, diclofenac

Anti-Inflammatory Drugs as Nanomedicines

Anti-inflammatory drugs represent a broad range of molecules, many with the potential for topical delivery. Reports on nanoparticle-delivered drugs with anti-inflammatory properties for topical use include aceclofenac, betamethasone-17- valerate, celecoxib, clobetasol propionate, corticosterone, flufenamic acid, flurbiprofen, glycyrrhetic acid, ketoprofen, naproxen, nimesulide, prednicarbate, and triptolide. These drugs can be divided into steroids, e.g. corticosterone, and non-steroidal anti-inflammatory drugs (NSAIDs), e.g. naproxen. Corticosteroids work to reduce inflammation by binding glucocorticoid receptors, whereas NSAIDs work by inhibiting cyclooxygenase.[44]

Introduction to Route of Administration: Skin

Skin is a widely used route of delivery for local and systemic drugs and is potentially a route for their delivery as nanoparticles. Nanoparticle delivery to the skin is being increasingly used to facilitate local therapies. The skin provides a natural physical barrier against particle penetration, but there are opportunities to deliver therapeutic nanoparticles, especially in diseased skin and to the openings of hair follicles.

Barrier Properties of Skin

The Epidermis Skin consists of two main layers. The underlying dermis contains a variety of cell types, nerves, blood vessels, and lymphatics embedded in a dense network of connective tissue. Above the dermis and separated from it by the basement membrane, the epidermis is composed mostly of layers of stratified keratinocytes, where the SC cells or corneocytes are bathed in a protein-rich envelope with an outer lipid envelope, surrounded by an extracellular lipid matrix. Keratinocytes undergo a process of keratinization, in which the cell differentiates and moves upward from the basal layer (stratum basal), through the stratum spinosum and stratum granulosum, to the outermost layer, the stratum corneum (S Corhorny layer). On reaching the SC, cells become nucleated and flattened and are eventually sloughed off.[45] Interspersed amongst the keratinocytes in the viable epidermis are cells with roles such as melanin production (melanocytes), sensory perception (Merkel cells), and immunological function (Langerhans and other cells). In addition to the structured cellular components of skin, there are appendages including the pilo sebaceous units (hair follicles and associated sebaceous glands), and apocrine and eccrine sweat glands.

The Stratum Corneum Barrier

The SC represents the main physical barrier of the skin, so for a substance permeating across the skin, diffusion through the SC is the rate-limiting step.[46] Conversely, the SC is also the main barrier to the diffusion of water out of the skin. The flattened, nuclear, protein-rich corneocytes of the SC are densely packed within the extracellular lipid matrix which is arranged in bilayers.[47] This is often referred to as a 'bricks and mortar arrangement. The corneocytes are held together by corneodesmosomes, which help to form a tough outer layer by maintaining cellular shape and regular packing. The eventual degradation of the corneodesmosomes by proteolytic enzymes leads to desquamation.[48] Transport of substances across the SC occurs mainly by passive diffusion and based on the dual-compartment bricks and mortar structure of the SC, interrupted by appendages, is considered to occur via three possible routes. These are the transcellular, intercellular, and appendageal routes. Covering the corneocytes on the SC surface is a thin (0.4–10μm), irregular and discontinuous layer consisting of sebum secreted by the sebaceous glands, along with sweat, bacteria, and dead skin cells. This layer is considered to have an eligible effect as an additional barrier to permeation through the SC.

Inter-Cellular Spacing

For most penetrants, the intercellular route is favored. Small molecules can move freely within the inter-cellular spaces and diffusion rates are governed largely by their lipophilicity, but also physicochemical properties such as molecular weight or volume, solubility, and hydrogen bonding ability.[49] However, the free movement of macromolecules or particles may be physically restricted within the lipid channels, which have been estimated by vande Merwe et. al. to be 19 nm and by Baroli et. al. to be 75 nm. This suggests that for such materials, the SC could present an additional barrier that is not present for small molecules.

Viable Epidermis

Tight junctions

The existence of functional tight junctions has been demonstrated in mammalian stratum granulosum, although many constituent tight junction proteins have been identified in other epithelial layers, as well as follicles. Tight junctions are regarded as important elements of the epidermal barrier system and localization and expression of tight junction proteins be altered in diseases characterized by a compromised skin barrier, such as psoriasis. Skin deactivation

of nanoparticles by skin metabolism and other mechanisms. As well as acting as a physical barrier, the skin functions as a chemical or metabolic barrier, with enzymes mainly located in the basal layer of the viable epidermis, as well as the extracellular spaces of the SC and the appendages in the dermis. Some nanoparticles are biodegradable through hydrolysis, enzyme activity, and physical forces causing, for instance, liposomes to merge with intercellular lipids.[45]

Hair follicles

Hair follicles were regarded as significant potential routes for drug delivery, covering only 0.1% of the human skin surface area, their complex vascularization and deep vagination with a thinning SC have led to a reappraisal of this view. Lademann discussed the finding that 300–600 nm particles penetrated follicles best on massage as a consequence of the distance between the scales on the hairs, and suggested that the movement of the hair acted as a geared pump to push the particles into the follicle. They viewed follicles as an efficient reservoir for nanoparticle-based drug delivery.[50]

The Dermis

The “true” skin, the dermis, is made up of connective tissue and lies below the epidermal layer, supporting and binding it to the underlying tissues. It is made up chiefly of collagenous and elastic fibers which provide it with a tensile strength equal to that of a thin steel wire. From the structural point of view, the superficial part of the dermis is compact and forms the papillary layer because its ends innumerable finger-like projections into the prickle cell layer of the epidermis. The deeper part of the dermis is composed of rather loose connective tissue and is infiltrated with fat.

Factors Affecting Drug Delivery to the Skin

Physicochemical Factors

The delivery of drugs to the intended target site in the body, in the right dose, and at the right time, by topical application presents several significant challenges. Drugs may often have limited solubility, suffer poor distributions, and experience breakdowns before they reach their target sites due to metabolism. There are several issues to consider when formulating a compound as a topical ingredient, particularly its passive permeation and penetration ability across the skin.

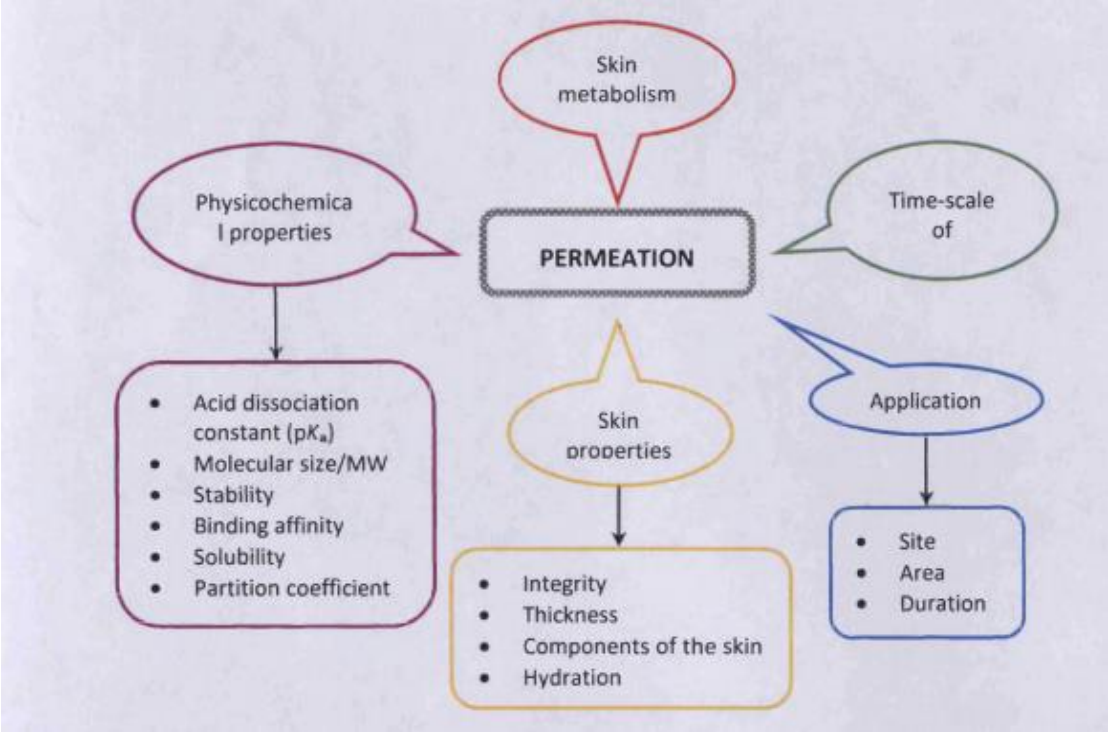


Figure. No. 5. General factors influence the permeability and penetration of a compound across the skin

Compounds intended for transcutaneous delivery should ideally possess physicochemical properties within the listed ranges: (i) Log P (octanol/water) in the range of 1 -3, log P is a measure of the partition coefficient, which is the ratio of a compound concentration between two phases[51-53] and is calculated as follows:

$$\text{Lop P}_{(\text{octanol/water})} = \frac{\text{Log solute}_{(\text{octanol})}}{\text{solute}_{(\text{water})}}$$

Log P is preferably applied to small chemical compounds with fewer polar side chains.

(ii) MW < 500 its is suggested that an inverse relationship existed between transdermal flux and MW of the compounds. This effect is much more relevant for larger molecules such as peptides and proteins.[53-55]

(iii) Aqueous solubility > 100 pg mL"1- lipophilic compounds are ideal candidates for transdermal delivery, however, the compounds must possess some aqueous solubility to provide sufficient concentration since most formulations are generally formulated in an aqueous form. In addition, beyond the optimum lipophilicity, permeation decreases due to the aqueous environment of the viable epidermis.[53]

(iv) Melting point < 200°C- most compounds with high melting points are relatively lipophilic and may have lower aqueous solubility at ambient temperature and pressure.[51]

(v) Daily dose < 10 mg day'1 - generally limited for potent compounds, as one simply cannot transfer a high amount of any compound across a small surface area within a short period.[53]

(vi) Polar center so f£4 - may pose potential interactions such as hydrogen bonding or van der Waals force between the compounds and skin components which may retard the diffusivity of the compounds, resulting in lower permeability across the skin.[51,56]

Physiological Factors

The major obstacle facing delivery is the skin anatomy itself. Between the area of application and the site of action, there are numerous barriers and issues to be dealt with. Once the formulation is applied to the skin, active compounds must partition into the outermost layer of the skin, the SC. The layer imposes the major rate-limiting barrier to the permeation of the majority of exogenous compounds.[54] The structure constitutes only 10% of the entire skin but contributes a significant role (80%) in the cutaneous barrier function.[57] Comprised of corneocytes (dead cells) in a lipoidal matrix, the barrier is essentially lipophilic and a highly selective membrane for passive permeation of exogenous compounds, especially those that are polar and hydrophilic.

The compounds must permeate through the membrane without significantly interacting with keratinocytes and enzymes present in the skin. The spectrum of enzymes and metabolic reactions in the skin are comparable with those found in other tissues for example the liver.[40,58,59] However, the enzyme activities detected in the skin are low, reported as only 10% of the liver activity.[58] A great variety of endogenous enzymes such as deaminases and esterases are present in the extracellular compartment of the SC, sebaceous glands, and near hair follicles, although different anatomical sites of the skin have different levels of enzymatic activities.[53,57]

Further evidence has highlighted the epidermis as the main site of metabolism in the skin and an important limiting factor for the dermal delivery of drugs.[40,53,60] The epidermis consists of actively dividing cells that slowly evolve outwards to form a layer of dead cells, the SC.[61] An essential component of the differentiation process is the physiologic degradation of the keratinocyte components (e.g. proteins or lipids) by lytic enzymes in the viable layer of the epidermis.[61,62] At the same time, these enzymes are functionally capable of reacting to

exogenous compounds.[61] Therefore, the viable epidermis potentially represents an enzymatic barrier for topically applied compounds, as reduced availability of the compounds would affect their optimum benefits.

In addition to the above factors, skin flora that reside on the skin may also impose a barrier to the compounds by reducing their availability before entering the skin. Normal human skin is colonized by a range of microorganisms including staphylococci, micrococci, and propionibacteria.[63] The skin flora possesses a wide range of enzymes capable of metabolizing some topically applied molecules. Furthermore, the compounds could potentially serve as a food substrate for skin flora. Microorganisms for example Staphylococcus epidermidis may metabolize topically applied compounds before penetrating the tissues.[53]

The absorption involves the passage of the solute from the surface of the skin - partitions out of its vehicle into the SC layer and subsequently diffuses through the SC and underlying epidermis and the dermis. The dermis contains blood vessels that can take up transdermally administered solutes for systemic circulation.

Topical drug delivery

Topical drug delivery can be defined as the application of a drug via the skin to directly treat or cure skin disorders. These systems are generally used for local skin infections like fungal infections or in a place where other routes of the drug administration fail. Topical dosage forms are generally confined to a small area anywhere in the body through the ophthalmic, rectal, vaginal, and skin routes.

Skin is one of the most easily accessible organs of the human body. The skin of an average adult body covers a surface of about $2m^2$ and receives around one-third of the blood circulating through the body. Over the past three decades, controlled drug delivery has become increasingly important in the pharmaceutical industry. The surface of human skin is known to contain, on average, 10-70 hair follicles and 200 to 250 sweat ducts on every cm^2 of the skin area. Skin is a very difficult barrier to the ingress materials allowing only small quantities of drug molecules to penetrate over some time.

Transport of hydrophilic or charged molecules is especially difficult attributable to the lipid-rich nature of the stratum corneum and its low water content; this layer is composed of about 40% lipids, 40% protein, and only 20% water. The transport of lipophilic drug molecules is facilitated by their dissolution into intercellular lipids around the cells of the stratum

corneum. Absorption of hydrophilic molecules into the skin can occur through 'pores' or openings of the hair follicles and sebaceous glands, but the relative surface area of these openings is barely 1% of the total skin surface. This small surface area limits the amount of drug absorption.

Percutaneous absorption of drug molecules is a key factor of particular importance in the case of topical drug delivery systems because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout use. In general, once drug molecules cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily. Drugs with a lipophilic character, are better suited for topical delivery. These systems ensure that the drug gets into the body and reaches the area where it is needed. These preparations are applied onto the skin surface for providing local or systemic effects.

The topical route favors the safe and effective delivery of drug molecules with lower doses as compared to the conventional system. Drugs via skin reach the desired area in optimum concentration, dropping the chances of side effects and leading to increased bioavailability and increased patient compliance. Dermatological conditions i.e skin disease affects the population and has been observed as one of the top 15 medical conditions for which prevalence and healthcare spending have increased in the last decade.

Advancements in the life sciences united with a growing market for dermatological have facilitated the emergence of better topical formulations and drug delivery systems. The present and emerging approaches to optimizing the topical dermatological agents delivery (i.e small and large molecules) include the use of chemical enhancers, liposomes, bio-polymers (sodium hyaluronate), particulate carriers (microspheres and lipid nanoparticles), occlusion (via dressings and patches) topical peels, topical sprays and foams, temperature (heat), iontophoresis and ultrasound. These delivery approaches are a significant advancement over conventional systems (i.e creams, lotions, ointments, and pastes) and are likely to enhance efficacy and tolerability, improve patient compliance (which include dermatology life quality), and also fulfill other required needs of the topical dermatological market. However, the limited dermal and transdermal delivery of many small and large molecules is a significant challenge because of the unyielding barrier properties of the skin.[64]

Modes of Topical Delivery

Modes of delivery of a compound across the skin can be categorized into topical, transdermal, and transcutaneous. Examples of compounds that can be delivered through several potential target sites in the skin. There are several requirements to be met for an active compound formulated for delivery via the skin to offer excellent effects - it has to be potent; low molecular weight (MW); highly skin permeable; has no significant interaction with the skin components; and stable against skin action (e.g. metabolism activities by enzymes).[65]

When the target sites of therapy are restricted within the skin layers (SC, appendages, epidermis, and dermis) with minimal or no permeation, this type of delivery is regarded as topical. Cosmetics (e.g.moisturisers and anti-aging peptides), dermatological (e.g. benzoyl peroxide and tretinoin), and drugs (e.g. corticosteroids and antibiotics), are classes of compounds that are commonly intended for various skin conditions such as diseases, anti-aging, etc. They are formulated into appropriate dosage form systems such as gels, creams, and ointments to attain their delivery into the target sites in the skin. Most cosmetic and dermatological products commonly target the SC and/or epidermis, whereas drug formulations, for example, MTX for psoriasis treatment are intended to be localized in the epidermis (i.e. stratum spinosum and stratum basale layers).[66]

Topical delivery systems also cover formulations that require their active ingredients to be delivered only onto the surface of the skin. These include antiseptics, antibiotics, and cosmetic products (e.g. sunscreen and deodorant). Systemic effects are unnecessary for topical formulations and thus, permeation beyond the dermal layer is undesirable. However, a small amount of the compounds could be possibly absorbed systemically, as further penetration beyond the viable epidermis may offer access to the dermal microvasculature (transdermal) or deeper skin tissues (transcutaneous).[57]

Transdermal delivery refers to a compound that traverses through the multilayered structure of the skin and into the systemic circulation to illicit its pharmacological effect. Drugs such as hormones, opioids, and antihypertensives are commonly delivered via a transdermal route. Fentanyl, a potent opioid member indicated for the management of moderate to severe chronic pain is one of the drugs successfully formulated for transdermal therapy. The United States Food and Drug Administration (US FDA) approved its transdermal patch formulation system, Duragesic® for commercial use in 2005.[67]

For transcutaneous delivery, it is intended that the compounds are delivered across the skin into the underlying tissues for example muscles or joint capsules. Members of non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ketoprofen and ibuprofen) are suitable for transcutaneous delivery, as they can offer pain relief for conditions such as joint pain or arthritis.[66]

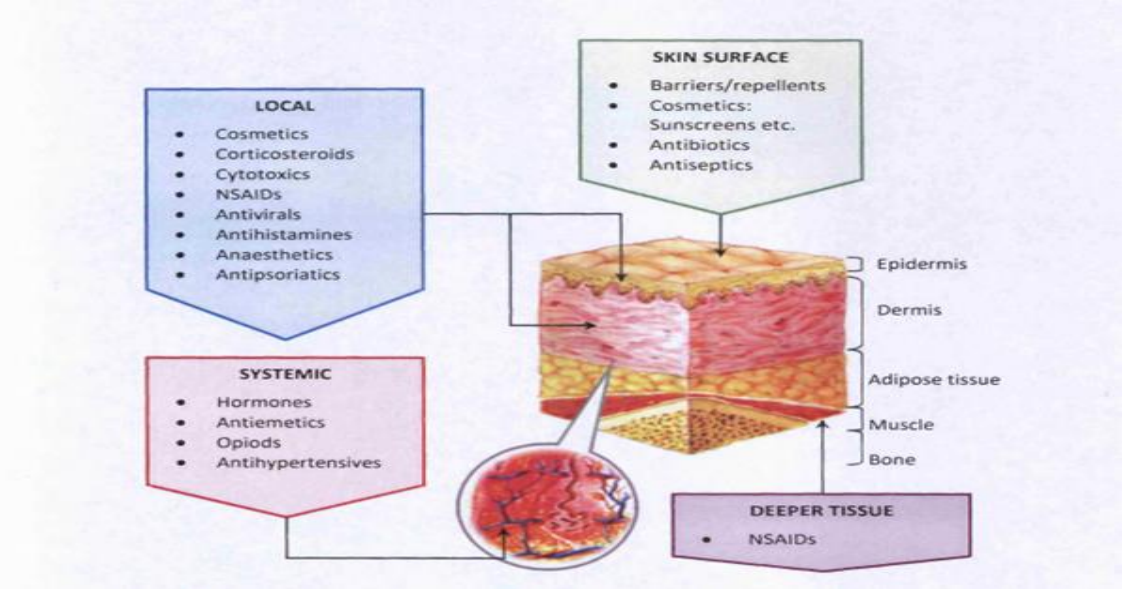


Fig. 6. Illustration of the potential targets for some examples of compounds that can be delivered through the skin. The magnified illustration represents blood vessels embedded within the dermis.

Strategies and Innovations for Enhancement of Topical Drug Delivery

Over the past years, advances and improvements have been made in topical drug delivery technology and these can be broadly subdivided into 'physical' or 'chemical' approaches. Their role is to increase the driving force of drug diffusion and/or enhance the permeability of the intact skin.

Chemical Approach

The chemical approach includes the use of chemical enhancers such as surfactants (e.g. Tween* or propylene glycol), fatty acids (e.g. palmitic acid or oleic acid), and solvents (e.g. ethanol). They can reversibly alter the barrier properties of the skin through several possible mechanisms.[67]

(i) Reversibly disrupting the packed structure of lipids in the SC layer to enhance 'fluidity'.

(ii) Increase skin/vehicle partitioning of a permeant.

(iii) Increase solvent transport into or across the skin.

For the latter mechanism, it has been suggested that eicosapentaenoic acid (EPA), ethanol, and 1,8-cineole exert an enhancing effect by a 'pull' or co-permeation mechanism.[68,69] Co-permeation enhancement effect refers to the concomitant transport of vehicle and permeant across the skin barrier, where the movement of the vehicle facilitates the movement of the active solutes.

This phenomenon has been established in multiple works involving the co-formulation of NSAIDs (ketoprofen and ibuprofen) with essential fatty acids (EPA and docosahexaenoic acid, DHA).[68,69] However, the success of chemical enhancers is limited to low molecular mass permeants and their inclusion in the formulation may enhance the absorption of components other than the permeants, which can lead to skin damage and irritancy problems.[52]

Chemical strategies based on formulation include the use of loaded carriers such as emulsions, liposomes, and nanogel particles. They can be customized based on size and chemical composition. Other methods involve adjustment of the thermodynamic activity of permeants e.g. supersaturated systems or modification of the active compounds in a manner designed for chemical or enzymatic action: prodrugs and the related technique of co-drugs.[54,55]

Physical Approach

Physical enhancement generally utilizes external energy to physically reduce the biological barrier of the SC to promote penetration of exogenous compounds.[26] They can be classified based on energy force used to assist the delivery - electrical (i.e. iontophoresis, electroporation); mechanical (e.g. microneedles and abrasion); and miscellaneous methods (e.g. ultrasound and laser wave).[54] These approaches are preferable for large and hydrophilic molecules such as peptides and proteins. However, the devices developed for physical methods are quite costly, and complicated and may pose potential safety risks (electrical components). Furthermore, some of these techniques are usually associated with discomfort sensation and mechanical damage to the skin barrier.[55]

Routes of Penetration

The external layer of the skin (SC) is considered an effective barrier, essential for the protection of the internal milieu from the external environment. Permeation through this barrier usually signifies permeation through the skin, due to its overwhelming rate-limiting step in the dermal or transdermal delivery of drugs. However, there are several potential routes of access for exogenous compounds, from the surface of the skin to reach the sub-epidermal tissue region – the trans appendageal or shunt route; the transcellular route; and the intercellular pathway.

The Trans appendageal or shunt route involves the diffusion of compounds into the skin through sweat gland pores (diameter: 60 - 80 pm)[70] and hair follicles with associated sebaceous glands (diameter: 10 - 70 pm).[44] Initially, this route was considered to be negligible, as evidence suggested that the fractional area offered is very small and not more than 0.1%.[74] However, the density and proportions of the skin appendages vary greatly according to the body regions, where the largest surface was found on the forehead, ~13.7 % of the skin surface.[75]

These structures may offer a potential route for drug delivery as they originate in the dermal tissue but are accessible as they can be found on the surface of the skin.[53,76] Therefore, the compounds could directly reach the dermis without having to traverse the 'intact barrier of the SC. Studies have suggested that the follicular penetration route may be especially relevant in the penetration pathways for hydrophilic and high molecular weight molecules[77,78], as well as by particle-based drug delivery systems (e.g. liposomes).[75] A pump mechanism is suggested to be one of the responsible mechanisms for the particle-based drug delivery systems penetration - the movement of hair follicles may act as a geared pump due to the zigzag structure of the cuticular layers along the hair shaft, where particles of a similar size to hair cuticles are pushed deep into the follicles.[79,80]

Additionally, the hair follicles represent an efficient reservoir for topically applied substances, which is comparable to the reservoir of the SC on several body sites.[80,81] For example, hair follicles of the calf region are comparable with those at the scalp.[52] The reservoir of the hair follicles is usually located deep in the skin tissue up to 2000 pm and their reservoir depletion occurs only through the slow processes of sebum secretion and hair growth.[75,82]

The reservoir of the SC, in contrast, is mainly located in the uppermost cell layers of the SC (~5 pm), where it only provides a short-term reservoir due to continuous depletion from textile contact, washing, and the physiological process of desquamation. The intercellular pathway relates to compounds that pass through the continuous lipid domains of the SC between the keratinocytes into the viable epidermis.[53] This route is considered to be the predominant pathway for the penetration of exogenous compounds through the skin.[40,83]

Generally, it is accepted that the compounds traversing the SC through this structured lipoidal pathway are dependent upon their physicochemical properties and thus, most lipophilic compounds will follow this pathway.[77] This pathway is very tortuous and much longer in distance than the thickness of the SC.[78] Additionally, it was proposed that the permeation of polar compounds was mediated via the intercellular route.[83] The laminar organization discontinuities within the intercellular lipids (imperfections in the SC lipid bilayers) create aqueous regions, or micro-channels, that act as polar pathways.[78]

The structural defects are usually observed in lipid lamellar systems as grain boundaries, fault-dislocations, or nanoscale pinholes. The precise size of these defects depends on the type of defect which may span a length scale of 1 to 10 nm. The transcellular route is often regarded as providing a pathway for polar compounds, possibly through hydrophilic regions present in the lipid layers of the SC.[53] The compounds diffuse through the keratinocytes (keratin-filled corneocytes) which provide an aqueous-based porous pathway but still need to partition into the hydrophobic domains of the lipid layers.

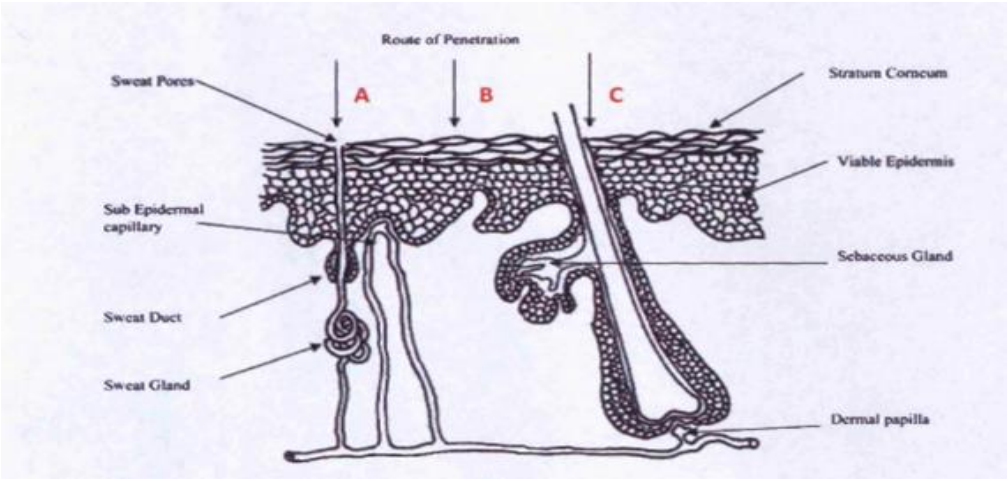


Fig. 7. A simplified diagram of skin structure and possible routes of penetration for exogenous compounds. A) Sweat gland pore; B) directly across SC (transcellular and intercellular); and/or (C) hair follicle with its associated sebaceous gland

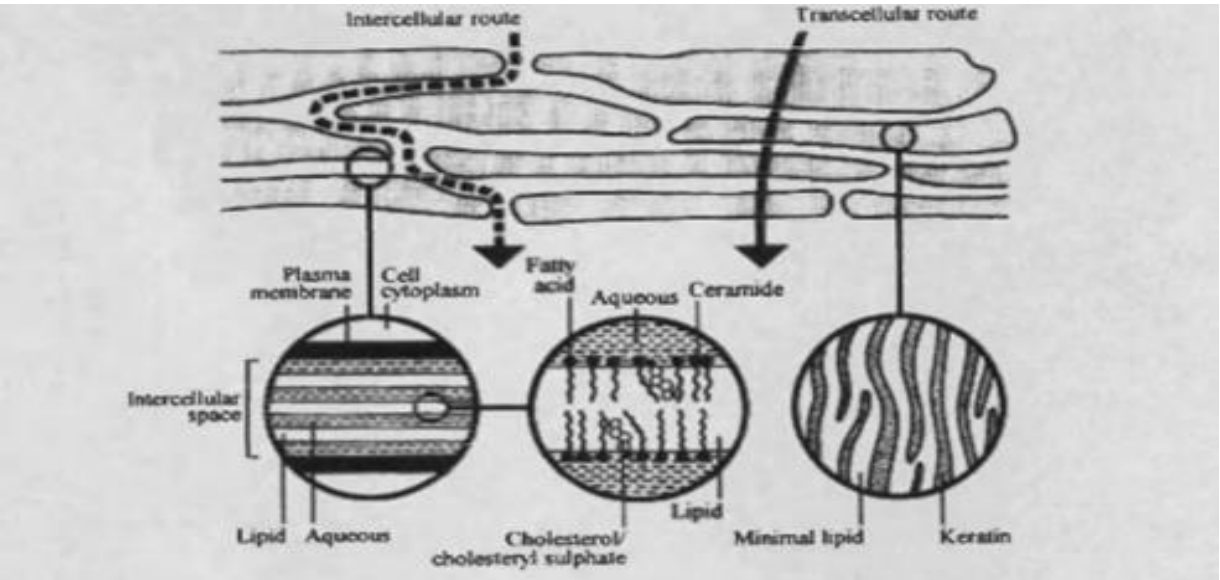


Figure no.8. Schematic representation of permeation routes through the SC via intercellular (lipid matrix between the corneocytes) and transcellular (across the corneocytes and the intercellular lipid domain).

Nanoparticles

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated, or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed.[84-87]

In recent years, biodegradable polymeric nanoparticles, particularly those coated with a hydrophilic polymer such as poly(ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes.

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties, and release of pharmacologically active agents to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action, and reducing toxicity or side effects, their applications

are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of the water-soluble drugs in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled-release properties.[88,89]

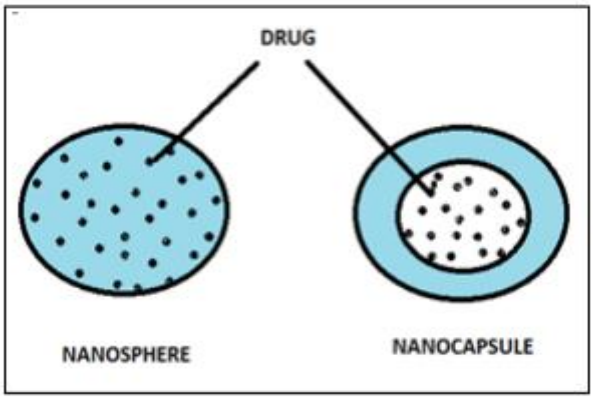


Fig. 9. Differences between nanosphere and nanocapsule

Properties and Benefits of Nanoparticles

Nanoscale technology is an exciting area of scientific development which offers potential in various areas, especially in medicine, computing, textiles, and cosmetic products. Nanotechnology may be able to overcome some of the problems associated with the drug delivery area. The nano-sized structures can be designed as drug delivery vehicles which may offer significant benefits over conventional delivery mechanisms. These benefits include better stability, the possibility of transporting hydrophilic and hydrophobic drugs, high loading capacity due to the greatly increased surface area, greater bioavailability, systems that allow controlled and sustained release rates or release upon an external stimulus, and the possibility to exploit a range of patient-friendly delivery routes, e.g. oral, cutaneous or inhalation. In cosmetics, nanotechnology-based materials are widely used.

Currently, they are primarily utilized as ultraviolet filters (e.g. titanium dioxide and zinc oxide)and delivery carriers (e.g. hydrogels, liposomes, niosomes, and nanostructured lipids). Amongst the available nanomaterials already described in the literature, hydrogels have already proved their value in diverse biomedical applications. These materials can be tailored in size, composition, and stimuli-responsive properties as carriers for drug delivery purposes. In this chapter, we especially aim to highlight some of the most important properties of

hydrogels, particularly nanogels (<1 pm) with an emphasis on their application to enhance the transport of active compounds into and across the principal skin barrier, the SC.

Advances in polymer sciences have led to the development of several novel drug-delivery systems. Proper consideration of surface and bulk properties can aid in the designing of polymers for various drug-delivery applications. In addition, for polymers to be used as drug carriers, they should have a well-defined structure and should be biocompatible, and non-toxic. This led to the invention of novel polymers with desired physiochemical properties to exploit them in drug delivery systems. Due to these superlative properties of polymer various drug-delivery systems such as biodegradable drug-delivery systems, diffusion-controlled drug-delivering systems, and responsive drug-delivering systems have been developed over years. These unique polymeric delivering systems are differentiated based on the mechanism of controlling the release of drugs from polymers.

Moreover, among these novel classes of polymeric-delivering systems, the biodegradable system is most favored to target specific areas of the body such as inflammation or tumors. The literature review shows an investigative study on anti-inflammatory agents such as aspirin, ibuprofen, ketoprofen, naproxen, and diclofenac for treating inflammations.[90]

Incorporation of the drug into a particulate carrier can protect the active substance against degradation *in vivo* and *invitro,* improve therapeutic effect, prolong biological activity, control drug release rate, and decrease administration frequency. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. Biodegradable polymers could be classified into synthetic and natural (biologically derived) polymers. Both synthetic and natural biodegradable polymers have been used for drug delivery, and some of them have been successfully developed for clinical applications.[91]

At present, biodegradable polymers like starch, dextran, pullulan, chitosan, and alginate are being used to encapsulate proteins and peptides. Although several synthetic biodegradable polymers have been developed for biomedical applications, i.e., PLA, PLGA, PCL, and poly-alkyl-acyanoacrylateetc, the use of natural biodegradable polymers remains attractive because of their abundance in nature, good biocompatibility, and ability to be readily modified by simple chemistry advances in biomedical applications, including newer drug delivery techniques.[92]

Among all the recent materials used for polymeric NPs synthesis, chitosan (CS), a natural plentiful biopolymer obtained by chitin deacetylation has gained considerable interest. CS has promising biological implications such as nontoxic, biocompatible, biodegradable, bacteriostatic, and fungistatic. In addition, CS also has strong mucoadhesive and adherence ability to conjugate with negatively charged sialic acid on the physiological membranes.[93]

Nanoencapsulation in Biodegradable Polymer

Biodegradable polymeric nanoparticles(NPs) have attracted prominent interest in the past few decades as a novel drug carrier due to their longer half-life and greater drug entrapment efficiency. The drug is dissolved, entrapped, adsorbed, attached, or encapsulated into the nanoparticle matrix. The nanoparticle matrix can be of biodegradable materials such as polymers or proteins. Depending on the method of preparation, nanoparticles can be obtained with different properties and release characteristics for the encapsulated therapeutic agents.

Nanoencapsulation of medicinal drugs (nanomedicines) increases drug efficacy, specificity, tolerability, and therapeutic index of corresponding drugs. These nanomedicines have many advantages in the protection of premature degradation and interaction with the biological environment, site-specific targeting, enhancement of absorption into a selected tissue, bioavailability, retention time, and improvement of intracellular penetration attributed to its nanoscale particle size.

Nanomedicine formulation depends on the choice of a suitable polymeric system having maximum encapsulation (higher encapsulation efficiency), improvement of bioavailability, and retention time. The desired nanomedicines are generally achieved by the hit and trial method (no specific rule) however, the encapsulation process with polymeric nanoparticles is in the more advanced condition in comparison to other nanoparticle systems.[94] These drug nanoformulations (nano drugs) are superior to traditional medicine concerning control release, targeted delivery, and therapeutic impact. These targeting capabilities of nanomedicines are influenced by particle size, surface charge, surface modification, and hydrophobicity. Among these, the size and size distributions of nanoparticles are important to determine their interaction with the cell membrane and their penetration across the physiological drug barriers. The size of nanoparticles for crossing different biological barriers is dependent on the tissue, target site, and circulation. For the cellular internalization of the nanoparticles, the surface charge is important in determining whether the nanoparticles would cluster in blood flow or would adhere to, or interact with oppositely charged cells membrane.

The release mechanism can be modulated by the molecular weight of the polymer used. The higher the molecular weight of polymer slower will be the *invitro* release of drugs.[95]

Introduction to Formulation

Chitosan Nanoparticle

There are at least four methods reported for the preparation of chitosan nanoparticles ionotropic gelation, microemulsion, emulsification solvent diffusion, and polyelectrolyte complex. Ionotropic gelation is based on electrostatic interaction between amine groups of polyanion such as TPP.[96] Chitosan is dissolved in acetic acid in the absence or presence of the stabilizing agent. Polyanion was then added and nanoparticles were spontaneously formed under mechanical stirring. In the microemulsion method, a surfactant was dissolved in an organic solvent like n-hexane. Then chitosan in acetic acid solution and glutaraldehyde was added to the surfactant/hexane mixture under continuous stirring at room temperature.[68] Polyelectrolyte complex(PEC) or self-assemble polyelectrolyte is a term to describe complexes formed by self-assembly of the cationic charged polymer and plasmid DNA. The mechanism of PEC formation involves charge neutralization between cationic polymer and DNA leading to a fall in hydrophilicity as the polyelectrolyte component self-assembly. In this method, nanoparticles are spontaneously formed after the addition of DNA solution into chitosan dissolved in acetic acid solution under mechanical stirring at or under room temperature. Several drug molecules are successfully encapsulated for their in vivo use.[97]

Chitosan Nanoparticles: Drug Loading and Controlled Release

Usually, drug loading in nanoparticulate systems is achieved using one of the two following methods; (a) incorporating the drug during the preparation of the particles and (b) after the formation of the particles by incubation of the drug with them. In both systems, the drug is physically embedded into them texas well as adsorbed onto the surface. Both water-soluble and water-insoluble drugs can be loaded by these techniques. The water-soluble drugs are generally incorporated by mixing with an aqueous chitosan solution to form a homogeneous mixture, followed by particle production as described. Water-insoluble drugs and drugs that precipitate in acidic solutions are usually loaded by incubation which involves soaking the pre-formed particles in a saturated solution of the drug. The drug release from chitosan particulate systems usually follows three different, mechanisms: (a) release from the surface

of particles, (b) diffusion through the swollen rubbery matrix, and (c) release due to surface erosion.[98]

In most cases, drug release follows more than one type of mechanism. In case of release from the particle surface, the adsorbed drug dissolves on contact with the release medium; similarly, the drug entrapped onto the surface layer of particles also follows this mechanism but perhaps a little slower. These types of drug release lead to a burst effect which is encountered in all delivery systems whereby the drug onto the surface is rapidly taken up followed by a slower diffusion release from the inner matrix of the particle. Diffusion-controlled drug release occurs in three steps;(a) water penetrates the particulate system, (b) the glassy matrix becomes rubbery and swells, and (c) the drug diffuses from the swollen matrix. Hence, this type of release is initially slow but becomes faster as the drug dissolves and the matrix swells.[99]

The Higuchi equation is one of the traditional methods which were used to describe the release of a solute from a flat surface, but not from a sphere. A good fit indicates that the release rate is dependent on the rate of diffusion through the matrix.

To describe the diffusion from a sphere, the release mode is determined using equations developed by Guy et. al. The most commonly used equation for diffusion controlled matrix system is an empirical equation used by Ritgerand Peppas, in which the early time release data can be fitted to obtain the diffusion parameters,

$$\frac{M_t}{M_\infty} = kt^n$$

where, Mt/M∞ is the fractional drug released at time t,

k is a constant characteristic of the drug–polymer interaction and

n is an empirical parameter characterizing the release mechanism.

The drug transport can be classified as Fickian behavior (n=0.5), Case II transport (n= 1),non-Fickian or anomalous behavior (0.5 < n< 1) and super Case II (n >1), based on the diffusion exponent.[100]

A good correlation for the cumulative drug released vs. the square root of time was obtained by Jameelaet. al. This indicated that drug release from the microsphere matrix is diffusion

controlled and obeys the Higuchi equation. In addition, the smaller sized microspheres released drugs faster than the large microspheres due to their relative greater surface area and that the diffusion path length was shorter from the smaller particles into the dissolution medium.[101]

As stated earlier, the release of a specific drug from chitosan-based particulate systems depends upon several factors, such as the cross-linking, morphology, size and density of the particles used. Other considerations involve the physicochemical properties of the drug as wellas the presence of adjuvants. *In-vitro* release also depends on pH, polarity and the presence of enzymes in the dissolution media.

Nanogels

Nanogels are nanometric scale networks of chemically or physically cross-linked polymer particles.[102,103] They have a porous sponge-like structure that swells in a particular solvent under specific environmental stimuli such as temperature[104], pH[104,105], ionic strength[105,106] and type of solvent (e.g. water, ethanol or buffer)[107-109], then, undergoing rapid conformational changes and releasing the solvent again following the environmental stimuli changes. The swollen nanogel particles contain a considerable amount of aqueous solvent whose diameter typically ranges from 100 -1000 nm at ~ 25°C.[107,109]

Different definitions of the terms 'nanogel' and 'microgel' have been used. The definitions are very subjective and that has complicated the understanding of the gel size. Cross-linked polymer particles in size range between 10 nm and several micrometers (pm) are often referred to as microgels and the term was first used in 1949.[110] Earlier, the International Union of Pure and Applied Chemistry (IUPAC) Commission on Macromolecular Nomenclature proposed the term micro-network to be applied on microgel.[111,112] The micro-network is defined as a highly ramified macromolecule (polymer molecule) of colloidal dimensions. In the current work, the term "nanogel' is employed to refer to polymers in the submicron size range (<1 pm).

Swelling and De-swelling Behaviours of Nanogels

Swelling and de-swelling of nanogel particles in water are primarily controlled by several factors including concentrations of cross-linker and monomers used during synthesis, charge density (for polyelectrolyte gels), and environmental parameters (e.g. pH, ionic strength, and temperature).[104,110,113] A nanogel particle can change in volume up to 100-fold when its

surrounding conditions vary continuously. The classical theory of gel swelling was proposed many years ago. The theory assumes uniform distributions of polymer segments and cross-linker throughout the polymer network. The physical dimension of a cross-linked nanogel particle is set by a balance between the osmotic pressure and the polymer elasticity.[114]

Nanogels in Topical Drug Delivery

Nanogel particles can be designed as carriers for drugs or compounds of interest due to their open network structure and their ability to undergo conformational transitions (swelling <-> de-swelling) upon interaction with suitable stimuli including temperature, pH, and ionic strength. These stimuli can be used to modulate the release of drugs from the particles. The incorporation of compounds into the polymers and the subsequent release depends on the octanol/water partition coefficient (Log P) and solubility of the respective compounds. Under certain conditions, the polymers would be suitable for controlled or triggered drug delivery via the cutaneous route. With optimization of their network composition, size, and morphology, nanogels can be tailor-made to sense and respond to environmental changes to ensure spatial and stimuli-triggered rug release. The nanogels properties could be designed by manipulating skin physiological environments such as temperature (average surface temperature,32°C) and/or pH (4.0 - 7.0), where these two properties could be used to modulate the release of nanogel load either in a controlled rate or dump-dosing manner. External stimuli in addition to the skin's physiological features could also be beneficial to the stimuli-modulated nanogel system.[113]

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