Chapter 1

An Introduction to Low Molecular Weight (LMW) Gels and their Applications in Drug Delivery

1.1 Introduction

Designing molecular components with self-assembled crosslinked nanostructures predefined by the molecular structures remains a significant challenge, particularly if self-assembly is being used to control not only the shape and size of supramolecular compounds, but also to control their material function and surface chemistry.[1] Low molecular weight gel-phase material that self-assembles as fibrillar nano/micro structures has attracted the attention of the scientific community because it can easily penetrate memberanes.[2] Recent approaches of molecular gels[3] in the disciplines of tissue engineering,[4] molecular electronics, and biomineralization,[5] demonstrate the development of this area of nanoengineering.[6] However, the interpretation of framework relationships that support self-assembly within gels is still unclear. Besides the exponential spike in the number of structurally diverse low molecular mass gelators such as saccharides,[7] nucleobases,[8] urea and peptides,[9] steroid derivatives,[10] and dendrimers[11] based systems, etc., and their elevated applications, a basic understanding of the specificities and features of molecular self-assembly as well as gelation remains limited. The process of gelation is challenging and a significant amount of research is still needed to be done to identify possible gelator molecular structures by screening huge numbers of molecules and a broad range of solvents that could sustain gel phase networks. An important area is the creation of helpful models to explain the assembling of molecules into molecular-scale fibres and the mechanism of fibril-fibril interactions to create a sample-spanning system.[12] Some researchers have recently developed a practical gelation framework for explaining the transformation of low molecular mass gelators into three-dimensional crosslinked networks, with the

formation of low molecular mass gels primarily understood in aspects of a mechanism that involves the nucleation and growth of a gel matrix. Aggeli *et al.*[13] established a self-assembly framework based on a theoretical statistical mechanics model by linking the chemical structure of a heterogeneous collection of peptide molecules to multilayer gel formation. In a recent study, Meijer and colleagues[14] established a model to analyze the advanced and early stages of self-assembly of oligo (*p*-phenylenevinylene) derivatives. The self-assembly of molecular-scale building blocks like pyromellitamide[15] and bis(urea)[16] into linear networking has also been studied. These mechanisms were described as cooperative working transitions from isotropic solutions to supramolecular linear networking, which in some cases resulted in macroscopic gelation. Terech and coworkers[17] have shown that gelation proceeds by instant nucleation and one-dimensional fibre formation by employing various approaches to explore growth and nucleation kinetics. The formation of fibre-fibre interactions after fibers development is also interesting. Fages and co-workers[18] reported that, after one-dimensional fibre growth on nucleation, different structural interactions between fibres would be an alternative option to modify the tertiary gel structure, resulting in either crystallization or gelation of the sample. Clearly, the growth and nucleation of gel fibres are of interest. The mechanism of two-component gel assembly[19] has also been studied. John and coworkers[20] demonstrated a nucleation-growth mechanism in the fibre formation of the gel produced by 4-chlorophenol and bis(2-ethylhexyl) sodium sulfosuccinate. Nandi and colleagues[21] used a variety of methodologies to investigate the temperature effects on the networking of riboflavin-melamine hydrogels and identify activation barriers. To summarize, manipulating and understanding the development of large supramolecular polymeric assembly and elucidating the

interactions that facilitate their macroscopic organization is extremely desirable for any self-assembling low molecular weight gelator. Such research could lead to the development of gelation rules with some predictive power, allowing for a more advanced structure-based gelator design.

1.2 Gels

Generally, small molecules and polymers are the two most common types of gel-forming materials. The bottom-up strategy of employing small molecules having developed functions to create useful supramolecular frameworks is an essential way to develop functional supramolecular assemblies. Among all the types of molecular self-assemblies, low molecular weight gelators (LMWGs) have received huge interest in recent years because of its smaller size which can easily permeate the cell memberane. Supramolecular gels became extremely popular in the 1990s after a long break from their development in the 1930s, when it was discovered that some LMW organic molecules could convert into gel like materials by trapping organic solvents. Despite the wide applicability of these gels like materials as lubricants and thickness, they did not receive much attention at that time. In 1970s and 1980s it was realized that the formation of gels by these low molecular weight gelators is a classic example of a supramolecular chemistry. But what exactly are gels? it still could not be defined properly. Most people come into contact with gels on a regular basis, frequently without noticing it.[22] The gel phase has long been identified for over 150 years from a ' 'researcher's standpoint. Nonetheless, the concept of a gel has long been a topic of controversy, as the term "gel" can refer to a wide range of chemical and physical systems.[23] "While the hardness of the degree of crystallinity locks out exterior

expressions, the smoothness of the viscous colloid partakes of fluidity, and allows the colloid to become a channel for liquid transmission, resembling water itself," Thomas Graham wrote in 1861.[24] Researchers sought to clarify the "gel" state more precisely in the preceding years. Dorothy Jordon Lloyd stated in 1926 that the "gel" phase is tougher to define than to recognize[25] and proposed: "Gels must be made up of two components, a solid substance i. e. gelator and a liquid at considering temperature." Gels are semisolid substances that contain an exterior solvent phase, which is hydrophilic or hydrophobic in nature and is immobilized inside a three-dimensional network structure. Gels can be classified as physical and chemical gels based on their network crosslinks. In chemical gels, the two networks have been covalently crosslinked, resulting in a permanent framework unless the covalent linkers are disrupted, while in the case of physical gels, non-covalent interactions are used between the network components resulting in a 3D network and are thermoreversible in nature.[26] Physical gels can be made from various compounds, such as clays, proteins, polymers, colloids, and small organic molecules as solid network-building components in water or organic solvents as the liquid component. Supramolecular gels are a type of physical gels that can be prepared by small organic molecules having low molecular mass (less than 2000 Da) known as low molecular weight gelators (LMWGs).[27] The LMWGs can be classified as hydrogelators or organogelators based on entrapped solvent (water or organic solvent), respectively. The gels from LMWGs can be prepared by heating the gelator into the solvent until complete dissolution, followed by cooling, resulting in a supersaturated solution. Supersaturation enables the gelator compounds to rapidly assemble into elongated fibres with a diameter of 5–100 nm, which then assemble into a fibrous 3D interconnected network, transforming the liquid into the supramolecular gel.

Supramolecular gels are thus a demonstrative example of supramolecular chemistry. The structural integrity of synthetic gels are very unique and maintains the materials elasticity and rigidity isotropically.[22] The applications of gel varied wide range of uses such as cosmetics, biomaterials, medicines and food technology.[28-30] Furthermore, gels are primarily made up of a liquid solvent with a solid matrix as a small component.[31] To generate a homogeneous dispersion, a compound like natural gum or a carbomer is used, which diffuses in water. Compared to ointments and creams, gels allow higher drug solubility and enhance drug migration across the vesicle due to their higher water content. Gels can also moisturize the skin by holding a large extent of transepidermal H_2O and make drug delivery easier.[32] The gels could be an effective medium for topical drug administration on the skin, as in the case of injuries or severe musculoskeletal problems. This study aimed to provide the optimal therapeutic approach in topical drug delivery on skin disorders using gel systems (organogels, bigels, oleogels and hybridgels). The medical application of various gel-based drug delivery systems is scrutinized underneath sections. Gels are usually classified into two groups based on the nature of their solvent phase. Organogels (oleogels), for example, comprise an organic solvent, whereas hydrogels contain water. Other types of gels, such as bigels, proniosomal gels, aerogels and emulgels, have been reported recently for druggability on the skin disorder.

1.2.1 Hydrogels

Hydrogels are 3-dimensional crosslinking hydrophilic polymer assembelies capable of absorbing huge amounts of water inside the crosslinking networking membranes.[33] Hydrophilic polymers such as sodium alginate and carbapol have been studied as

gelators previously.[34,35] Physical or chemical crosslinks can be used to create hydrogels with physical stability and networked structure. Crystallites, hydrogen bonding, van der Waals interactions, and entanglements, are examples of physical crosslinks. "Physical" or "reversible" hydrogels are hydrogels made from physical interactions.[31,36] Hydrogels described as "permanent" or "chemical" gels, are made up of covalently connected crosslinked networks.[28,30] Chemically stimulated hydrogels in response to external stimuli such as enzymatic action, pH and temperature,[37] effectively widen the pores aperture and allows to diffuse the encapsulated drugs. This type of technique can be employed to deliver drugs to target specific tissues. Drug delivery via diffusion is more prevalent for regional drug release. In contrast, the release of the drug via chemical inducement has seen more usage for oral drug administration and can provide control for targeted treatment.[33,38] Hydrogels have recently seen a growth in biomedical sciences, such as tissue repair, cell encapsulation, and controlled drug delivery. To meet the growing needs of the medical and pharmaceutical fields,[39,40] novel hydrogel-based delivery platforms have been formulated and manufactured. In addition, hydrogels developed from acrylated poloxamine have been studied for tissue engineering[41] and drug delivery. A recent trend in gel technology is the study of polymerized oligolactides[42] and poloxaminehydrogels[43] as delivery vehicles for bioactive molecules and hydrophobic drugs. Chitosan hydrogels have been investigated for targeted drug delivery of medicines with low bioavailability due to poor dissolution after oral administration.[38] Furthermore, the application of chitosan hydrogels in the active s-enantiomer of racemic propranolol[44] and the transport of berberine alkaloid has been investigated. Wound healing is still a challenge and hence gel based therapeutic approach has been employed and many therapeutic compounds have been placed in

hydrogels for proficient wound healing, including astragaloside IV,[45] triamcinolone acetonid and curcumin.[46] The astragaloside IV-based hydrogels have angiogenetic actions on wound repair. To aid in the healing of cutaneous wounds, a thermosensitive hydrogel containing curcumin-loaded micelles has been tested. The combination of thermosensitive hydrogel and curcumin bioactivity was found to promote tissue rebuilding processes and offers potential against cutaneous wound healing.[46]

Hydrogels have a wide range of applications in the field of foods, pharmaceutical, and tissue engineering fields.[33,47] Hydrogels have a high commercial value because they are easy to prepare, biodegradable, less expensive, versatile and patient compliance (non-oily, cooling effect and ability to wash with water). Although hydrogels are patient-friendly, their potential to incorporate a broad range of drugs and penetrate the skin's lipophilic barrier is limited.[48] These drawbacks were sought to overcome by using organo/oleogels, bigels and emulgels. Organogels, on the other side, have been studied since the early 1990s.[49,50]

1.2.2 Organo/oleogels

Organogels are dispersion gels that contain non-polar solvent or oil as a dispersion medium (also referred oleogels). Organogels are organic liquids encased in a three-dimensional thermoreversible crosslinked gel assembly. Organogels are solid-like structures made up of low-molecular-weight components that form a three-dimensional arrangement that entraps liquid components known as organogelators.[51,53] Organogels are made in the same way as hydrogels, which have weak hydrogen bonding or van der Waals forces.[54,55] Many organic solvents, like hexane, benzene, edible oils, like almond oil, olive oil and mustard oil (as a liquid component)[53,56,57] and waxes, such as rice bran,

candelilla, sugarcane and carnauba waxes[58,59] have been studied in the progress of a medium for transdermal drug administration of lipophilic compounds.[60,61]

Considering the facts about vegetable-derived oils, it appears that developing organogels with vegetable-derived oils could provide additional benefits during transdermal and topical drug administration. Vegetable oil-based oleogels may have applications in the cosmetic and food industries, in addition to drug delivery applications. The gelation of the oils aids in the prevention of oil mobility in foods, composite pharmaceuticals and cosmetics items by extending their shelf life. Organogels stabilize many heterogeneous systems and provide consistent texture.[51,62] Organogels can improve drug permeation into the stratum corneum (SC) due to their lipophilic composition, in addition to their simplicity of preparation. Permeation boosters include fatty acids, glycols, surfactants, terpenes, and essential oils, which are all common organogel components. Many fatty acid components are referred to as permeation enhancers as they are expected to form distinct domains that are highly permeable pathways, enhancing fatty acid permeation into the stratum corneum's (SC's) lipid bilayer. Phospholipids and surfactants penetrate into the stratum corneum (SC) and enhance tissue hydration, resulting in increased drug penetration, particularly in hydrophilic active agents.[63] Lecithin organogels have recently gained much attention for transdermal drug delivery because of their potential to dissolve compounds with various physiochemical properties, as well as their biocompatibility,[64-66] thermoreversiblity, thermodynamic stability, resistance to microbial contamination, and less moisture sensitivity. Lecithin protects the skin from UV-induced ageing, it has additive anti-aging effects when combined with integrated bioactive compounds.

Incorporation of guest molecules, including vitamins C and A, NSAIDS, hormones, local anaesthetics, amino acids, peptides, and antifungal agents into the lecithin organogels, have been effective against topical and transdermal activity.[64-67] Organogels are commercially valuable because they can be easily prepared, have good mechanical strength, less expensive, thermoreversible, resistant to microbial contamination and high permeability through the skin. No doubt, organogels are very valuable because of their unique properties, but there are also some drawbacks associated with these, like they can be good choices only for lipophilic drugs, heat can create an issue for their stability, they are sticky and not easily washable. So, researchers tried to overcome these drawbacks associated with organogels by creating emulgels and bigels.

1.2.3 Emulgels

An emulgel is a mixture of a gel and an emulsion. Despite the apparent benefits of gels, the administration of hydrophobic medications has always been a source of worry. Emulgels were developed to overcome this limitation [68,69] and have been utilized to transport hydrophobic drugs. Gelling ingredients in the aqueous phase transform a traditional emulsions into emulgels. Emulsions of oil-in-water (o/w) and water-in-oil (w/o) have been utilized to transport pharmaceuticals. Thixotrophicity, spreadability, long shelf-life, removability, emollient, greaselessness, and a nice appearance are just a few of the cutaneous features of emulgels.[70-72] Furthermore, because emulgels include the benefits of both gels and emulsions, they have a high patient acceptability as compare to organogels. Emulgel formulations made from carbopol have high absorption and diffusion rates, ease of preparation is simple, and have optical clarity.[73] Microemulsions diminish the stratum corneum's permeation barrier[74,75] while exhibiting

acceptable physical qualities, like minor skin irritation and drug release.[70,76,77] Furthermore, emulgels have demonstrated their utility as a carrier for skincare treatments that protect from ultraviolet A and B radiation.[78] Microemulsion gels have recently attracted much attention as a viable topical drug administration mechanism on the skin.[79-85] These gels are similar to emulgels but due to smaller particle size they are comparatively more stable. Gelatin is formed when a gelling ingredient is dissolved in a hot o/w or w/o microemulsion followed by slow cooling. Microemulsion provides a better thermodynamic stability resulting in a viable delivery medium for transdermal and topical drugs. Nanotechnology is often used to improve the stability and skin permeation of emulsion-based gels by lowering particle size to nanoscales.[86] In microemulsion gels and emulgels, drug passing through the stratum corneum is based on a standard diffusion process, but fatty acids and surfactants in the oil phase can act as permeation enhancers, causing enhanced drug permeation and deposition inside the skin. As emulgels can deliver both lipophilic and hydrophilic drugs and can easily permeate the lipophilic skin barrier, they are proposed as the transporters for transdermal and topical drug administeration. But because of their oily residues and stickiness, these emulgels are less appreciated by patients. Therefore, to overcome these problems, a new type of gel i. e. bigel is prepared using organogel and hydrogel, retaining each gel system's benefits.

1.2.4 Bigels or bi (phasic) gels

Bigels are topical compositions made up of lipophilic (organogels) and an aqueous (hydrogels) system. When applied to the skin, bigel compositions have the cooling impact, increased moisturizing effect, easy spreadability, emollients, and easy

washability of both gels. Bigels are the combination of hydrogel and oleo/organo gel and are stable and do not contain any surfactants or emulsion stabilizers.[87] Lipophilic and aqueous systems are mixed at a high shear rate to produce these homogeneous solutions. Bigels differ from emulgels and creams in terms of composition as they lack an emulsifier agent. In bigels, both the oil/organic phase and water phase are present, which can generate a reinforcing effect such as increased drug penetration and hydration of the stratum corneum. The method of drug permeation through the skin will be similar to that of gels and hydrogels. Bigels can be employed as a topical drug administration vehicle on the skin in the cosmetics and pharmaceutical sectors since they contain the characteristics and benefits of both hydrogels and organogels. The formation of bigels[88] has been explored using carbopol oleogels made from liquid paraffins and sweet almond oil. Despite the fact that bigels are simple to make, only few researchers have looked at them for pharmacological or cosmetic applications. Inspite of their advantages, there are some problems such as difficulty in generating a stable organogel and hydrogel mixture without using an emulsifier, thermoreversibility and stability could also be be an issue at a higher temperature.

1.2.5 Aerogels and xerogels

Aerogels, generally referred to as inorganic gels, are made of silica using the sol-gel method. When silica gel is wet and dried over normal atmospheric pressure, then dramatical shrinkage takes place by yielding a solid substance having small pore size identified as xerogel. During supercritical drying, the unusual porous network is conserved in the consequential aerogel by avoiding shrinkage. The use of aerogels as drug delivery vehicles has been investigated and has been found potent for chronic

treatments.[89] Aerogels have been studied for cutaneous drug delivery; although, more research is required for their certain potential.

Aerogels are versatile in the form of their structure, pore size and surface area.[90] Also, aerogels are more efficient than xerogels due to their bioavailability and better drug solubility and their release kinetics can be controlled by adding various functional moities.[91] Hydrophilic aerogels may result in exceptionally rapid drug release, which is especially beneficial for pharmaceuticals that are poorly water soluble.[92] The hydrophilic aerogel network collapses in the aqueous phase because of surface tension existing within the pores. Xerogels do not exhibit structural collapse, unlike aerogels. Silica aerogels (hydrophilic) offer a new way to deliver drugs to the skin. The drug loading process (supercritical gas adsorption) provides homogeneous drug dispersion within the aerogel matrix, resulting in non-crystalline drug presence inside the porous matrix. A drug-loaded aerogel matrix have been shown to increase drug release and permeation capabilities, along with stability.[91] Though silica aerogels being a promising drug carrier, their usage is limited because they are non-biodegradable. Numerous biodegradable aerogels have been prepared with polysaccharides to avoid the non-biodegradability of silica aerogels[93-96] and to make a dry drug carrier accessible to high loadings of an active pharmaceutical compounds.[97] Aerogels based on polysaccharides as drug delivery systems have shown promising by combining both organic and inorganic (polysaccharide) constituents in hybrid aerogels. The physicochemical characteristics of the aerogel will be innovative and excellent as a result of combining these disparate components in a single matrix. It was recently reported[98] that polysaccharides (chitosan) can be used to make aerogels for tissue engineering. For sustained drug release, alginate-multi-membrane aerogels have been

prepared. It is already reported that the amount of drug incorporation and the time of drug delivery could be extended by increasing the number of alginate memberanes. The extended-release medicines that arise potentially have some benefits in therapeutic outcomes and patient compliance.[99]

Undoubtedly, there are numerous applications associated with the various types of gels in several fields such as pharmaceuticals, foods, optoelectronics, environmental remediation, energy storage, and cosmetics.[100] However, creating self-assembled gels with desired shapes and structures, which could open up new possibilities for low molecular weight gelators, is challenging. [101] Gels with the appropriate shape and size can usually serve as a drug delivery agent.[102] To modify the structure and shape of the gel, several approaches have been devised, including moulding and photopatterning,[103] 3D printing,[104] electrochemistry,[105] and surface-mediated processes[106] and many possible ways for obtaining shape-controlled precision have also been used,[107] but there are just a few examples in the literature in which gels are produced as spherical particles. Miravet and co-workers reported the formation of gel microspheres by dropwise adding the gelator-DMSO solution in the anti solvent.[108] Polymer gelators and low molecular weight gelators (LMWGs) are used to make hybrid gels, where the polymeric gel system can speed up the nature of LMWGs[109,110] and control their structure and shape.[101] Alginic acid is a fascinating polymer gel that is biodegradable, versatile and biocompatible.[111] Furthermore, water soluble sodium alginate when combined with Ca^{2+} ions, forms hydrogels. Alginate gel beads can be formed by dropping alginate solution into calcium chloride solution dropwise.[112] Another substance that occupies the core of the alginate beads can be used to make more complicated core-shell shaped alginate beads.[113] Smith

and colleagues were the first to announce that LMWG had been incorporated into an alginate microgel bead.[114]

Nanosized particles (NPs) embeded three-dimensional gels have attracted the attention of many researchers as the superior alternate in medical applications [115-118] because of their special properties and structure and the growing need for new and efficient non-traditional antimicrobials. Nano - particles such as gold, platinum, silver, nickel, cobalt, and copper, as well as metal oxide nanoparticles, metal alloys, and salts, are of significant interest. The scientific research community has worked hard to develop appropriate synthetic procedures for synthesizing nanoparticles, considering the synthetic limitations imposed by heavy metal pollution.[119] Thoniyot *et al*. explained how nanoparticle-loaded hydrogels can be created by combining NPs with hydrogels by several processes.[117] Moreover, many investigations have been conducted into the various components, varieties, and features of hydrogels, including the physicochemical properties and production methods of nanoparticles.[120-123] Furthermore, many investigations were hypothesized which debated the efficacy of nanoparticle-hydrogel as potential antimicrobial agents against bacteria, fungi and virus, particularly those with antibiotic resistance. Many writers[124,125] focused on the application and utilization of nanoparticles as antimicrobial agents. Zhao *et al*.[118] evaluated recent achievements in the design, functionalization, synthesis and applications of nanocomposite hydrogels with improved mechanical, physicochemical and biological properties. Various reviews[115] have been published on nano-hydrogel-related specific elements. These evaluations pointed out some shortcomings in current research, such as the lack of *in vivo* testing on animal studies and their rheological properties. Optimizing the elements of the NPs-hydrogel

composites is required because of their goal as anti-biofilms and antibacterials in medical applications, particularly in wound healing, where the skin and its properties play a crucial role. Because of their powerful anti-biofilm and antibacterial capabilities, AgNPs are receiving much attention among metallic nanoparticles.[115] These nanoparticles are widely manufactured and employed as a broad-spectrum antimicrobial agent against gramme positive and gramme negative bacteria, as well as antibiotic-resistant bacteria.[126] Many researchers have coated AgNPs with various polymers for various goals, including lowering nanoparticle toxicity on the bacterial host and achieving antimicrobial advantages.[127,128] Several researchers examined the development of hydrogels and the inclusion of AgNPs into such hydrogels.[115,118,122,129-131] As a result, the selection of gelling agents, particularly those with antibacterial activity, and their application in hydrogels are of significant interest to improve the antibacterial efficacy of AgNPs optimally and synergetically toward the production of a perfect hydrogel.[132] According to the findings and literature research, there are various elements and subjects that need to be investigated concerning the development of optimal AgNPs-hydrogel composites, primarily for topical applications.

1.3 Drug delivery

Drug Delivery Systems are the devices or formulations that enable the delivery of therapeutic ingredients in the body by improving their safety and efficacy by controlling the time, rate, and target of their release. This method involves the incorporation and delivery of the dynamic pharmaceutical substances via the biological membrane to active site. Drug delivery method is a network between the drug and patient. It may be a device or drug formulation to deliver the active ingredients for remedial purpose. It is

very important to differentiate between the device and the drug because this is the decision factor for administrative control of the transportation method by the drug control organization. If a system is administered for the delivery of the drug or to avoid the complications, it is categorized as a device. There is a broad spectrum between the devices and drugs, and their category division can be decided individually.

1.4 Drug delivery routes[133]

There are various structural routes depending on the desired effects, diseases, product availability and target of action, for the administration of the drug into the human body. The drugs can be introduced either directly to the diseases effected organ or systematically deliver to the sick organ. There are various drug delivery methods on the basis of structural routes for example oral, parenteral, subcutaneous injection, intramuscular injection, intravenous injection, intra-arterial injection, buccal and sublingual routes, nasal drug delivery, rectal, pulmonary, cardiovascular drug delivery, central nervous system drug delivery and topical and transdermal drug delivery.

1.4.1 Oral drug delivery

Traditionally, the oral drug administration route has become novel and conventional route for drug delivery system because of the following advantages:

- Ease of administration
- Most convenient for prolonged and repeated use
- Self-administered
- Minimal acute drug reaction
- Broad range acceptance by the patients.

Major drawbacks of oral route of drug delivery are:

- Not appropriate for patients having emergency because of slow action of orally taken drugs
- Not suitable for unconscious patients
- Orally taken drugs have variable serum concentrations and variable absorption rate which can be irregular. This requires the development of controlled and sustained release systems.
- The digestive juices and gastric acid can degrade some active ingredients before absorbing into the bloodstream and this problem is particularly associated with ingested proteins.
- Many drugs are insoluble in the digestive tract due to low pH levels which reduces their bioavailability.
- Not suitable for highly irritant drugs
- Not suitable for patients with severe vomiting and diarrhea

1.4.2 Parenteral drug delivery

Substances delivered to the body by other routes than the gastrointestinal tract are termed parenteral. However, this is usually applied to the injection of compounds through the skin, intramuscularly, intravenously, and intra-arterially. Drugs are delivered to specific organs of the body via injections are described under several therapeutic areas. Nowadays, the delivery of drugs by the parenteral route is widely used in medical practice and is the most common invasive drug delivery methods. There are some significant drugs which are accessible only in parenteral form. Conventionally plastic (disposable) and glass syringes with needles are used.

Parenteral drug delivery route's advantages:

- Fast outset of action
- Almost complete and Predictable bioavailability
- Prevention of the gastrointestinal tract facing complications during oral drug delivery
- Provides a consistent route for drug delivery in very sick and dragging patients, who are unable to swallow anything orally.

Drawbacks of parenteral drug delivery route:

- Drug reversal is not possible
- Emboli and infection risks
- Cost and the possibility of hypersensitive reactions
- It is difficult for patients to comply with injections because they are painful.

There are several type of injections for parentral drug delivery as explained below.

1.4.3 Subcutaneous

In this treatment, a hypodermic needle is used to inject the drug into a layer of fatty tissue beneath the skin. Subcutaneous injections can be given to large portions of the body by patients themselves, such as insulin for diabetes. Following factors affects the subcutaneous drug delivery.

- Molecular size affects penetration rate, as larger molecules penetrate at a slower rate.
- Viscosity can inhibit drug diffusion into body fluids.
- It usually takes longer for subcutaneous injections to absorb and to begin acting than intravenous or intramuscular injections.

Disadvantages of subcutaneous injection are:

- It is difficult to control the rate of drug absorption via subcutaneous route
- These injections are painful and can cause irritation at acting sites
- Change the injection site frequently so that the unabsorbed drug does not accumulate, causing tissue damage

Peptides and macromolecules can still be delivered reliably and controlled via the subcutaneous route.

1.4.4 Intramuscular injections

These are delivered deeply into the skeletal muscles, typically the gluteal muscles or the deltoids. Intramuscular injections start acting quicker than subcutaneous injections, but are slower than intravenous injections. Diffusion control of the drug's absorption occurs, but it is quicker in muscle tissues since they are very vascular. As a result of various physiological factors, such as blood circulation and muscular activity, absorption rate varies depending on the injection solution's physicochemical qualities.

Intramuscular drug delivery route's disadvantages:

- Painful injections
- The amount of injection is limited by the available muscle mass
- An injection site can degrade peptides
- The injection site can develop hematomas and abscesses, as well as peripheral nerve injuries like complications.

Generally, most of injectable drugs in the several forms like colloidal suspensions, oil in water emulsions and most injectables can be administered intramuscularly. This method is

accessible in a variety of dose forms, including oil-in-water (o/w) emulsions, regenerated powders and colloidal suspensions. The drugs in less dissolvable form show prolonged effects with slow and steady absorption. Intramuscularly introduced drugs usually store in the muscular mass, where the active pharmaceutical ingredient is absorbed slowly.

The release rate of drug from such a store depends on the following factors:

- A more diffuse and less compact depot results in a faster release
- Particle size and concentration of drug in the medium
- Solvent nature in injection
- Drug's physical form
- Viscosity of the drug
- Injection volume

1.4.5 Intravenous administration

In this type of administration, aqueous form of drug is injected into deep/superficial veins via placing a catheter or needle. This route is preferred in case of emergency because of rapid action. Alongwith it can control infusion rate for continueous and prolonged administration and also requires smaller doses as compare to other administration routes. The drug targeting to the different organs depends on the particle size in intravenous solution, for example, particles of diameter 0.1 to 7 μm can be absorbed by spleen and liver while particles larger than 7 micrometres are taken up by the lungs, and those smaller than 0.1 micrometres are retained in the bone marrow.

Intravenous route's disadvantages:

- Injections of peptides and protein can cause immune reactions
- Strain to veins can cause thrombophlebitis.

- Drug solution extravasation into extravascular space can result in tissue necrosis and irritation.
- Infections can occur where catheter or needle is introduced
- Sucked air can cause air embolism

Drugs given intravenously can now be modified according to their disposition kinetics and metabolic profile by incorporation of the drug into the nanovesicles like liposomes.

1.4.6 Intra-arterial

It is not common to administer therapeutic drugs directly into the arteries. Angiography has been performed by puncturing an artery and injecting contrast material. Most of the arterial perfusions or intra-arterial injections positioned in arteries via catheters are for local chemotherapy of limbs and organs. Generally, Intra-arterial chemo has been used to treat malignant brain tumors.

1.4.7 Transmucosal drug delivery

By this route, drugs can be administered into the body at different anatomical sites because all interior channels and orifices are covered by the mucous membrane. The penetrants can diffuse through the mucous membranes and at steady state, the quantity of a substance diffusing across the tissue per unit time is constant, and the concentration of the solutions does not influence the permeability coefficients. The permeation pathways are intracellular instead of intercellular through epithelial barriers, as with the epidermis of the skin and the permeability can be increased by the surfactants for example sodium lauryl sulfate. Advantages of transmucosal drug delivery over injection drug delivery route:

- Avoidance of injection pain
- Increased therapeutic efficacy
- Peptides administration possibility
- Fast absorption in comparison to oral drug administration
- Higher patient adoption in compare to injections
- Having lower cost as compare to injections

Controlled-release mucoadhesives systems can enhance transmucosal drug delivery by ensuring an effective balance between the drug concentration and toxic levels, preventing water dilution in the body fluids, and enabling targeted delivery at specific sites.

1.4.8 Sublingual and Buccal routes

Buccal absorption is influenced by the non-ionized drug's lipid solubility, the partition coeffi cient which is a measure of the drug's relative affinity for the medium as compare to the epidermis barrier and salivary pH. A high partition index value suggests a low affinity of the drug's carrier. A low partition index number indicates that the drug and the vehicle have a strong connection, which decreases the drug's release from the vehicle. The optimum carrier is one that allows the drug to dissolve as little as possible.

Buccal medication administration provides the following advantages:

- Fast absorption into the circulatory system with quick beginning of effect due to absorption through the systemic veins and lymphatics' rich mucosal network.
- If an unfavourable reaction occurs, the tablet can be discontinued.
- Oral mucosal absorption skips first-pass hepatotoxicity, and a drug can stay in the buccal cavity for a long time, allowing for the improvement of compositions with a controlled release effect.

Buccal route limitations are:

- The pill must be held at site and not consumed if the buccal route is to be used.
- Abnormal salivary flow can cause the tablet to dissolve and absorb too quickly or flush it away. These problems have been avoided through a patch holding the drug which is administered to the buccal mucosa or use of the pharmaceutical drug in the form of a spray.

1.4.9 Nasal drug administration

For several years, pharmaceutical ingredients have been delivered nasally for both systemic and topical effects. Nasal congestion, sinusitis, rhinitis, and chronic disorders and related allergy can all be treated with topical medications. Corticosteroids, anticholinergics, vasoconstrictors, and antihistamines are only a few of the drugs available. The nasal drug route is an appealing target for delivery of choice drug, especially for overcoming oral administration's drawbacks like high first-pass metabolic process and distruction of drug in the digestive tract. Although the nasal route of drug administration has received a lot of attention in recent years for systemic administration of drug, it can be employed for direct delivery of drugs to the brain.

Factors affecting the extent and rate of absorption of drugs through nasal route are:

- Nasal secretions rate directly affect the drug's bioavailability.
- Ciliary movement has adverse effect on the drug’s bioavailability.
- The nose's vascularity; Faster drug absorption occurs when blood flow is increased
- Drug metabolic process in the nasal cavity. Despite the presence of enzymes in nasal tissues, they have little effect on the uptake of most chemicals, with the

exception of peptides, that can be destroyed with aminopeptidases. This could be owing to low enzyme levels and a short drug-to-enzyme time of exposure.

- Diseases of the mucous membrane in the nose. The impact of the cold or flu on nasal drug delivery is another something to think about.
- Rapid mucociliary clearance is a key drawback of nasal administration, resulting in inadequate absorption and thus poor medication bioavailability. To overcome this drawback and enable sustained delivery through the nasal route, *in situ* nasal gelling drug delivery methods have been investigated.

Nasal route's advantages:

- Nasal mucosa has a higher permeability than the gastrointestinal mucosa or the epidermis.
- It also has a highly vascularized subepithelial tissue and absorbs drugs quickly, typically within 30 minutes.
- Avoid the first-pass effect, which comes after gastrointestinal tract drug absorption.
- Avoiding vomiting effects, and stomach stasis in migraine sufferers.
- Nasal drops and sprays are easier to use.
- Drug bioavailability is higher as compare to gastrointestinal routes.
- Best route for delivery of peptides.

Disadvantages of nasal route of drug administration:

- Due to small absorption region and short absorption time, diseases and disorders of the nose may result in reduced absorption.
- It's plausible that injecting a medicine into a blocked nose or one with a lot of watery nasal discharge will cause the drug to be expelled.

- Polar drugs and some macromolecules are not absorbed in sufficient concentrations due to restricted membrane permeability, rapid evacuation, and enzymatic degradation into the nasal cavity.

Alternative methods for overcoming nasal obstacles are also being researched. Absorption stimulants such as surfactants and phospholipids are frequently utilised, but their content must be carefully monitored. To boost the bioavailability of medications administered intranasally, drug delivery methods such as cyclodextrins, liposomes, and nano and microparticles are being investigated. After weighing the benefits and drawbacks, nasal medication delivery emerges as a promising method of delivery that competes with gastrointestinal delivery systems, which also is showing significant promise. One of the most essential aspects is the nearly perfect bioavailability and dosing precision.

1.4.10 Colorectal drug delivery

Despite the fact that drug delivery via the rectum in humans started from 1500 BC, the significant proportion of pharmaceutical customers are cautious of doing so. The colon, on the other hand, is an ideal location for the slow and safe drug absorption that are aimed to the large intestine or are intended to act systemically. Food only takes a few hours to travel through the small intestine, but it can take up to three days to transit through the colon. The following are the basic conditions for medicine distribution to the colorectal area:

- The medicine should be eaten orally in a targeted form or slow-release, or administered directly to the colon through rectal suppository or an enema.
- The medicine must get beyond the intestinal mucus' physical barrier.

- Drugs must withstand metabolism transformation via a variety of bacterial kinds found in colon, most of them are anaerobic and have a broad range of enzymatic activity.

Factors affecting colorectal route:

- The pace of flow of blood to the absorptive epithelium influences the rate of medication absorption from the colon.
- Molecules are trapped within polysaccharide chains by components of diet.
- Passive diffusion efficiently absorbs lipid-soluble compounds.
- The pace of gastric tract and the time it takes for food to pass through the small intestine.
- The amount of medicine absorbed depends on delivered drug to the rectum, whether it is delivered to upper or lower colon.

Benefits of the rectal route:

- It is possible to administer a high dose of the medicine.
- Oral administration of the drugs are degraded with stomach acid and metabolized by gastric juices.
- Rectal route is convenient, especially for the elderly and infants.
- It is also effective for emergency situations in infants, like seizures, whenever intravenous passage is not usable.
- Digestion or the stomach emptying rate has no effect on drug absorption from the rectum, and the influence of different adjuvants is probably more successful in the rectum than upper gastrointestinal system.
- Absorbed drugs via the lower rectum skip the liver, and drug destruction in the rectal lumen is significantly lower than upper gastrointestinal system.

Rectal route disadvantages:

- Some hydrophilic medications, such as peptide pharmaceuticals and, antibiotics are difficult to absorb through the rectum, necessitating the use of penetration enhancers.
- The drug can cause rectal irritation and occasionally proctitis, which can lead to bleeding and ulceration.

Orally given drugs with a colonic effect are also available. Colon targeting has a number of therapeutic benefits, including the oral administration of medications that would otherwise be eliminated by stomach acid or processed by pancreatic enzymes. Drugs that are released slowly into the intestines can help with nighttime angina, asthma, and arthritis. The administration of medications to the affected region improves colonic diseases treatment such colorectal cancer and Crohn's disease. For the colorectal cancer treatment, specific-site oral anticancer medicine administration to the colon enhances its concentration at the specific location, requiring a lower dose with lower incidence of adverse effects .[134] Colonic diagnostic agents, and colonic distribution of vermicides on the other hand, necessitates lesser doses.

1.4.11 Pulmonary drug delivery

Despite aerosols in different forms have been used to treat respiratory problems since about the 20th century, the interest in using pulmonary route for systematic drug administration is relatively new. The demonstration of the lung's potential value as a gateway for peptide absorption and the viability of gene delivery for the cystic fibrosis have piqued interest in this method. For optimal utilization of this pathway, it is necessary to recognize the process of absorption of macromolecule via lungs.

Pulmonary route's advantages:

- Absorption surface area is large.
- Close vicinity to the circulation of blood.
- Prevention of first-pass metabolic process.
- To get the same therapeutic results as the oral route, smaller doses are required.

Disadvantages of pulmonary drug delivery

- For optimal medication deposition, the lungs contain adequate aerodynamic filter that should be overcome.
- The accumulated particles are cleared towards the throat by the mucus lining in the pulmonary airways.
- When utilizing a traditional inhalation device, only 10–40% of the medicine leaves the device and is absorbed in the lungs.

Pulmonary routes's future prospects:

The pulmonary pathway for medication delivery has now been developed for systemic drug delivery. This method can be used to deliver a wide range of drugs; however it is particularly useful for protein and peptide administration. Several biotechnology organizations will get involved in this region as the protein and peptide therapeutic medicines grow. Advancements in dry powder composition will be just as crucial as device design for delivery of the drug to the lungs. This provides the way for future study into using this technology to carry a wide range of chemicals to the lungs with potentially better release than traditional carrier particles. In the transition from physically and chemically durable small particles to some more potent and sensitive big

molecules, challenges of microparticle production for lung delivery will become increasingly significant. Despite these drawbacks, pulmonary pharmaceutical delivery remains a worthwhile and feasible objective. Nanoparticles have been studied for pulmonary medication delivery, with promising findings so far. Many of the concerns about safety have been resolved. Besides of biotherapeutics, drugs for inhalation are being developed, including therapies for reducing the influenza symptoms, minimizing vomiting and nausea after cancer chemo, and also providing vaccinations, which are either on the marketplace or in production.

Inhalable antibiotics could be used to treat lung infections like tuberculosis among high, local dosages in the future. Alternatively, drugs that induce stomach trouble, such as erythromycin, migraine pain relievers, or antidepressants, could be packed for inhalation. Inhalable medications have the potential to eliminate frequent oral dose side effects such as limited solubility, low bioavailability and food interactions. Many medical disorders, such as seizures, pain, anaphylaxis, and spasms, could benefit from fast-acting medicines since inhalable reach the circulation faster than tablets as well as some injections. In the future, the medical cabinet may contain a variety of inhalable pharmaceuticals that will substitute not only unpleasant injections, but also those drugs that have multiple negative effects when administered orally. The broad difficulty of getting biotherapeutics and other drugs to the lungs will be aided by new techniques.

1.4.12 Cardiovascular drug delivery

Because of the physiology and anatomy of the circulatory system, which distributes nutrients and blood to all of the body's organs, drug distribution to the cardiovascular

system differs from drug administration to other systems. Drugs can be injected into the bloodstream to have a systemic effect or can be targeted to a specific organ by the local supply of blood. Devices are utilized alongwith traditional pharmaceutical compositions such as sustained release. The devices can be used in a significant portion of the cardiovascular therapy, mainly for large and serious diseases. Some of them are surgically implanted, while others are introduced through catheterization and minimally invasive techniques. The utilization of advanced cardiovascular imaging technologies is critical for device placement. Drug administration to the cardiovascular system includes more than just preparing drugs for controlled release; it also includes delivering novel treatments to the heart.[135] The delivery of cardiovascular drugs is covered in more detail elsewhere.[136] The following are some methods for administering medications to the circulatory system locally:

- Delivery of drugs through the cardiovascular venous system
- Cardiac catheter injections into the coronary arteries
- Intrapericardial medicine administration
- Drug release from drug-eluting stents into arterial lumen

1.4.13 Drug delivery to the central nervous system

In the treatment of central nervous system (CNS) problems, transporting drugs to the brain is difficult. The blood–brain barrier (BBB), which avoids drugs to reach to the brain material, is the most significant impediment to CNS drug delivery. In the past, systemically delivered drugs were used to treat CNS disorders. This pattern is continuing. The majority of CNS disease research is focused on developing medications and compositions for sustained release, little considerations have been devoted to how

these drugs are delivered to the brain. The BBB endures the most difficult barrier to medication administration to the CNS.

The growth of BBB preclinical studies to identify, characterise, and evaluate new nanoparticles relevant to brain administration *in vitro* is discussed.[137] The authors offer a method for screening nanoparticles of varying surface and size chemical modification in order to describe the physicochemical parameters that enable the arrangement of nanoparticles that can cross the BBB efficiently.

1.4.14 Topical and transdermal drug release

More than 20 years have passed since transdermal drug delivery achieved a stage where it is possible to administer clinically effective drugs via transdermal systems. A total of 51 transdermal/dermal drug delivery candidates are currently under clinical evaluation in the USA.[138] The transdermal patch market in the US is estimated to be worth more than $3 billion annually, with the worldwide demand exceeding $4 billion. As a non-oral system of systemic delivery, this is the most successful technique. The introduction of nicotine patches revolutionized the prevention of tobacco smoking about 13 years ago. Likewise, nitroglycerin for angina, scopolamine for movement disorder, clonidine for hypertension and estradiol for estrogen inadequacy are delegate instances of effective transdermal patch substances.[139] However, the big challenge in the transdermal drug transportation framework is to build the assortment of drugs that can be delivered. This market is scattered among just eighteen FDA-endorsed dynamic agents: scopolamine, clonidine, dynamite, testosterone, estradiol-norethindrone, nicotine, fentanyl, ethinyl estradiolnorelgestromin, lidocaine-tetracaine, oxybutynin, 17-β estradiol, lidocaine-epinephrine, lidocaine, estradiol-levonorgestrel, 2 selegiline, fentanyl HCl,

methylphenidate, rivastigmine androtigotine. Just few drugs are accessible using transdermal patch frameworks due to low skin permeability (particularly the outer most stratum corneum film), which restricts daily drug doses to around 10 mg through a satisfactory measured patch. Besides, transdermal drug delivery doesn't apply to all drugs, nor is it legitimized for all treatments. The vast majority of drugs transdermally directed ought to be lower in molecular mass, profoundly lipophilic and require little dosages.[138,140,141]Just a few drugs have been effectively administered into the skin, so different strategies like iontophoresis, sonophoresis, electroporation, micro needles, stratum corneum removal and compound enhancers have been examined.[142] Usually, active ingredients are mostly delivered to the body by intermittent applications. In clinical treatment, drugs are administered in intervals by intake of pills, fluids, or injection and afterwards regulate throughout the whole body. The concentration of the pharmaceutical active ingredients rises and falls, and high concentrations might be poisonous and create side effects both to the objective organ and adjoining structures. While the low concentration of active agents is difficult to monitor and requires cautious estimation of the measure of the leftover active agents ought to be made to avoid overdosing. Because of regular metabolic cycles, a subsequent dose should be administered to control the minimum effective level.[143] In transdermal administration of prescription, the above issues can be disposed of because the drug diffuses over a delayed timeframe directly into the circulation system of the blood stream. The advantages of transdermal drug administration include persistent plasma concentration profile, decrease side effects, improvement of patient consistence by reducing dosing plan, avoidance of the main pass digestion, convenience, patient-amicability, and non-persistent administration.[144] Disregarding the plentiful benefits of transdermal drug delivery, there are a few obstacles

to its extensive application. Transdermal delivery of drug molecules is slow because of the low penetrability through the stratum corneum, outermost layer of the skin. One more genuine hindrance to transdermal drug administration is the chance of adverse skin responses known as contact hypersensitive dermatitis.[143]

1.4.15 Topical and transdermal drug delivery: Background

Skin as a route of medication administration has a long history, dating back centuries to when particular plants and herbs were utilized to cure diseases and general health issues. Using plant pastes for topical application was one of the most extensively used procedures during the long age of traditional treatments.[145] Over 100 conventional herbal compounds have been identified which were utilized topically to reduce inflammation, manage pain, or heal tissue in the prevalence of musculoskeletal injuries.[146,147] Topical treatment for gastrointestinal (GI) problems such as dyspepsia, GI ulcers, gastritis, intestinal worms, inflammatory bowel disease, and infections has a long history in traditional Persian medicine. They're usually applied to the trunk, back or stomach region and absorbed by the skin. Poultices, ointments, rubbing oils, gels, lotions, pastes, and baths were all regularly used herbal remedies.[148] It's unclear whether any active ingredient in these traditional herbal medicines crosses the epidermal barrier to produce pharmacological effects.[147] However, it is evident that our current knowledge and progress in pharmaceutics distribution via topical and transdermal routes is based on ancient expertise. The earliest identified deterministic approach in topical drug handling was proposed by the well-known Persian physician Ibn Sina (Avicenna, 980-1037 AD) in his treatise The Canon of Medicine, in which he presented two states for delivery of drugs through skin: the smooth part that penetrates the skin and the hard part that does not penetrate the skin.[149]

Beginnings of side effects following topical treatments, such as headaches,[150] systemic poisoning[151] and led to the realization that exposure to topically applied chemicals might have both helpful and detrimental (or toxic) consequences. The major organ in the human body by weight and surface area, the skin, serves as a platform for medication administration via transdermal and topical and trans routes. Topical delivery aims for therapeutic efficacy at the cutaneous level and prevents systemic influence, whereas transdermal delivery targets therapeutic efficacy in deeper layers to impose a systemic impact beyond skin. Topical distribution methods are, by default, less intrusive than transdermal delivery systems.[152] One of the most well-known functions of the skin is to defend the body from external assaults, with the stratum corneum serving as the principal barrier in this aspect. If drugs administered transdermally or topically are to have an effect, they must pass through this barrier. While certain chemicals can diffuse through the SC without being induced, many compounds must be induced to permeate the SC through physical or chemical mechanisms. Continuous advancements in topical and transdermal delivery have yielded several new technologies that optimize regulated dosing, precise targeting, and increased penetration, allowing for the delivery of a broad spectrum of medicinal substances through the skin. Over 20 transdermal therapeutic medicines have been advanced and effectively produced for topical distribution in various forms such as gels, patches, gels, cutaneous solutions and ointments in recent decades.[153,154]

1.4.16 Transdermal drug delivery route

It involves the topical application of medicine to healthy skin, either for targeted treatment of tissues beneath the skin or for systemic treatment. The drug is absorbed via the skin into the wide circulation for systemic effects in this form of therapy.[155-158]

1.5 Skin structure description

The four separate tissue layers of skin are:

1. Epidermis that is no longer viable (stratum corneum)
2. A healthy epidermis
3. A healthy dermis
4. Connective tissue beneath the skin (hypodermis)

1.5.1 Epidermis (non-viable)

It is the outermost layer of skin, and it acts as a physical barrier to most of the substances which come into contact of skin. Layers of 10 to 20 cells make up the cell structure. Every cell is plate-like structure that is brick-like in design. Cell size: 25-36μm in breadth, 34-44 μm in length, and 0.5 to 0.20 μm thicker. Composition of cells: 5-15 percent lipid (cholesterol,phospholipids, cholesteryl suphate and glycolsphingolipids), 75-85 percent protein (keratin).

1.5.2 A healthy epidermis

It is present between dermis and the stratum corneum. The cells in live epidermis have a physicochemical structure comparable to that of other living tissues. Cell diameter: 50-100μm; cell thickness: 50-100 μm, 90% of the cells are made up of water.

1.5.3 A healthy dermis

The dermis layer lies under the viable epidermis. Cell structure: fibrous protein-rich connective tissue encased in an amorphous ground substance. The thickness of the cells ranges from 2000 to 3000 μm. Fibrin is a non-globular protein that is found in cells.

1.5.4 Subcutaneous connective tissue (Hypodermis)

Before entering the hypodermis, the drug permeates through the skin and enters the systemic circulation. The fatty tissue could act as a medication storage facility. Cell structure: fibrous connective tissue with a loose texture that contains blood, sweat gland secretory pores, lymph vessels, and cutaneous nerves.[159,160]

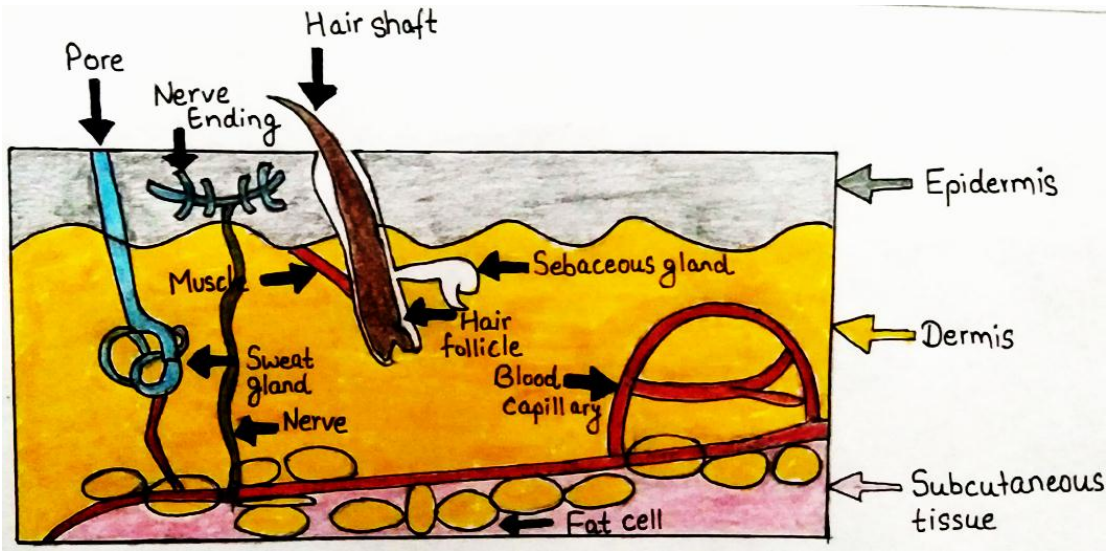

Figure 1.1: Skin components and layers.

Pathway of transdermal permeation

Diffusion can cause permeation via

1. Sweat glands and sebaceous permeation.
2. Stratum corneum (SC) permeation
3. Hair follicle (transappendaged)[160,161]

1.6 Transdermal drug delivery system: Basic principle

The most significant layer for TDDS is the stratum corneum. The medicine can reach the bloodstream if it can permeate the stratum corneum. The only way to transport typical

medications that are both water and lipid-soluble is by a mechanism known as passive diffusion, which proceeds too slowly for practical usage. The drug enters the blood stream immediately through the skin via a diffusion process. Because the patch has a high concentration and the blood has a low concentration, the medicine will take quite a long time to diffuse into the blood. The ideal combination is around half of the medicine being hydrophilic and half being lipophilic. This is because lipid-soluble compounds may easily permeate through the intercellular bilayer cell membrane, but water-soluble medications can bypass the restricting steps in the transdermal drug delivery mechanism. Hair follicles and sweat ducts are drug entry points, however, they are rather insignificant.[162]

1.6.1 Factors affecting permeability

1. Physiological factors

- **Age:** the skin of newborns and the aged is more porous than others.
- **Ethnicity:** Caucasians' skin is more porous than that of Africans and Americans.
- **Body regions:** Permeability also varies with the skin of the different body regions.
- **Skin status:** Wet, broken, warmer, thermal burn and sunburn skins are more permeable.

2. Factors of formulation

- Transport physical chemistry
- Membrane and carriers used
- Penetration enhancer used

Advantages of transdermal drug delivery

Compared to traditional dose forms, transdermal medication administration has various advantages.

- Less variation in drug plasma levels: Drug penetration across the skin is more consistent, resulting in more sustained serum drug concentrations. Intravenous infusion produces stable plasma levels, but it is more intrusive than transdermal medication delivery.
- The absence of plasma concentration peaks may lower the probability of adverse effects. As a result, transdermal medication administration is ideal for treatments that require relatively stable plasma levels.
- Easy drug delivery termination: If toxicity develops from a transdermal drug, the effects can be reduced by removing the patch.
- Dosage can be lowered, resulting in better patient compliance.
- For transdermal medication delivery, medicines with low therapeutic efficacy and short biological half-life are ideal.
- It is a different method of administering oral dose forms. In patients who are sick or unconscious, this is a huge benefit.
- Because transdermal administration minimizes direct effects on the intestine and stomach, drugs that induce gastrointestinal discomfort may be suitable candidates for transdermal drug delivery.
- Avoiding 'first pass' drug metabolism: Drugs which are destroyed by enzymes and gastrointestinal acids may be possible targets. Transdermal administration can avoid first-pass metabolism, which is necessary for oral medication delivery.

Transdermal drug delivery's disadvantages

- There will be local discomfort at the application site. The medication, adhesive and excipients in patch formulations might produce erythema, edoema, and irritation.

- The drug is not included in a transdermal drug delivery system that meets the following requirements.
- Drugs with a molecular weight greater than 500 dalton do not enter the stratum corneum.
- The drug partition coefficient is not reached into blood circulation if it is very high or lower.
- In the lipid and aqueous phases, high melting point drugs are less soluble.[163,164]

The skin is the biggest organ in the human body. It protects the entire body against external germs and other environmental exposure such as chemical, heat, toxin infiltration, and dehydration.[165] The danger of harm to the skin's integrity or emergence of localized disease is particularly significant because the skin is the most exposed organ to the environment. Transdermal drug delivery advantageous because it prevents the hazards and difficulties connected among intravenous therapy, such as fluctuating stomach pH, hepatic metabolism and emptying time. Because of the skin's impenetrable nature, transdermal medication delivery is difficult. The stratum corneum, which ranges in thickness from ten to several hundred micrometres, acts as a "permeability barrier," preventing macromolecules from easily passing via the dermal layer.[166] The stratum corneum is made up of dead keratinocytes layers surrounded by a lipid matrix, analogous to a "brick and mortar system," making medication molecules difficult to penetrate through the skin.[167,168] Although recent advances in nanotechnology have improved the capacity of molecules to penetrate through the skin by enhancing drug pharmacokinetics, an acceptable vehicle to assure drug delivery via non-invasive approaches has to be created.

1.7 Topical drug carriers (LMW gels and dendrimers)

There are various LMW gels and dendrimers reported for topical and transdermal drug delivery applications. Dendrimers are ideal candidates for drug delivery applications because of their globular shape and nanoscale diameter.

1.8 Dendrimers

Dendrimers are nanosized, 3-dimensional, synthetic, hyperbranched, mono-disperse macromolecules with a central core and numerous functionalities at periphery.[169-172] They have a spherical shape with a succession of branches encircling an inner centre.[173,174] A conventional dendrimer is made up of three topological components: a focal centre, basic components with many internal layers made up of repeating units, and multiple functional groups at the periphery.[175] Dendrimer is originated from the Greek terms 'dendron' (branch-like) and 'meros' (parts), and was developed by Tomalia in 1985 to describe its structural shape.[175-177]. The surface functioning can be 'adapted' to attach a range of genes, drugs and targeting molecules, as well as the inner centre can act as a 'host' for the 'guests' (drugs) according to their distinct properties.[170,178] As a result, several useful applications of dendrimers like nanoscopic devices have been investigated.[175] The therapeutic effect of different drugs is often restricted by their lack of capability to get access to the property of action in an acceptable dose due to the drug's low solubility inside the body's aqueous system.[179] Over the last two decades, a large variety of dendrimer topologies have been produced and explored for biological and drug-delivery applications based on inspiration from biological systems.[169,175] Furthermore, there are numerous publications available[180] that examine the drug-holding capability of dendrimers, whether chemically or physically inked, as well as

their capabilities to deliver it in a regulated manner. As drug-delivery systems, they have unique strengths of multivalency and monodispersity which depend on their size, surface functional groups and production.[170,181] Moreover, their well-defined design may reduce ambiguity about the size and shape of molecules and improve drug delivery precision.[174] As a result, dendrimers can act as gene-delivery carriers. It has been observed that dendrimers can accommodate both hydrophobic and hydrophilic drugs, exhibiting their diversity. Poly(propylene imine) (PPI), poly(amidoamine) (PAMAM), andare three types of dendrimers that have been demonstrated to have such capability[172,176] PPI is the first full dendrimer family which is synthesized, described, and commercialized.

The repetitive monomer unit of these synthesized macromolecules[182] is represented by the very symmetrical branching units, which are grouped in layers called "generations." Dendrimers can thus be made from basic branched monomer units in a systematic and regulated manner from the trunk to the branch and leaf "surface groups." ' 'Dendrimer's three-dimensional structure affords a variety of interesting properties, including nanosized globular structure, well-defined functional moieties at the periphery, hydrophilic or hydrophobic cavities in the interior, and relatively low polydispersity, and hence a broad range of additional applications. Dendrimers are nanoparticles with benefits over micro or other particles because of their tiny size and ease of uptake by cells through endocytosis.[183,184] They are branched macromolecules with a central core unit with great molecular homogeneity, limited molecular mass, specified size and shape features, and a highly functionalized terminal surface. Beginning with a central initiator base, the construction process is a sequence

of repeating stages that generate shells. Every successive shell introduces a unique "generation" of polymer, along with a bigger molecular diameter, twice as many reactive surface sites, and about double the molecular mass of the previous generation. Dendrimers are taken up by the cell via endocytosis, encapsulating drugs "bound" with dendrimers within the cell. To eliminate the normal limitations of traditional treatment, good control over drug delivery is extremely beneficial. Polymer-based drug delivery has enhanced pharmacokinetics, sustained release of the drug, biodistribution, to the exact targeted site in recent years.[185] Because of their great water solubility,[186] polyvalency,[187] biocompatibility,[188] and exact molecular weight, dendrimers also received a lot of attention in biomedical application.[182] These characteristics make them an excellent carrier for drug administration and targeting. The biopermeability of dendrimers through biological membranes should be addressed when exploring them as drug delivery carriers.

1.9 Why it is important? What was the gap in this area to fulfill through our research?

Recently DAP (2,6-diaminopyridine)-derived amphiphiles have been used for self-assembly studies because of its inimitable symmetric depiction[189] such as their macrocyclic synthetic receptors and hydrogen bond motifs.[190]

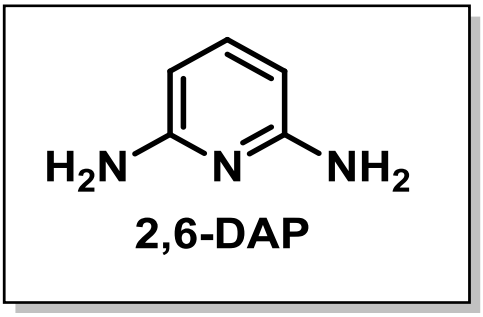

Figure 1.2: Structure of **2,6-DAP.**

Although, self-assembly studies of 2,6-DAP-derived amphiphiles have already been performed for potential applications in biochemistry, medicine and material science. These materials were self-assembled into solutions which gave various nanoarchitectures such as nanotubes, nanofibres and nano sheets[191,192] but gelation behavior has not been demonstrated yet. Considering the vast applications of gels in drug delivery and development processes, we have focused on synthesizing scaffolds that can self-assemble in various solvents without difficulty and can be easily scaled up.

1.10 2,6-diaminopyridine (2,6-DAP) derivatives and its applications

Heterocyclic chemistry is one of the major classes of organic chemistry and is immensely used in biological and industrial applications. . In medicinal chemistry, the heterocyclic nucleus has an important functionality and is thus used to make various therapeutic drugs. In the past century, any researchers have shown their interest in the nitrogen-containing heterocyclic compounds, and 2,6-DAP is the utmost research moiety. Most reported derivatives of 2,6-DAP are Schiff bases, an important biological active compound with various applications in organic chemistry. Much work has been done on the synthesis of transition metal complexes with Schiff base ligands, which are used in various catalytic, industrial and biological activities. Complexes of a variety of Schiff bases with transition metals were found to have antibacterial,[193] antifungal,[194] cytotoxic,[195] antiviral,[196] antioxidants,[197] anti-cancer,[198] anti-mitogenic,[199] and anti-inflammatory [200] activities. An intensive research in biologically active heterocyclic analogues is going on, and a lot is yet to be explored.

1.10.1 Structure and biological activities

2,6-DAP is a heterocyclic compound with important biological activities features. The planar structure of 2,6-DAP has a C_{2V} symmetry, and the Raman and the infrared

spectra of the molecule lie between 250 and 4000 cm^{-1}.[201] A neutron diffraction study carried out at 20K reported the compound to be orthorhombic.[202] 2,6-DAP has gained importance because of its N-donor ligand property which involves it in a class combining N- heterocyclic and primary aromatic amines. The ring nitrogen atom in 2,6-DAP has a localized pair of electrons, making it an important moiety for chelation. Incorporation of metals in form of complexes showed high degree of biological activities. Schiff base metal complexes have exceptionally attracted researchers for their physical, chemical, and biological properties. Some arylated azotized diaminopyridines were suitable for the treatment of germ infections produced by various cocci.[203] New compounds having bactericidal properties were prepared by condensing 2,6-DAP or its derivatives with aliphatic aldehydes.[204] 2,6-DAP is found as a common intermediate in the synthesis of aromatic azo chromophores, which are widely found in the hair-dyes[205] and pigments industry because of the photostabilization of the intermediate. 2,6 -DAP is extensively used in medicines and is an essential intermediate for the treatment of urological system in form of phenazopyridine hydrochloride.

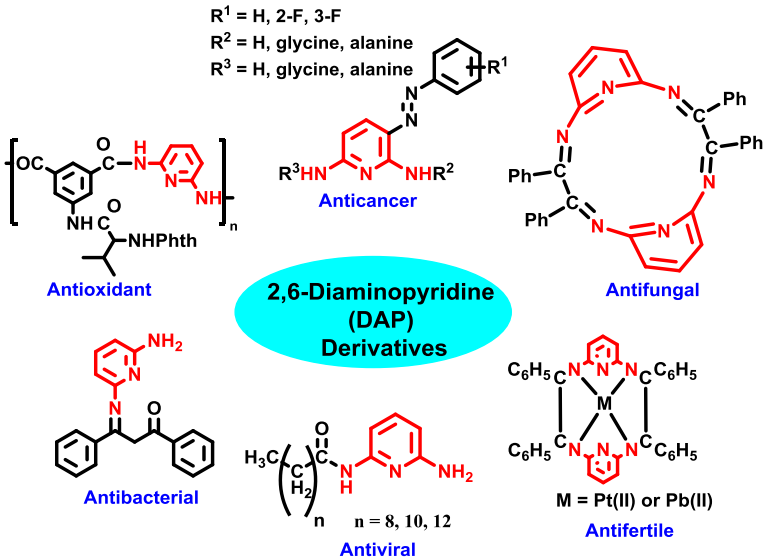

Figure 1.3: DAP-Derived Biologically Active Molecules

This literature survey shows that 2,6- DAP derivatives show various pharmacological activities such as antibacterial,[206] antifungal,[207] antiviral,[208] antioxidant,[209] anticancer,[210] antifertility,[211] and other activities.

1.11 Self-assembling

Thread-like self-assembly of LMWGs (low molecular weight gelators) on a nano-meter scale in several aqueous and organic solvents is a topic of interest because of their capability for functional materials.[212-227] The interactions involved in 1D (one dimensional) thread-like self-assembly of gelators are generally lipophilic interactions,[219] H-bonding,[213-217] dipolar,[220] interactions and aromatic π-π stacking.[218] However, H-bonding interaction is the most often used interaction for designing gelators. Yabuuchi and co-workers[228] synthesized bis-urea gelator having pyridyl moiety as shown in **Figure 1.4**, which effectively gelates common liquid crystalline and organic solvents with the formation of extended self-assembled threads in solvents.

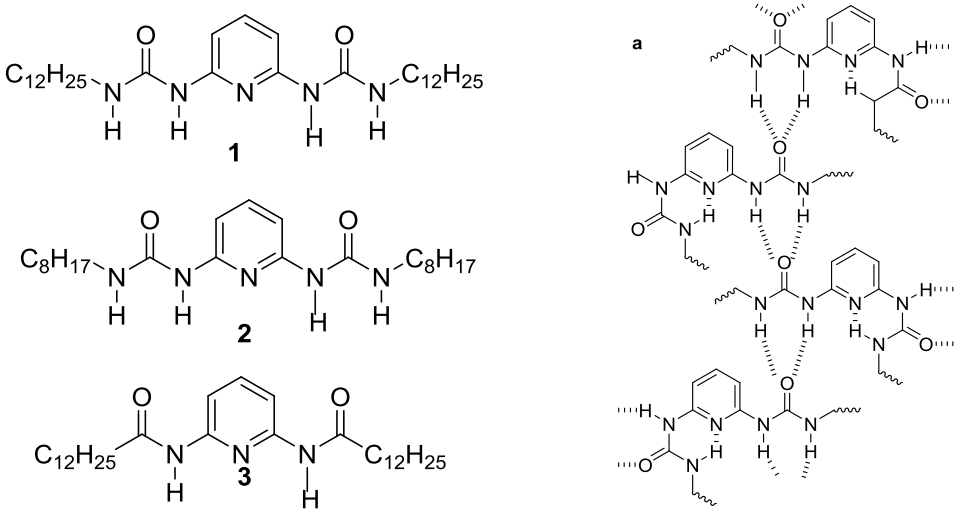

Figure 1.4: Bisurea compounds and a diamide compound.

Urea compounds have 1D molecular assembling properties and can form bifurcated H-bonds,[229] while pyridyl compounds are used in generation of supramolecular

materials.[230] ^{1}H NMR measurements and X-ray crystallography revealed that one of the urea units was involved in forming bifurcated intermolecular H-bonding by forming intramolecular H-bonding with the pyridyl nitrogen. There are many urea gelators that are synthesized by Hanabusa,[215] and Hamilton and their co-workers. It has pointed out that bis-urea gelators are not only good gelators for gelation but also worthwhile element of functional soft materials. Moreover, liquid crystalline gels obtained from pyridine base gelators exhibit good electro-optic properties.[224,225] Gupta and coworkers reported that the DAP-derived fatty acid amide systems self-assemble in solution and form nano/ micro architectures among hydrophobic domains get entry into the cells. They reported nontoxic behavior of sheets to the cells which makes them safe drug delivery agents to deliver drug molecules, therefore they have various applications in pharmaceuticals.[191] There are some other previous studies have been done by using the DAP derivatives in self-assembly, having monosaccharides head group forming nanotubes for molecular recognition.[231]

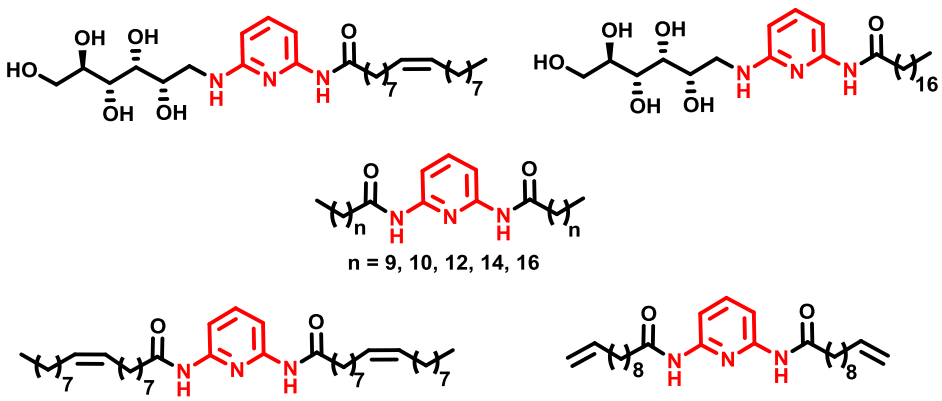

Figure 1.5: 2,6-DAP derivatives showing self-assembling behavior.

1.12 References

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