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A Review on Polymeric Nanoparticulate Hydrogels and its Drug Delivery

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Abstract

Nanocomposite hydrogels makes itself a crucial role in the field of pharmaceutical sciences along with other fields and it is one of the hybrid materials formed by combining both nanotechnology and material science. Various nanoparticles or nanostructures have installed into the hydrogel network to create these kinds of hydrogels, which aim to mitigate some of the benefits' disadvantages. Based on the composition of their nanoparticles, the nanocomposite hydrogels discussed here are divided into four categories: those containing carbon, those including polymers, those containing inorganic materials, and those containing metals. For a variety of tasks, different varieties are best due to their individual characteristics. The development of desirable qualities for intended applications and the strengthening of connections between nanoparticles and polymeric chains are mostly responsible for this trend. This research focuses based on use of nanocomposite hydrogels specially in drug delivery, as well as the most recent methods developed to address their limitations.

Keywords: Nanocomposite Hydrogel; Polymeric Nanoparticles; Carbon Nanotubes; Metal and Meta Oxide Nanoparticles

Introduction

Nanotechnology along with the combinations of other streams of science has gained attention during the past decade. Many strategies exist for combining nano-scale and traditional technologies in the pursuit of superior material production. Nanoparticulate hydrogels is one of the hybrid materials by combining both nanotechnology and biomaterial science [1]. Loading nanoparticles into hydrogels reduces the likelihood of risks to health and the ecosystem, which is most important aspect of nanoparticles' application. The idea behind the novel combination of two variables materials was to achieve not just structural diversity but also several property benefits. Such property makes the nanoparticle hydrogel in improved mechanical strength and stimuli-responsive [2]. Overall incorporation of two various materials into a formulation having unique properties that even one of the materials can't be achieved individually [3]. The loading or incorporation of nanoparticles into hydrogels has been designed for the purpose of improving the properties like optical and mechanical. For example, adding magnetic NPs to hydrogel particles makes them easier to separate and recycle [4].

Nanoparticle-loaded hydrogel system

NPs are colloidal structures made specifically for carry medications over barriers. Between 100 and 200 nm is roughly where they operate at their best size. They provide a sustained and localized release while extending the half-life, enhancing bioavailability, and protecting medicines from degradation. Additionally, its surface might be altered for targeted distribution, which would lessen side effects and the toxicity of the medications brought on by systemic absorption. Due to their great uniqueness, polymeric NPs have been a popular choice among them as DDS in many biological applications. These NPs' ability to encapsulate medications that are both hydrophilic and hydrophobic is another benefit. Additionally, by changing their composition or surface charge, one may control their loading capacity, drug release kinetics, and biological function. The persistence of these NPs at location until full drug release is unknown, although they prone to premature burst release of medicines [5].

To make a hydrophilic substance with a gel-like macromolecular structure, natural or synthetic polymer chains are woven together and crosslinked. They may be up to 99% water or biological fluids and can grow to several times their dry weight. This highly hydrated, (3D), porous network can simulate the microenvironment of native tissues, and it is frequently used to store, release, or collect molecules.

Depending on the technique of manufacture, these types of gels can be differentiated into two categories: chemical (thermosetting) gels and physical (thermoplastic) gels. There are many ways to covalently cross-link chemical gels, such as by heating, ultrasonication, ultraviolet (UV) or irradiation, polymerization in the presence of a cross-linker, or cross-linking an already-existing polymer. Hydrophilic polymers form an amorphous network in physical gels, hold together by weak bonds like hydrogen bonds and van der Waals forces. On the other hand, chemical gels swell but do not dissolve in water, while physical gels can be melted by applying heat. Hydrogels are substances that are very water-retentive and have excellent solute permeability. They have the capacity to store molecules in very effective manner and gradually releasing the drug may leads to less toxicity in the remaining tissues. However, there are a few limitations to the use of hydrogels as effective drug delivery. These gels have poor mechanical qualities; for instance, after swelling, their mechanical property falls.[6]

Table 1: Polymer Source

Natural polymers[3]	Synthetic polymers[5]
Alginate	Polyacrylamide
Chitosan	Poly (hydroxyethyl methacrylate)
Collagen	Polyvinylpyrrolidone
Gelatin	Poly (vinyl alcohol)

Hydroxypropyl methylcellulose (HPMC)	Poly (ethylene Glycol)
Hyaluronic acid (HA)	Poly-ε-caprolactone

Incorporation of Nanoparticles into Hydrogel

Different approaches can be used to incorporate NPs into hydrogels. Adding NPs to (a) Previously developed hydrogels; (b) subsequent gelation of polymer solutions, with or without the introduction of NPs as cross-linkers; or (c) monomer solutions prior to co-crosslinking polymerization. Additionally, there are methods for growing the NPs from precursors included into the polymer network.

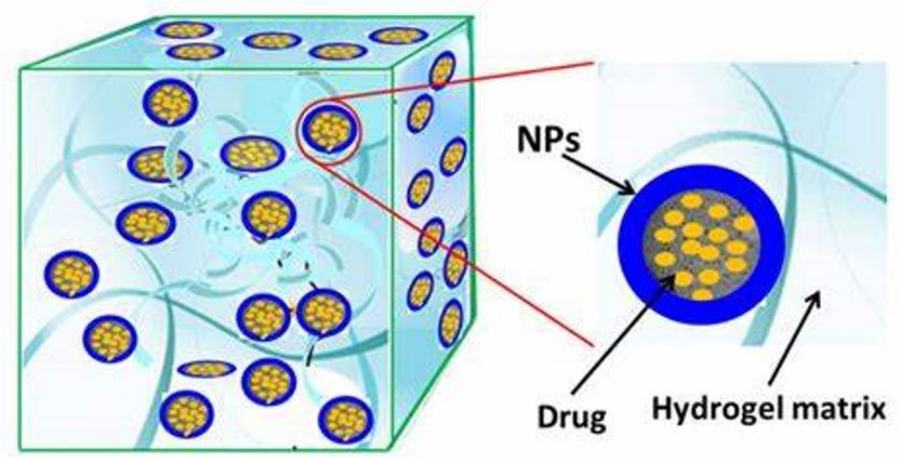

Figure 1: Presence of nanoparticles in the hydrogel

Nanoparticle Addition to Pre-Formed Hydrogels

The process of adding NPs can be broken down into two types: in situ conversion, in which NPs are synthesized utilizing polymer networks as scaffolds, and hydrogel addition, in which NPs are added already formed as shown in the figure 1. In each of the polymer voids, an NP may theoretically be grown using the microgel structure (who's dimensions are thus modulatable via cross-linking density). NPs can be employed, for example, to control drug burst release when other components, such as medicines or tiny proteins, are put in the gels in addition to the NPs. The microgel can be made sensitive to changes in temperature, light, or pH by studying the composition of the polymer network [7] [8].

Since NP aggregation prevented the polymer film from forming in the presence of NPs, this method was adopted. It is hypothesized that the NPs stay inside the gels are submerged in acetone and begin to de-swell because of the physical entanglements and collapse of the polymer chains. According to the authors, each breathing cycle resulted in an increase in the NP concentration inside the gel, and the NPs were evenly distributed throughout the film. Although loss of NP from hydrogel may take place over time in aqueous solution, it was unclear if such systems are stable in that environment. In order to Create a microgel from colloidal gold and poly(N-isopropylacrylamide) (PNIPAm), a different method was used. This method involved centrifuging the microgel particles with the NPs, removing the supernatant, and then gently heating, agitating, and sonicating cycles to redisperse the Gold particles throughout the microgel pellet. Light exposure has the potential to further modify the resulting composite; researchers have looked into the possibility of local heating and subsequent local deswelling in the PNIPAm microgels as a result of the absorption of light by the Au plasmons. The network's mesh size at different cycling settings and how will mesh size is influenced by the molecular parameters can be determined, even though the method appears to be working. This could provide more fundamental understanding of the NP incorporation-through-breathing procedure. Such a method may provide more fundamental understanding to the design of NP-hydrogel composites by enabling designers to better manage the efficiency of the integration process and the leaching of NPs through altering the size of NPs in proportion to the mesh size of the

network [9].

NP Addition to Polymer Solutions Before Network Formation

Iron oxide NP—hydrogel composites are prepared using the previously discussed synthesis approaches, which include in situ synthesis of NPs in a prefabricated hydrogel network. Other approaches include iron salts are combined with the polymer chains or the chains are cross-linked before being added to the pre-formed NPs to generate both NPs and a network while cross-linking the polymer chains [10]. Various approaches have been established within the former. The simple process of NP addition to solution polymerization then gelation can be used. for instance, Instantaneous gelation was used to create hybrid gel particles, which involved mixing the three components' aqueous solutions first before dripping the mixer via needle into a bath of sodium hydroxide. In order to remove dyes from aqueous solutions at a cheap cost, and the addition of the magnetic NPs enables magnetic fields to separate and recycle the gel particles [11].

The report did not explain the technique used to keep the NPs contained within the gel. After combining POSS and CMC, the pH was gradually lowered by the hydrolysis of the additional D-(+)- gluconic acid -lactone, which, according to the scientists, caused the hybrid network to develop as a result of hydrogen bonds forming between POSS-NH2 and CMC. It is not apparent if the connection of CMC with POSS-NH2 is caused by hydrogen bonding. As the pH is reduced, it is anticipated that the presence of charged COO- groups will make it easier for the NH2 groups in the POSS to protonate, and vice versa [12]. In fact, it has been discovered that the pKa of these groups changes considerably when they are in the presence of macromolecules with opposite charges, and they can retain a charge over a larger pH range than pure substances. Recent research, but hints that electrostatic interactions between the CMC and the POSS NPs may still be responsible for the development of a polymer network. Instead of firmly engaging with one (or few) NP(s), which results in the creation of neutralised big complexes, the polymer chains will likely engage with and bridge numerous NPs, establishing a network, when the pH is increased (precipitate). Poly (sodium acrylate) (PANa) grafted with monomeric groups that demonstrated low critical solution temperature behaviour in water (N-isopropylacrylamide, NIPAm) and SiO2 NPs were mixed to construct hybrid networks. In spite of the electrostatic repulsions between the PANa backbone and the silica NPs, the formation of hybrid networks with viscoelastic properties similar to those of covalently cross-linked gels was observed [13][14].

Monomer Polymerization in the Presence of Nanoparticles

The most popular method to include NPs into polymer networks is most likely the network formed by polymerizing monomers, with the help of pre-made NPs is present. According to one theory, polymerization begins at the clay's (big) surface, which, when it diffuses through the solution, forms a network with clay particles acting as cross-links and has a diameter of 20–30 nm and a thickness of 1 nm. Hydrogels that are physically composites because to the interaction of polymers and NP but lack a cross-linker [15]. With the goal of enhancing the gels' mechanical properties, this technology has been expanded to create composite hydrogels consisting of modified clay particles, spherical silica, or titanium oxide NPs. This can be done both with and without the use of cross-linker agents. This method has been investigated for the creation of hydrogel composites incorporating sheets of metal-oxide at nanoscale scales in addition to inorganic clay and metal nanoparticles (nanosheets, NSs). The two-dimensional nanomaterials known as NSs have recently been studied. They have a variety of unusual chemical, physical, electrical, and optical properties, as well as unusually large aspect ratios [16]. Intriguingly, NSs can also act as reinforcing fillers and add functionality to hydrogels. Hydrogels can be made using photo-initiated free-radical polymerization even in the absence of cross-linkers; nevertheless, cross-linkers significantly increase the gels' mechanical strength [17]. This dampening is attributed to the stability of the colloidal products as a result of either depletion or an increase in the effective viscosity of the synthesis media [18].

Aside from the fact that NPs and hydrogels are both biocompatible, biodegradable, and non-toxic as individual offers advantages that each one could obtain on its own. Both NPs and hydrogels are capable of drug loading. This gel inhibits the NPs from aggregating, shields them from deterioration, and aids in the localization of medication delivery when used together. Hydrogel

mechanical characteristics, including as strength, stiffness, and degradation, can be improved by adding NPs in a concentration-dependent manner. Additionally, NPs may crosslink the hydrogel and strengthen the hydrogel's ability to respond to stimuli. Although hydrogels and NPs can increase the bioavailability of medicines and slow their release over time, their combination creates a depot at the administration site that prolongs local drug retention. With the help of this dual delivery method, pharmaceuticals are double-encapsulated, drug release kinetics are controlled, and the initial burst release is avoided. Additionally, it can encapsulate both hydrophilic and hydrophobic medications [19].

Types of NP-Hydrogel Composites

Nanoparticles and hydrogels are creatively combined to provide synergistic, distinctive, and possibly valuable qualities. The type of nanoparticles used in the composites determines its properties, which in turn are influenced by the intended use for the created composite. Below are descriptions of various nanoparticle-hydrogel composite kinds, along with the corresponding properties and uses [20].

Polymeric NP-Hydrogel Composites

Numerous applications have called for the development of polymeric NPs. These polymer particles themselves have numerous functional groups, thus adding them to a hydrogel makes it more versatile which is shown in the figure 2. There are numerous designs with biological uses, such as medication delivery and biosensing. The physical inclusion of poly amidoamine dendritic NPs improved the biological stability of collagen according to Zhong et al. Since there were so many interconnections within the hydrogel network as a result of this physical integration, the mechanical characteristics were improved, which in turn led to an increase in the proliferation of human conjunctival fibroblasts [21].

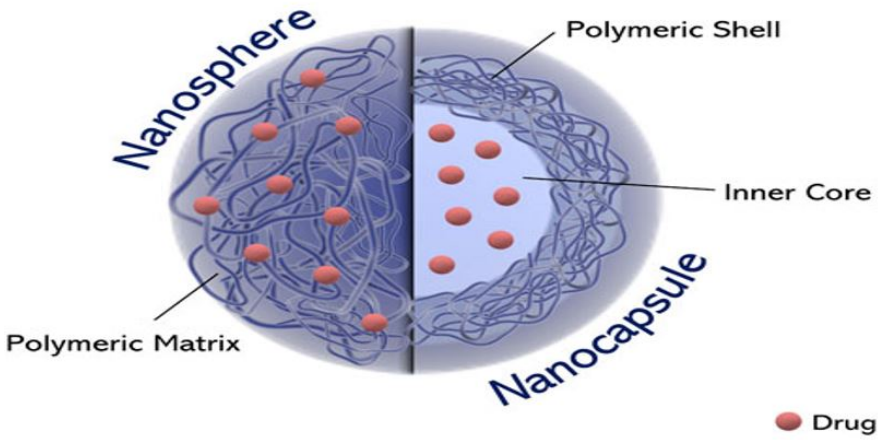

Figure 2: Polymeric Nanoparticle

Dendrimers/Hyperbranched polymers

Dendrimers, due to their highly branched porosity structure and the abundance of functional groups towards their periphery, are particularly well-suited applications give them a high degree of reactivity and loading efficiency. The concentration of dendrimers affects the hydrogels' stiffness, degradation characteristics, and hydration kinetics. High stress absorption capability is demonstrated by the resulting dendrimer-containing nanocomposite hydrogels. There was a dramatic rise in the synthesis of type II collagen and proteoglycans is seen, and the globular morphology of the chondrocytes enclosed within the hydrogel nanocomposite is preserved [22]. Another study found that alterations to wettability and surface form, as well as the introduction of new functional groups, significantly improved cell adherence and proliferation in collagen-grafted nanocomposite films. It has been noted that the hydrophobic structure inside the holes of photocrosslinkable hyperbranched polyester (HPE) hydrogels allows them to encapsulate hydrophobic medicinal molecules. As the HPE concentration rose, hydrogels with an exceptionally porous

and interconnected structure were created by functionalizing HPE with photocrosslinkable acrylate moieties, structurally tough network, and improved fibroblast adhesion on the surface [23].

Liposomes

Liposomes are tiny bubbles made from the same material as cell membranes (phospholipids). Disrupting a bilayer or monolayer of membrane phospholipids causes them to reconstruct into tiny spheres smaller than a typical cell. Liposomes make up the bilayer structures as shown in Figure 3. Micelles are the name given to the monolayer formations. Liposomes have hydrophilic surfaces and cores but hydrophobic outer layers. Consequently, they can hold molecules that are either hydrophobic or hydrophilic, such as pharmaceuticals, bioactive compounds, nucleic acids, and genes. To deliver drugs to their target region, drug-loaded liposomes can be mixed with a matrix or carrier, such as a biodegradable polymer, and then crosslinked to form a nanocomposite hydrogel [24].

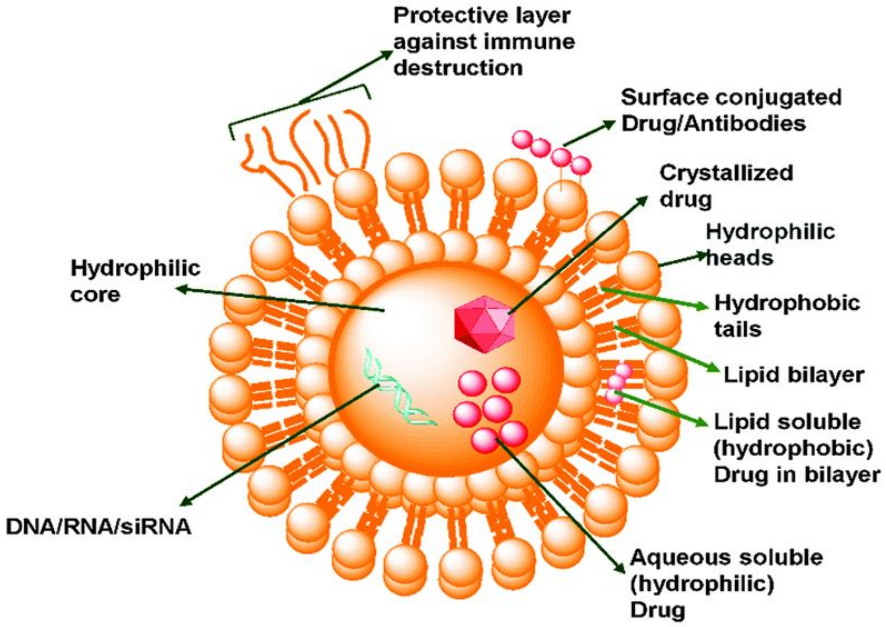

Figure 3: Liposomes integrated with drugs

Carbon-based nanocomposite hydrogels

C nanomaterials with potential for use in biomedicine include carbon nanotubes (CNTs), graphene, etc. The strong characteristics of CNTs and graphene in particular make them very popular materials. CNTs are carbon (graphite)-based hollow cylindrical. The only way that CNTs differ from graphite is by a very small proportion. The wide range of precise distances resulting from the Van der Waals forces is a characteristic of CNT. Ions of all shapes, charges, and sizes can easily enter CNT pores. These nanomaterials are suitable for building electrically conductive tissues, such as nerve, muscle, and heart tissues, because they possess these characteristics [25].

Carbon nanotubes

Carbon-based compounds' interactions with hydrophilic polymers are constrained by their hydrophobic character as shown in the figure 4. Because of this, CNT surfaces are either grafted with various polymer chains or changed with a variety of polar groups in order to increase the dispersion of the CNTs. Hydrogel networks can benefit from the reinforcement provided by CNTs, which can also, in some situations, adapt the hydrogel to react to heat and electricity. Hydrogels composed of poly glycerol sebacate are strengthened by the addition of 1% CNTs. The PGS's hydroxyl groups combine carboxyl groups on COOH-functionalized CNTs to form an ester. Here, the CNTs serve as both covalent and physical crosslinkers. When compared to pure PGS, the tensile and

compression modulus are significantly higher due to CNTs and polymer chains can form covalent crosslinks, maintaining the network's flexibility [26].

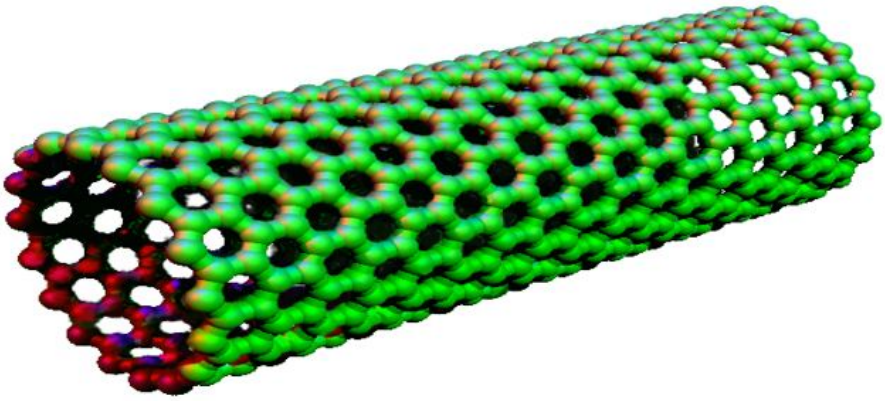

Figure 4: Carbon Nanotubes

Inorganic-based nanocomposite hydrogels

The majority of these nanoparticles, including nanohydroxyapatite are important minerals for healthy tissue activities. Especially for applications involving bones, these various forms of ceramics are widely used in implantable materials[27].

Ceramic Nanoparticle-Based Nanocomposite Hydrogels

Inorganic ceramic nanoparticles and organic or synthetic polymeric hydrogels can be combined to create a variety of sophisticated NCHs. Many other bioactive nanoparticles can be employed for this purpose, including HAP (hydroxyapatite), artificial silicate nanoparticles. Due to their great mechanical strength and the fact that they are composed of minerals that are essential for maintaining normal homeostasis, ceramic nanoparticles can reinforce the hydrogel and also supply the final NCH with beneficial biological cues. These two qualities make them particularly well-suited for use in the various fields. These characteristics of ceramic nanoparticle-based NCHs are crucial for regenerative medicine applications that have competing requirements for hard tissue creation [28]. In spite of their appealing qualities, while natural scaffolding has many desirable properties for usage as scaffolding, limiting usefulness. However, because PEG and other synthetic hydrogel materials are bio-inert, they can't foster the conditions necessary for cells to stick together and tissues to form. As a result, some form of bioactivation technique is necessary. In both situations, using these nanoparticles to produce NCHs can help to meet these demands [29].

Nanocomposite hydrogels comprised of metal and metal oxide

Metal and metal oxide nanoparticles have shown promise as a novel class of biomaterials due to their fascinating properties, such as antibacterial , sensitivity to various stimulations. The main parts of metallic nanoparticles are noble metals like platinum (Pt), gold (Au), and silver (Ag)[30]. Metallic nanoparticles can give NCHs antimicrobial activity because they can bind to bacterial membranes in a non-specific way and cause structural changes in bacteria that make membranes more permeable. Nanoparticles made of metals or metal oxides are also renowned for their electrical conductivity, ferromagnetism, and semi conductivity [31]. NCHs containing silver nanoparticles have garnered considerable interest in the context of antimicrobial materials due to their potent antibacterial action. Wound and burn dressings, as well as dental filling applications, have used Ag-based NCHs as the functional covering to prevent infection. To acquire antimicrobial capabilities that are generally non-toxic to healthy cells, metallic nanoparticles have been incorporated within the hydrogel matrix using a wide variety of naturally occurring substances, as well as synthetic substances [32]. When these tissues were electrically activated, the cells constricted in unison. These hybrid matrices allowed for the growth of tissues that were both thicker and more symmetrical than those grown on pure alginate. The bioactivity of hydrogels can also be improved by NCHs that contain metal oxide nanoparticles.In particular, osteoblast adhesion and

proliferation can be improved by HAP and titania nanoparticles encapsulated in a polymeric matrix made of PLGA. Nanocomposite hydrogels based on metals or metal oxides are being studied for a variety of other purposes, including sensing, diagnosis, actuation, and controlled medication release in response to external stimuli. [33]. In instance, the nanoparticles included into the hydrogel network produced heat when subjected to an external magnetic field causing the polymer chains to change from coil to globule and releasing therapeutic chemicals from the hydrogel nanocomposite. It has also been used to create light-responsive hydrogels, which can be used for medication delivery and tissue regeneration. Nanoparticles' response to electromagnetic stimuli has been applied to this process as well. The photodegradation of the hydrogel and subsequent release of the encapsulated medicines take place when it is exposed to 980 nm light. The quick nature and ease with which it can be supplied makes the stimulus of light quite intriguing as well. For drug delivery and cell instruction, one can use a light-responsive substance. The activation of the polar groups in CHI strands due to nanoparticle dispersion in CHI under a near-infrared light improves tissue adherence [34][35].

Routes of Drug Administration

Topical	EpidermicIrrigationInstillation [26,31]
Enteral	OralSublingualRectal [23,27]
Parenteral	Local InjectionIntravenous injectionSubcutaneous injectionIntradermal injectionIntramuscular injection [12]
Inhalation	NebulizationVaporizationGas inhalation [29]

Topical

The topical method entails taking medications through the skin and mucous membranes, including the eyes or vagina. High patient compliance is attained by the topical application because it is easy to use, painless, and non-invasive. Additionally, it enables the administration of more medications at the required spot. This route bypasses liver, increasing medication availability in body fluids and therapy effectiveness. Each mucosa's limitations determine this route's downsides [36]. The skin acts as a barrier and has an pH (4.2–5.6), necessitating high level of moisture, potentially limiting the penetration of medications. Drug retention at the ocular tissue is low as a result of frequent drug loss caused by the eyes' aqueous environment and tear drainage. Furthermore, a treatment that is ineffective is caused by the drug's inadequate bioavailability. Degradative enzymes and vaginal fluid diminish the effectiveness of vaginal administration, lowering the medicines' bioavailability and residence length [37].

Enteral

Drugs administered by the oral, sublingual/buccal, and rectal routes are absorbed via the gastrointestinal tract when administered via the enteral route. The most popular method of drug administration for ambulatory patients is oral. For regular treatments that need for repeated intakes, this method is practical [38]. The therapeutic impact is compromised by various restrictions, notwithstanding the administration's simplicity, safety, economic benefits, and ease of use. The concentration of the drug is greatly reduced before it reaches its action site for the reason of unfavourable medication pharmacokinetics and pharmacodynamic characteristics like low oral absorption, low bioavailability, and enzymatic degradation. Poor drug targeting, which is another drawback of this mode of delivery [39].

Parenteral

Drugs delivered by the parenteral method often involve an injection and directly enter the systemic circulation. For medications with poor gastric solubility and stability, this method is recommended. The most popular injectable types include

(A) intravenous, in which medications are quickly injected into the systemic circulation effect;[36]

(b) intramuscular, in which the medication is injected directly into the muscle, which, because of its high blood circulation, which increases medication absorption; and

(c) Subcutaneous, in which the pharmaceuticals are injected into the subcutaneous tissue, which offers a slower absorption of drugs due to its lesser vascularization than intramuscular injection and is suited for therapies that call for repeated injections [40].

Drugs can, however, also be injected intradermally, intraperitoneally, intrathecally, or locally to give them. These pathways are constrained by systemic toxicity and consequent side effects that depend on the medications [41].

Inhalation

The inhalation technique encompasses local and systemic therapy via the nasal, gas inhalation, nebulization, vaporization. Due to their enormous permeability and wide surface area, the medicines are quickly absorbed into the respiratory epithelium. Additionally, in the event of pulmonary issues, this route offers a target delivery [42]. Inhalation has less systemic negative effects than other methods of delivery. However, factors such as the drug's size, mucosal turnover, and nasal epithelium, which reduces the drug's nasal residence time, may affect the drug's efficacy when inhaled [43].

Conclusion

NP-hydrogel systems, in the last few years have attracted a lot of attention because of certain promising potential uses. The creation of nanocomposite hydrogels has been suggested in a number of various approaches, from the addition of NPs to preexisting hydrogel networks to the one-pot synthesis of both NPs and hydrogel. Nanogels, which have been investigated for use in applications such as medication administration, can also be used to coat the nanoparticles.

The interlinkage between the NPs and the network of macromolecules that are not covalent are what cause nanocomposite hydrogels to form. In order to create systems with desirable properties, it is crucial to understand the intermolecular interactions that are happening between the macromolecular network and the surface of the NPs. If charged groups are present, it's possible that electrostatic are at work in the interactions between NPs and polymers. If monomers are, for example, methylated, impact on water repellency may be substantial factor concerning the adhesion of polymers to surfaces. Numerous studies contend that hydrogen bonds are what cause association, however hydrogels in water may not be particularly affected.

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