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Review Article

Promising Approach of Nano Drug Delivery System: Herbal Nanogel

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Abstract

In recent years, there has been a growing research interest in achieving controlled and sustained drug delivery using natural and biocompatible components. However, many herbal constituents face challenges related to their pharmacokinetics and pharmacodynamics. To address these issues, various innovative techniques and comparisons have been explored to enhance the use of herbal remedies in the pharmaceutical market. This review paper focuses on the fundamental aspects of nanogels, including their methodology, drug-loading techniques, release mechanisms, and their applications in the herbal medicine industry. Nanogels are defined as hydrogel nanoparticles composed of cross-linked hydrophilic polymers. They possess a high capacity for loading drugs and exhibit excellent permeation properties due to their small size. Nanogels can be administered through various routes, such as oral, nasal, parenteral, pulmonary, and intra-ocular, making them a preferred choice for herbal medicines due to their stability and ease of use. Nanogels represent a promising and innovative approach to herbal drug delivery systems, often referred to as future-generation drug delivery systems. They offer advantages such as high drug encapsulation capacity, uniformity, minimal toxicity, and enhanced stability.

Keywords: Herbal; Nanogel; Drug Loading Technique; Methodology; Evaluation

Introduction

Herbal medicine, derived from plant parts like leaves, roots, and flowers, is a traditional practice led by herbalists. It's defined as a therapeutic approach that predates modern medicine. Researchers study and apply herbal medicine, considering it an alternative treatment for various diseases, including cancer and diabetes. Herbal medicines have influenced modern pharmacology, favoured for their minimal side effects. Despite their efficacy, they face challenges like solubility and bioavailability. Optimizing their use can reduce doses and enhance accessibility, making them a cost-effective alternative to modern medicine. Curcumin is a widely researched herbal compound, especially in cancer studies. Herbal medicine, known for its therapeutic value and fewer side effects, has been practised globally for centuries, trusted by both physicians and patients. In recent years, nanogels have emerged as a promising vehicle for delivering and releasing medications to patients, representing a crucial dimension of nanomedicine, which encompasses the fusion of nanotechnology, medicine, and pharmaceuticals. Nanogels are crosslinked polymer networks that exist on a nanoscale and possess the remarkable ability to absorb substantial amounts of water [1]. Essentially, nanogels are hydrogels but at a size scale of 20–200 nm. Hydrogels themselves are polymer-based gels formed by linking polymer chains into a macromolecular network, a process that can be achieved through various methods [2]. These networks can encapsulate pharmaceuticals within their pores and subsequently release them as needed. Nanogels, on the

other hand, are a subset of hydrogels typically produced through emulsion polymerization.

Nanogels can be administered to patients orally, through pulmonary inhalation, nasal routes, parenteral injection, or intraocular application. The release of medications from nanogels can occur through different mechanisms, often involving a change in their internal properties triggered by external stimuli. This physical alteration, causing the polymer network to either swell or compress, facilitates the targeted delivery of the medicinal payload [3,4]. The source of stimulation can vary, originating either from the immediate physiological environment within the body or from an external stimulus. Internal-external factors like specific pH levels or alterations in temperature within a defined volume are commonly employed to induce physical changes, often referred to as the volume phase transition temperature. Conversely, external stimuli, such as light, are frequently utilized, initiating photochemical and photoisomerization processes that lead to the release of the drug or drug carrier [3,4]. Nanomedicines have demonstrated considerable potential in enhancing the bioavailability of various chemical and herbal bioactive compounds [5]. Nanogels, classified as nanomedicine products, offer exceptional stability, high drug-loading capacity, biological compatibility, effective penetration abilities, and responsiveness to environmental stimuli. They have found applications in diverse sectors, including gene delivery, chemotherapy drug delivery, diagnostics, organ targeting, and herbal medicine delivery [4]. In recent times, nanogels have played a significant role in biotechnology, particularly in genetic research, protein synthesis, and enzyme immobilization, presenting innovative treatment possibilities in the field of medicine [6]. Additionally, a specific type of nanogel, known as amphiphilic nanogels, is notable for its capacity to load drugs effectively using aggregation and sedimentation processes [7]. The primary objectives of next-generation nanogels revolve around ensuring safer and more effective drug targeting and even showcasing potential applications in tissue engineering [8].

Mechanism of action

Many herbal drugs face limitations, including difficulty reaching the target site, the need for high drug concentrations, low bioavailability, and poor absorption [9]. Nanogels offer an ideal delivery system for herbal drugs due to their enhanced permeability, bioavailability, high drug loading capacity, biocompatibility, and the ability to accommodate both hydrophilic and hydrophobic drugs.

Nanogels designed for targeted drug delivery, particularly in transdermal systems, are of great interest. These smart carriers support both passive and active permeation. Passive targeting relies on passive diffusion and accumulation through the Enhanced Permeability and Retention (EPR) effect, while active targeting involves specific interactions with certain cells, facilitated by the surface coating of the nanogel. For instance, polyNIPAM-based nanogels have demonstrated effective penetration through the skin's epidermis at body temperature [10].

There are several processes by which medicines are released from nanogels at the site of action [11]:

- Simple drug diffusion from the nanogel
- Nanogel degradation
- pH-triggered release
- Ionic exchange with the environment is factor
- External energy sources are factor

Drug release from nanogels can occur through various mechanisms:

- **Diffusion:** In this scenario, the medication moves from a region of higher concentration within the gel to a region of lower concentration outside the gel. For instance, a polymeric nanogel made of poly(ethylene glycol) and poloxamer releases the anticancer medication doxorubicin over the course of more than a week through sustained diffusion. Drug breakdown is slowed down by hydrophobic interactions during encapsulation [12].
- **Degradation:** Nanogels can be made to break down, which promises lesser toxicity and prevents unintended drug accumulation when given repeatedly. The polymer's backbone contains cleavable linkages that can degrade in reaction to particular reducing agents, pH changes, or enzyme activity.
- **pH-Stimulated Release**: Some nanogels have cationic or anionic groups suspended from their polymer structure. Electrostatic repulsion and pore enlargement occur within the gel as a result of these groups ionising at specified pH and ionic strength levels. As a result of the process' increased water inflow, the medication is released and the nanogel swells.
- **Thermosensitive Release**: Poly(N-isopropyl acrylamide) is one example of a thermosensitive nanogel with a lower critical solution temperature (LCST). Hydrogen bonding between the polymer and the water below the LCST cause hydration.

Hydrophobic interactions become more dominant as the temperature rises, breaking hydrogen bonds and releasing the medication into the environment [13].

- **Ion Exchange**: Drug release can result through ion exchange between negatively charged particles on cell surfaces or in the environment and negatively charged pharmaceuticals contained in cationic nanogels.
- **Photosensitive Release**: When exposed to UV light, certain molecules or chromophores in nanogels go through cis-trans isomerization. The hydrophilicity of the molecule is altered by this modification. This change can be reversed by light or temperature, which starts the release of the medication. A chromophore molecule linked to the polymer's backbone and photothermal effects are involved in energy-triggered medication release. The nanogel transforms light energy into heat energy when exposed to light at its resonance wavelength, resulting in a volume phase shift and medication release into the environment [14].

Advantages of nanogel [15]

- Smaller quantities of the drug suffice for effective treatment.
- Offer protection against the natural degradation of drug molecules within the body.
- Nanogel size can be tailored to match the specific delivery molecule.
- Alleviate the harmful effects of drugs.
- Nanogels possess the capability to traverse physiological barriers like the skin and the blood-brain barrier.
- Nanogels loaded with medication can be safely introduced into the body with no adverse consequences and are also suitable for topical application.
- Easily adaptable for large-scale production and follows a biocompatible formulation approach.
- Well-suited for a diverse array of bioactive compounds, encompassing proteins, antibodies, peptides, and more.

Characteristics of nanogel

- Targeting
- Low level of toxicity
- Controlled and sustained delivery [15]
- High encapsulation [16]
- Size control
- Biocompatible and degardable [17],
- Higher capacity of drug loading [18],
- Swelling in aqueous
- Stimuli activated by nanogel like pH stimulated [19], temperature-sensitive [20], enzyme responsive [21], multi responsive [22].

Techniques of drug loading in nanoogels

Controlled self-assembly [23]

With polyelectrolyte-based nanogels that spontaneously self-assemble when exposed to oppositely charged molecules including surfactants, polynucleotides, proteins, and synthetic polyions, controlled self-assembly involves non-covalent drug conjugation [23]. A method similar to covalent conjugation is used in non-covalent drug conjugation, where the drug release can be influenced by outside variables. Disulfide bonds frequently help this method by allowing medications to connect with nanogels and release the drug when activated. Disulfide cross-linked nanogels have a high drug loading capacity, especially for medicines like Paclitaxel and Doxorubicin that are susceptible to variations in pH and temperature [27]. In an aqueous environment, amphiphilic compounds quickly self-assemble nanoparticles, improving drug interaction and release from the nanogel. The hydrophilic portions of the drug molecule are exposed to the polar or aqueous medium in this structure, while the hydrophobic portions are contained within the core.

Physical entrapment [24-26]

Ionic, lipophilic, and hydrogen bonding are examples of non-covalent interactions that might result in drug entrapment inside nanogels [24]. For instance, cholesterol-containing hyaluronic acid can self-assemble into nanogels, allowing for continuous protein delivery after injection. The encapsulation of curcumin in chitin nanogel for the treatment of skin cancer is an illustration of hydrogen bonding. Due to its biocompatibility, biodegradability, skin-friendly qualities, availability, and affordability, chitin is preferred for the synthesis of nanogels. It is capable of forming polyelectrolyte complexes thanks to the abundance of its -OH and -NHCOCH3 reactive groups. Skin penetration is facilitated by the positive charge of chitin and the lipophilic properties of both chitin and curcumin. Despite the fact that nanogels are hydrophilic, it is preferable to achieve a hydrophilic-lipophilic balance in the chitin-curcumin nanogel. Through its terminal -OH group and the -OH and -NHCOCH3 groups in chitin, curcumin interacts end to end with chitin.

Covalent conjugation [27]

Due to their intrinsic functional groups, which are crucial in determining the structure and capabilities of nanoparticles, nanosystems provide an effective method for drug administration. The overall stability of the drug contained is improved when the medication is covalently attached to the cross-linked nanogel. Polysaccharides have hydroxyl groups that easily interact with other hydroxyl groups, frequently by forming ester bonds with the drug's carboxyl groups. However, in these circumstances, the action of enzymes such esterases, which cleave these functional groups, may result in the medication being released too soon.

Methodology

Various methods used for preparation

- Use of Photolithography
- Micromolding technique
- System for synthesising biopolymers
- (W/O) Water in oil technique of heterogeneous emulsion
- Method of inverse nanoemulsion
- Micellar reversal technique
- Method of membrane emulsification
- The process of heterogeneous free radical polymerization
- Microscopic gel method conversion
- Method of chemical cross-linking

Photolithographic techniques

Hydrogel particles, microgels, and nanogel rings are made using photolithography for drug delivery. Five phases make up this procedure: preparing the substrate, moulding, removing the template, removing the residual layer, and collecting the particles. Particle Replication In Nonwetting Templates (PRINT), a top-down technique, allows for fine control over the size and shape of submicron-sized microgels. Proteins, DNA, and medicines are all compatible with PRINT. It provides versatility in particle form (from 200 nm to microns) and size. PRINT is also a GMP-compliant platform appropriate for mass particle synthesis.

Micro molding method

These approaches, which are similar to photolithographic ones, provide an alternative that lessens the need for pricey lithographic machinery and clean room facilities. In this procedure, cells were dispersed in a water-based hydrogel precursor solution that contained either methacrylated hyaluronic acid (MeHA) or PEGDA as well as a photoinitiator. The resultant mixture was applied to hydrophilic PDMS patterns that had been plasma cleaned before being photo crosslinked with UV light exposure. Cell-filled microgels were obtained, hydrated, and harvested as a result. Additionally, they might take on different shapes like square prisms, discs, and strings.

Fabrication of biopolymers

Three biopolymers made of carbohydrates that are found naturally are chitosan (CS), hyaluronan (HA), and dextran (Dex). These biopolymers are produced into microgels utilising four basic techniques: spray drying, aqueous homogeneous gelation, water-in-oil (W/O) heterogeneous emulsion, and chemical cross-linking of Dex.

Water-in-oil (W/O) heterogeneous emulsion methods

Inverse (mini) emulsion method

- In W/O emulsion processes, there are normally two major steps:
- **Emulsification:** With the help of oil-soluble surfactants, aqueous droplets containing water-soluble biopolymers are emulsified inside a continuous oil phase.
- **Cross-Linking:** Water soluble cross-linkers are used to cross-link the biopolymers. For instance, while creating HA-based microgels, the HA's carboxylic acids are bonded together using the cross-linker adipic dihydrazide (ADH) in aqueous droplets containing ethyl-3-[3-dimethylamino] propyl carbodiimide (EDCI).

Reverse micellar method

Similar to the inverse mini-emulsion technique, the reverse micellar method similarly requires a dispersion in a water-in-oil (W/O) system. However, in order to produce a stable micellar solution where water droplets are scattered within the continuous oil phase, it uses a considerably higher number of oil-soluble surfactants. These submicron-sized micellar droplets typically have a diameter of tens to hundreds of nanometers. In one instance, reverse microemulsion technology was used to create nanogels that target tumours utilising chitosan (CS). Aerosol OT was used as a stabiliser in hexane and doxorubicin (Dox)-modified dextran was used (Dex). It was possible to crosslink CS using aqueous glutaraldehyde. The resulting CS-based nanogels that contained Dox were about 100 nm in diameter.

Conversion of microscopic gel technique

There are several synthetic techniques for making macroscopic gel networks, which are easier to prepare than nanogels or microgels because size isn't determined by exact control over synthetic factors. Usually, bulk polymerization is used to create macroscopic gel networks, resulting in solid structures with macroporous blocks. To create gels with the desired particle size, these blocks are next crushed, powdered, and sieved. However, this process consumes a lot of time and energy and causes substantial material loss. However, the micro- and nanogels produced with this technique contain particles of all sizes and shapes.

Membrane emulsification

The dispersed phase is passed across a uniformly porous membrane, frequently composed of glass or ceramic, in membrane emulsification. On the membrane's surface, emulsion droplets or microgels with a certain morphology are produced under precise circumstances. These created microgels or emulsion droplets are then collected as a continuous phase flows across the membrane. Water-in-oil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water (W/O/W) are only a few of the emulsion droplet types that can exist. These droplets' sizes are influenced by things like transmembrane pressure, continuous phase velocity, and membrane pore size.

Chemical cross-linking method

There are various different chemical cross-linking techniques that have been used to make biodegradable dextran (Dex)-based microgels and hydrogels. Carbodimide coupling, Michael addition processes, and free radical polymerization are some of these techniques.

Heterogeneous free radical polymerization method

Different "polymerization processes" are frequently used to produce well-defined synthetic microgels. Hydrophilic or water-soluble monomers participate in these reactions while being in the presence of bifunctional or multifunctional crosslinkers. These techniques, which frequently make use of an unregulated free radical polymerization process, include precipitation, inverse (small) emulsion, inverse microemulsion, and dispersion polymerization.

Evaluation of proniosomes

Before utilizing nanogels, it is essential to perform comprehensive characterization, and the following methods are commonly considered suitable for this purpose:

In-Vitro Release Test (IVRT)

Drug release from the dosage form is related to the API's effectiveness and safety. The IVRT is a tool for evaluating the quality of the pharmaceutical product. The FDA states that the vertical diffusion cell or an immersion cell are used for IVRT investigations on semi-solid dosage forms. The receptor and donor chambers in a vertical diffusion cell are divided by a receptor membrane. The dose form sample is kept in the donor chamber, while the receptor media are kept in the receptor chamber. A buffer or hydro-alcoholic solution can be used as the receptor media, depending on the API's solubility, sink condition, and stability. Based on the effective pore size, high permeability, and anticipated inertness towards the target, the skin-like receptor membrane is chosen.

Spreadability Testing

The topical dosage form's spreadability attribute guarantees even distribution of the dosage form, preventing stranded dose delivery that would otherwise impair efficacy. Spreadability is significantly impacted by the nanoemulgel's viscosity. For assessing the spreadability of the dosage form, there is currently no accepted standard procedure. A parallel-plate approach, human subject assessment, and other tests are a few that are frequently employed to get a decent idea of spreadability. Due to its simplicity and relative affordability, the parallel-plate method (also known as the slide and drag method) is an extensively used technique. Two glass slides of equal length make up the instrument setup; one is stationary and attached to the wooden block, and the other is moveable and attached to a pulley.

Rheological characterizations

Rheology is the study of the deformation and flow of materials. The rheological characterization of materials reveals the influence of excipient concentrations like oils, surfactants, and gelling agents on the formulation's viscoelastic flow behaviour. If a formulation's viscosity and flow characteristics vary, this may influence its stability, drug release, and other in-vivo parameters. In this instance, the formulation's shear thinning tendency generates a thin layer on the

skin surface, improving permeability, whereas a thicker formulation decreases permeation. Therefore, the rheological behaviour is an extremely important factor in the formulation of nanoemulgel and several unique types of viscometers can be used to determine the rheological behaviour. FDA recommends the evaluation of complete flow curves whenever possible, plotted as both heat stress versus shear rate and viscosity versus shear rate across multiple shear rates until low or high plateaus are observed. If a formulation exhibits plastic flow, yield stress values should be evaluated [30].

Bio-adhesive property

The amount of force necessary to separate the drug carrier system from a biological surface is calculated using the bio-adhesive strength. If a topical dose form must be used for prolonged contact, this characteristic is crucial. Rat or pig skin is typically used for this test; pig skin is favoured because it closely resembles human skin. There are many ways to measure this attribute, but none of them have FDA approval. One such method involves covering the upper mobile probe and immobile bottom base plate in skin for the texture analyzer. The base plate's skin is covered with the dosage form. The lower base plate is made contact with by lowering the upper probe, and the contact is kept for at least one minute. The upper probe is steadily raised until the skin sheets separate. The force required to separate the two skin sheets will be measured by the instrument and represented as the area under the force-distance curve [31].

Dynamic light scattering (DLS)

To evaluate the size distribution properties of nanoparticles in liquid environments, dynamic light scattering (DLS) is used. Micro-second-scale data on light scattering is recorded. The effective hydrodynamic particle radius can be determined using DLS, making it easier to quantify how cross-linkers and polymer chain charges affect nanogel size. DLS is also helpful in determining the degree of nanogel swelling in various media. It should be emphasised that smaller polymer particle populations might not be adequately accounted for by DLS data [32]. Combining analytical methods is frequently required to have a complete knowledge of the object's characteristics. The average particle diameter and polydispersity index are also examined using DLS.

Scanning electron microscopy (SEM)

A useful method for clarifying particle surface shape and size is scanning electron microscopy. It can provide information on the morphological characteristics of nanogels and precisely measure particles with a size range of 50 to 80 nm.

Zeta potential

A coating of ions known as the stern layer often covers the surface of the particles in a solution. An electrical double layer, which also includes the stern layer and a diffuse layer of weakly bound ions, exists next to the stern layer. The ions in the diffuse layer that move with the particle and those that stick with the bulk dispersant are separated by a barrier. The electrostatic potential at this "slipping plane" border is known as the zeta potential. Zeta potential measurement serves as a technique to analyse batch-to-batch consistency and offers an indirect measurement of the net charge. Higher zeta potentials produce stronger repulsion, which increases the formulation's stability. . For instance, emulsion globules can't coalesce because to their high zeta potential. The surface charge can also be modified with a surface charge modifier. For instance, the zeta-potential value changes from positive to negative when a negatively charged surface modification is utilised [33]. The zeta potential can be measured using a variety of instruments such as the ZC-2000 (Zeecom-2000, Microtec Co. Ltd., Chiba, Japan), Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments), and others. Surface active ingredients (such as anionic or cationic surfactants) thus play a significant role in emulsion stability.

Droplet size measurement and polydispersity index (PDI)

The diameter of an analogous hard sphere that diffuses at the same pace as the active moiety is used to measure the size of the globule in nanoemulgel. This dimension is known as the hydrodynamic diameter. The standard deviation of droplet size divided by mean droplet size is known as the PDI, which determines the distribution of droplet size. The stability, drug release, *ex vivo* and *in vivo* performance of the dosage form are all directly correlated with the droplet size and polydispersity index. Furthermore, gauging uniformity between many batches is crucial. A zeta sizer or master sizer can be used to measure the formulation's PDI and globule size. The dynamic light scattering principle, which measures the transitional

diffusion coefficient by observing the interaction between the laser beam and dispersion, can be used to determine the globule size of the emulsion [34,35].

Size-exclusion chromatography (SEC)

Size-exclusion chromatography (SEC) has become the de facto method for determining the average molar mass and distribution of both naturally occurring and synthesised macromolecules over the past 50 years. Combining SEC with various detection methods enhances our understanding of the physicochemical characteristics of polymers [36,37].

Application

Nanocarrier as therapeutic carrier agent [38].

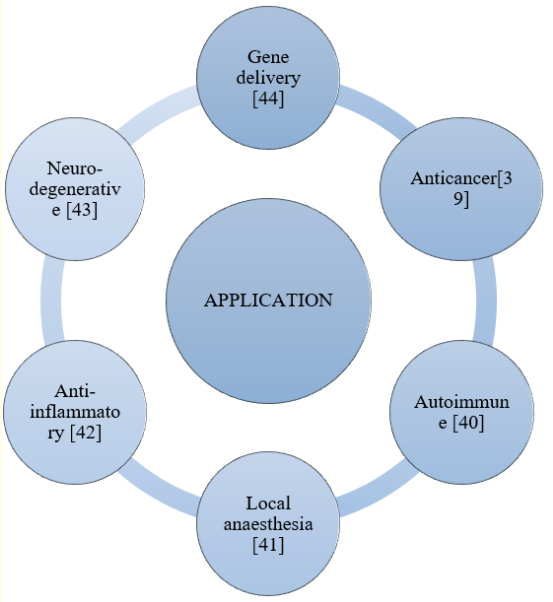

Figure 1: Application.

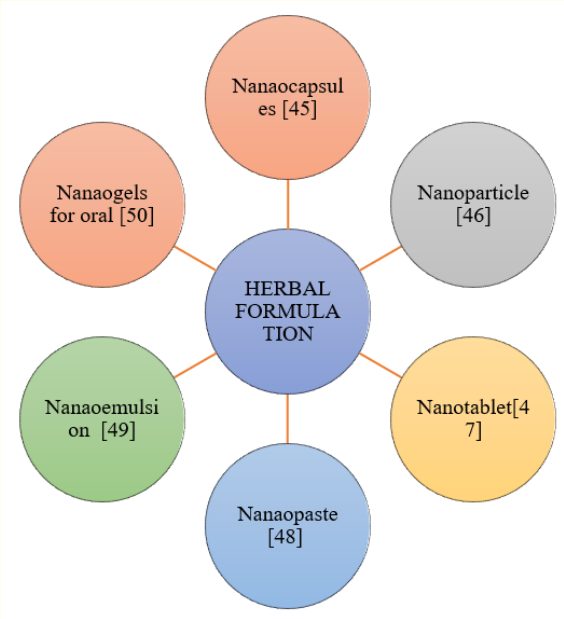

Figure 2: Herbal formulation.

Conclusion

The progression of nanotechnology in recent decades has led to the development and growing importance of nanocarriers in the field of biomedicine. Nanomedicine plays a pivotal role in combatting emerging coronaviruses, yet it encounters substantial challenges in clinical implementation, including issues related to *in vivo* behaviour, nanocarrier toxicity, and large-scale industrial production. Nanocarriers serve as carriers for traditional chemotherapeutic agents and serve as versatile platforms for combined therapy, multifunctional diagnostics, and theranostics, owing to their capacity to encapsulate drugs. They have been employed for various drug delivery strategies, including passive targeting through the Enhanced Permeability and Retention (EPR) effect, active targeting through surface modification with ligands, and site-specific, time-controlled drug release via stimuli-responsive nanocarriers. Among these nanocarrier systems, nanogels have emerged as a superior option, simplifying the drug delivery process and addressing shortcomings of previous techniques. The tremendous potential of functional nanogels as unique polymeric platforms in biomedicine is evident in their applications in drug and gene delivery, intelligent imaging techniques, responsive materials, and the adoption of multivalency as a therapeutic approach.

Challenges and Future Scope

Nanogels represent an innovative and highly effective approach to drug delivery, addressing a wide range of both traditional and contemporary healthcare challenges. These challenges encompass specific side effects and limited stability issues. Recent studies have unveiled distinctive polymeric mechanisms and mechanistic perspectives, offering potential therapeutic applications and avenues for nanogel design. In the realm of healthcare, nano gels are poised to play a pivotal role in managing various conditions, including ophthalmic disorders, nasal drug transport, and vaginal drug administration, as highlighted in a recent exploration of nano gels and nanotechnology. The pharmaceutical industry is witnessing a significant surge in the market for nanogels utilizing natural medicinal components. Nevertheless, substantial barriers persist in integrating natural remedies into clinical trials. Recent research underscores a promising future for nanogels in biomedical applications. For instance, an innovative poly(4-vinyl phenyl boronic acid-co-2-(dimethylamino) ethyl acrylate) nanogel, loaded with insulin-bound silver nanoparticles, has already been developed to manage diabetes. According to a World Health Organization report, 80% of the global population is anticipated to turn to herbal-based pharmaceuticals to address their health requirements. Despite the substantial market potential of conventional pharmaceuticals, many individuals seek alternative medicine as a complement to conventional healthcare practices. In light of evolving societal, political, and economic perspectives, the therapeutic utility of herbal medicines has undergone significant transformation. Nanogel formulations emerge as a viable platform for enhancing the attributes of herbal compounds. By employing herbal nanogels, natural products can be transformed into highly efficient pharmaceuticals capable of treating diverse ailments such as cancer, skin disorders, and diabetes. Cross-linked herbal nanogels, often composed of materials like chitin, chitosan, PLGA, PEG, and other polymers, show great promise in delivering medications through the skin. This approach minimizes adverse effects on patient compliance compared to oral pharmaceuticals. Despite the existence of numerous natural therapeutic remedies, not all of them are safe for consumption. Some can pose severe health risks and interact negatively with other medications [51-55].

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Conflict of Interest

"The author(s) declare no conflict of interest".

Bibliography

1. Molina M., *et al*. "Stimuli-responsive nanogel composites and their application in nanomedicine". *Chemical Society Reviews* 44 (2015): 6161-6186.
2. Annabi N., *et al*. "Khademhosseini AEngineered cell-laden human protein-based elastomer". *Biomaterials* 34 (2013): 5496-5505.
3. Soni KS., *et al*. "Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation". *Journal of Controlled Release* 240 (2016): 109-126.
4. Riehemann K., *et al*. "Nanomedicine—Challenge and perspectives". *Angewandte Chemie International Edition* 48 (2009): 872-897.
5. Singh N., *et al*. "Nanogel-based artificial chaperone technology: An overview". *American Journal of Advanced Drug Delivery* 1 (2013): 271-276.
6. Ghaywat SD., *et al*. "Overview of nanogel and its applications". *GSC Biological and Pharmaceutical Sciences* 16 (2021): 040-061.
7. Fonseca PL and Felisberti MI. "Thermo- and UV-responsive amphiphilic nanogels via reversible [4+4] photocycloaddition of PEG/PCL-based polyurethane dispersions". *European Polymer Journal* 160 (2021): 110800.
8. Mota AH., *et al*. "Chapter 19-Natural-based consumer health nanoproducts: Medicines, cosmetics, and food supplements". In: Mustansar Hussain C., editor. Handbook of Functionalized Nanomaterials for Industrial Applications. Elsevier Amsterdam, The Netherlands (2020): 527-578.
9. Pal SK and Shukla Y. "Herbal medicine: current status and the future". *Asian Pacific Journal of Cancer Prevention* 4 (2003): 281-288.
10. Mathur M and Vyas G. "Role of nanoparticles for production of smart herbal drug: an overview". *Indian Journal of Natural Products and Resources* 4 (2013): 329-38.

11. Kabanov AV., *et al*. "Nanogels as pharmaceutical carriers: finite networks of infinite capabilities". *Advanced Drug Delivery Reviews* 48 (2009): 5418-5429.

12. Seema A. "Recent development of herbal formulation-a novel drug delivery system". *IAMJ* 2 (2014): 952-958.

13. Samah NA., *et al*. "Nanogel particulates located within diffusion cell receptor phases following topical application demonstrates uptake into and migration across skin". *International Journal of Pharmaceutics* 401 (2010): 72-78.

14. Missirlis D., *et al*. "Doxorubicin encapsulation and diffusional release from stable, polymeric, hydrogel nanoparticles". *European Journal of Pharmaceutical Sciences* 29 (2006): 120-129.

15. Patra JK., *et al*. "Nano based drug delivery systems: Recent developments and future prospects". *Journal of Nanobiotechnology* 16 (2018): 71.

16. Sayantan M and Pragati T. "Recent Advances in Nanogels in Drug Delivery Systems". *International Journal of Pharmaceutics Sciences and Nanotechnology* 14 (2021): 5278-5286.

17. Mamatha B., *et al*. "Co-Processed Excipients: An Overview". *Rodriguésia* 6 (2020): 224-237.

18. Hans ML., *et al*. "Biodegradable nanoparticles for drug delivery and targeting". *Current Opinion in Solid State and Materials Science* 6 (2002): 319-327.

19. Oh NM., *et al*. "A self-organized 3-diethylaminopropyl-bearing glycol chitosan nanogel for tumor acidic pH targeting: In vitro evaluation". *Colloids and Surfaces B: Biointerfaces* 78 (2010): 120-126.

20. Ramos J., *et al*. "Temperature-sensitive nanogels: Poly (N-vinylcaprolactam) versus poly (N-isopropylacrylamide)". *Polymer Chemistry* 3 (2011): 852.

21. García MC and Cuggino JC. "12-Stimulus-responsive nanogels for drug delivery". In: Makhlouf A.S.H., Abu-Thabit N.Y., editors. Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications, Volume 1. Woodhead Publishing Cambridgeshire, UK (2018): 321-341.

22. Davari M., *et al*. "Nanotechnology". Springer Singapore: Nanomaterials: Implications on Agroecosystem (2017): 59-71.

23. Kabanov AV., *et al*. "Nanogels as pharmaceutical carriers: finite networks of infinite capabilities". *Advanced Drug Delivery Reviews* 48 (2009): 5418-5429.

24. Zhang X., *et al*. "Micro-and nanogels with labile crosslinks-from synthesis to biomedical applications". *Chemical Society Reviews* 44 (2015): 1948-1973.

25. Nakai T., *et al*. "Injectable hydrogel for sustained protein release by the saltinduced association of hyaluronic acid nanogel". *Macromolecular Bioscience* 12 (2012): 475-483.

26. S Mangalathillam., *et al*. "Curcumin-loaded chitin nanogels for skin cancer treatment via the transdermal route". *Nanoscale* 4 (2012): 239-250.

27. Sarika PR., *et al*. "Preparation, characterization and biological evaluation of curcumin loaded alginate aldehyde-gelatin nanogels". *Materials Science and Engineering: C* (2016).

28. Shah VP., *et al*. "In Vitro Release Test (IVRT): Principles and Applications". *International Journal of Pharmaceutics* 626 (2022): 122159.

29. Nikumbh KV., *et al*. "Formulation Development, in Vitro and in Vivo Evaluation of Microemulsion-Based Gel Loaded with Ketoprofen". *Drug Delivery* 22 (2015): 509-515.

30. Anand K., *et al*. "Nano-Emulgel: Emerging as a Smarter Topical Lipidic Emulsion-Based Nanocarrier for Skin Healthcare Applications". *Recent Patents on Anti-Infective Drug Discovery* 14 (2019): 16-35.

31. Amorós-Galicia L., *et al*. "Development of a Standardized Method for Measuring Bioadhesion and Mucoadhesion That Is Applicable to Various Pharmaceutical Dosage Forms". *Pharmaceutics* 14 (2022): 1995.

32. Sneha K and Kumar A. "Nanoemulsions: Techniques for the Preparation and the Recent Advances in Their Food Applications". *Innovative Food Science and Emerging Technologies* 76 (2022): 102914.

33. Krishna KV., *et al*. "Biophysical, Biochemical, and Behavioral Implications of ApoE3 Conjugated Donepezil Nanomedicine in a Aβ1-42Induced Alzheimer's Disease Rat Model". *ACS Chemical Neuroscience* 11 (2020): 4139-4151.

34. Striegel AM and Haidar Ahmad IA. "Determining the Chemical-Heterogeneity-Corrected Molar Mass Averages and Distribution of Poly (styrene-co-t-butyl methacrylate) Using SEC/MALS/UV/DRI". *Chromatographia* 81 (2018): 823-827.

35. Striegel AM. "Chapter 10—Size-exclusion chromatography". In: Fanali S., Haddad P.R., Poole C.F., Riekkola M.-L., editors. Liquid Chromatography. 2nd ed. Elsevier Amsterdam, The Netherlands (2017): 245-273.

36. Ranjan S., *et al*. "Nanoscience in Food and Agriculture". Springer Nature London, UK (2017).

37. Rashidipour M., *et al*. "Encapsulation of Satureja khuzistanica jamzad essential oil in chitosan nanoparticles with enhanced antibacterial and anticancer activities". *Preparative Biochemistry and Biotechnology* 51 (2021): 971-978.

38. Moradi SZ., *et al*. "Nanoformulations of Herbal Extracts in Treatment of Neurodegenerative Disorders". *Frontiers in Bioengineering and Biotechnology* 8 (2020): 238.

39. Sahoo CK., *et al*. "Intra Vaginal Drug Delivery System: An Overview". *American Journal of Advanced Drug Delivery* 1 (2013): 43-55.

40. Ooi LS., *et al*. "Antimicrobial activities of cinnamon oil and cinnamaldehyde from the Chinese medicinal herb Cinnamomum cassia Blume". *The American Journal of Chinese Medicine* 34 (2006): 511-522.

41. Lee JH and Yeo Y. "Controlled Drug Release from Pharmaceutical Nanocarriers". *Chemical Engineering Science* 125 (2015): 75-84.

42. Zarekar NS., *et al*. "Nanogel as a Novel Platform for Smart Drug Delivery System". *Journal of Nanoscience and Nanotechnology* 4 (2017): 25-31.

43. Vaginal Vadithya A., *et al*. "A review on vaginal route as a systemic drug delivery". *Critical Review in Pharmaceutical Sciences* 1 (2012): 1-19.

44. Boridy S., *et al*. "The binding of pullulan modified cholesteryl nanogels to Aβ oligomers and their suppression of cytotoxicity". *Biomaterials* 30 (2009): 5583-5591.

45. Lee J., *et al*. "Self-assembled glycol chitosan nanogels containing palmityl-acylated exendin-4 peptide as a long-acting antidiabetic inhalation system". *Journal of Controlled Release* 161 (2012): 728-734.

46. Mora-Huertas CE., *et al*. "Polymer-based nanocapsules for drug delivery". *International Journal of Pharmaceutics* 385 (2010): 113-142.

47. Abdul Manap AS., *et al*. "Bacopa monnieri, a Neuroprotective Lead in Alzheimer Disease: A Review on Its Properties, Mechanisms of Action, and Preclinical and Clinical Studies". *Drug Target Insights* 13 (2019).

48. Krishnan S., *et al*. "Nanotechnology-based therapeutic formulations in the battle against animal coronaviruses: An update". *Journal of Nanoparticle Research* 23 (2021): 229.

49. Supriya G and Kumari S. "Green synthesis of silver nanoparticles using Aloe vera extract and assessing their antimicrobial activity against skin infections". *International Journal of Scientific Research in Biological Sciences* 6 (2019): 60-65.

50. Choudhury H., *et al*. "Chapter 9-Nanoemulsions as Effective Carriers for the Treatment of Lung Cancer". In: Kesharwani P., editor. Nanotechnology-Based Targeted Drug Delivery Systems for Lung Cancer. Academic Press Cambridge, UK (2019): 217-247.

51. Shanbhag VKL. "Curcumin in chronic lymphocytic leukemia-A review". *Asian Pacific Journal of Tropical Biomedicine* 7 (2017): 505-512.

52. García MC and Cuggino JC. "12-Stimulus-responsive nanogels for drug delivery". In: Makhlouf A.S.H., Abu-Thabit N.Y., editors. Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications. Woodhead Publishing Cambridgeshire, UK (2018): 321-341.

53. Kabanov A., *et al*. "Nanogels as Pharmaceutical Carriers: Finite Networks of Infinite Capabilities". *Angewandte Chemie* 48 (2009): 5418-5429.

54. Zarekar NS., *et al*. "Nanogel as a Novel Platform for Smart Drug Delivery System". *Nanoscience and Nanotechnology Research* 4 (2017): 25-31.

55. Wu W., *et al*. "Multifunctional Hybrid Nanogel for Integration of Optical Glucose Sensing and Self-Regulated Insulin Release at Physiological pH". *ACS Nano* 4 (2010): 4831-4839.