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Review Article

HISTORIC REVIEW ON MODERN HERBAL NANOGEL FORMULATION AND DELIVERY METHODS

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ABSTRACT

Chemistry deals with herbal constituents are often coined as phytochemistry. Herbal constituents have profound improvements in drug discovery for several existing diseases. Many of these constituents are restricted from pharmaceutical discoveries due to two important reasons: pharmacodynamics and pharmacokinetics. There are many new technological strategies and comparisons have been studied to improve the herbal discoveries in the pharmaceutical market. This review paper will highlight historical evidence of nanogels which is the most important strategy applied to several herbal medicines with high patience compliance, delivery rate, and efficiency. Nanogels are nanoparticles combined with cross-linked polymer networks with desirable features to carry hydrophilic or hydrophobic drugs in a more stable condition. Nanogels are highly preferred substances for herbal medicine in terms of stability and rapid response to the external stimuli factors. Nanogel can facilitate the herbal products with higher cellular penetration than existing and hence, it proves to be the new dimension for both oral and transdermal drug delivery for several unmet diseases like cancer, diabetes, and chronic disorders. By the way, including the recent technological constituents to herbal drugs, it can possess high bioavailability, low toxicity and enhance the sustained release mechanism with suitable delivery modes.

Keywords: Herbal, Bioavailability, Drug Permeation, Nanogel, Drug Delivery, Transdermal

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INTRODUCTION

Herbal medicines from traditional herbs or natural herbs are seamlessly considered as alternative medicines in this modern era to treat most communicable diseases as well as non-communicable diseases such as cancer and diabetes. Herbal medicines have played a crucial role in setting up the foundation for current pharmacopoeia which is in the pharmaceutical market [1]. Herbal medicines can be defined as "the therapeutic practices that have been in existence for hundreds of years, before the development and spread of modern medicines". This branch of alternative medicines that exploits medicinal plants for therapy is applied as herbal medicine which is highly explored by many researchers [2], and earliest use of medicinal plants dates back to the era of Neanderthals [3]. There are remarkable reports on identifying the alternative medicines from plants sources, such as aspirin from willow bark, digoxin from foxglove, and morphine from opium poppy [4], curcumin from *Curcuma longa*. One-fourth of the world's population depends on herbal components for their basic medicinal needs every day, and they have been considered as alternatives to other regular medications. Preference of herbal medicine is deemed to be a healthier option for the patients due to their minimal side effects compared to that of modern medicines [3]. In addition, 80% of the world's population utilizes herbs to treat skin-based diseases [4], viral, fungal, hypertensive disorders, cancer, diabetes, etc [6, 7]. Despite their high pharmacological activity, they are less preferred in medicinal practice due to several other reasons such as poor solubility, low bioavailability, high rate of first-pass metabolism and high dose requirement [1]. They can be made preferable by increasing patient compliance and their bioavailability to the system using scientific approaches [8]. This, in turn, reduces the dosage amount required for the pharmacological activity. Moreover, easy accessibility and affordability of these traditional medicines make them more desirable for regular usage as alternative medicines [9]. There are approximately 35% of the top pharmaceutical products that are formulated with herbal composition [6] and the total world market for the herbal medicinal product is around 60 billion USD [10] which contributes about 50% of the approved drugs [11]. Herbal medicinal products are now being prescribed by the doctors in many countries in various formulations to meet the demand in this modern medicine era [12].

Nanoformulations of herbal medicines

Developing a complete herbal medicine is irksome for pharmaceutical companies, as many factors influence the plant herb's biological efficacy and reproducibility of its therapeutic potential. There are some conditions where the rapid onset of action is needed in medicaments for certain complexities such as asthma, pain, fever etc. and in controversy prolong the duration of action is also needed in chronic treatments such hypertension, cancer, diabetes etc. However, the herbal medicines are highly restricted in both the phases due to their physiochemical properties. These factors have certainly reduced their dominance in the modern medical practice [13]. In recent years, many research investments have been made to bring effective deliverables in herbal medicines. However, to obtain the desired efficacy of herbal drugs, nanotechnology strategy is incorporated to manipulate the effectiveness of active phytoconstituents in the system [14, 15]. Nanotechnology has proved to increase the chance of implementation of herbal-based drugs by improving the potential of drug action, promoting the sustained release of active constituents, reducing the required dosage and improving the biological activity [15, 16]. Nanomaterials such as polymeric nanoparticles, solid lipid nanoparticles (SLN), lipid crystal (LC) systems, liposomes, and nanoemulsions have been attempted as carrier vehicles to protect the herbal drugs from an external source of degradation and increase their bioavailability [17, 18].

Plenty of studies reveal that nano-delivery system can help to optimize the physiochemical properties of herbal drugs per the necessity. Kesarwani and Gupta reported that nanoformulations had optimized the properties of herbal compounds [19] and Ghosh developed a lipid-based system to increase the bioavailability of active compounds from green tea and ginseng [20]. Considerably, active constituents from the extract of *Radix Salvia Miltiorrhiza Bunge (Lamiaceae)* had shown a significant improvement in the bioavailability [21]. In another study, nanostructured lipid carriers have facilitated better skin permeation of quercetin [22].

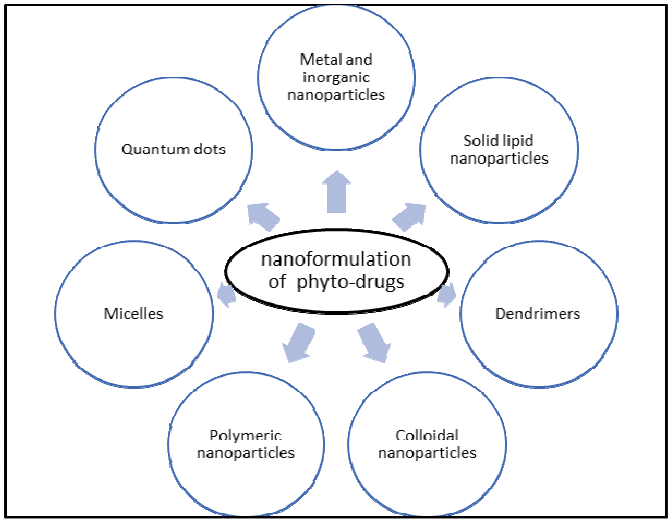

Fig. 1: Different types of herbal nanoformulations [17, 18]

Research in polymeric nanoparticles has predominantly grown in the present decade due to their inherent ability to target the site and response to the external stimuli factors. In designing a polymeric nanoparticle for herbal drug formulation, biotoxicity and stability of the polymer should be taken into considerations. Hence, the mechanism of delivery of such herbal compounds is very effectively practiced by biodegradable and biocompatible polymers such as PLA (polylactic acid), PLGA (poly (lactic-co-glycolic acid)), chitosan, etc [23, 24]. Some polymers like chitosan offer an excellent range of benefits for transdermal delivery application by enhancing the features like sustained, targeted drug release, high biocompatibility and biodegradability properties [25, 26]. The present opinion of this review paper summarizes; Though many polymeric nanoparticles have been extensively studied for herbal formulations, nanogels deserve a special consideration due to their favorable physiochemical properties for controlled drug delivery and affinity to aqueous solutions, superior colloidal stability, high cellular internalization property, and tendency to remain inert in the bloodstream is the major requirement in this modern pharmaceutical era. Moreover, present challenges in the herbal drug formulation can be easily met with nanogels. This review article focuses on various nanogel based formulations which can effectively improve the delivery of herbal compounds for better therapeutic applications. However, there is a less amount of literature is available to justify the applications of nanogels for herbal formulation. This review may be helpful to many pharma application scientists to utilize the bank of resources available for designing the alternative medicines and to know about the pre-requisites of these nanogels to formulate with herbal constituents for transdermal applications

Nanogel and its lineages

Nanogels are ionic or non-ionic nanoparticles composed of physically or chemically cross-linked polymers which can be of hydrophilic, hydrophobic or amphiphilic nature. These are made very effective to increase the drug payload in the target site and to control the leaking tendency of other nanocarriers. Nanogels possess the characteristics of both hydrogels and nanomaterials with a diameter ranging from 1 nm to 1000 nm. Nanogels are mostly used in nanomedical applications as novel drug carriers for response based therapy [27]. A novel drug carrier should possess two main characteristics namely delivery of the drug at a required rate and effective delivery of the drug to the site of action [8]. Thus, nanogels have many advanced features to equate the need for modern medicines. The United States Pharmacopoeia defines nanogel as "a semisolid system consisting of dispersion made up of either small inorganic particles or large organic particles enclosed and interpenetrated by liquid" [28]. Nanogels possessed important features such as enhancement *of* drug absorption across the physiological barrier and sustained drug release [29]. Over other transdermal delivery agents (oils/creams/lotions), nanogels pose as better carriers with stable and controlled drug release kinetics [30]. Nanogels are used for both local drug action and systemic drug action with their inherent property of swelling due to their chemical modification which helps to release the drug in the desired dosage form. They are highly water absorbent as they are made up of hydrophobic polymer chains. Nanogels are apt for formulating dermal patches, biosensors, and delivery of ionic drugs [29]. Nanogels can be prepared using various polymers, such as chitosan, alginate, poly (vinyl alcohol), poly (ethylene oxide), poly (ethyleneimine), poly (vinylpyrrolidone), poly (N-isopropyl acrylamide) [31] and carbomers. Carbomer polymer/carbopol is a synthetic polymer whose gelling depends on neutralizing its acidic pH. Fig. 2 depicts the scheme of the nanogel formation using carbomer polymer. Initially, the carbomer is in a highly-coiled state which upon hydration in water, partially uncoils. On adjusting the pH to 7 using sodium hydroxide/potassium hydroxide/ triethanolamine, complete uncoiling due to the salt formation is observed which then thickens to form a nanogel. Chitosan hydrogel based nanoparticulate are commonly used for the delivery of macromolecules like genes, peptides, proteins, antigens, and oligonucleotides. These nanogels can also be modified to release the drug upon stimulation. PAA (Poly(acrylic acid)) and PEG (Polyethylene-glycol)cross-linked hydrogels release oppositely charged proteins only when either calcium ions are added (that bind to the carboxylate groups of PAA and displace the drug) or when the pH of the medium is decreased from 7.4 to 5.5 [25]. Recently, a triple-layered nanogel (TLN) encapsulating vancomycin that undergoes degradation and releases the antibiotic in the presence of lipase enzyme has been reported. The nanogel is made up of a polyethylene glycol shell, the polyphosphoester core containing the drug and a lipase sensitive poly (Ɛ-caprolactone) cross-linked in between the layers. In the normal environment, the antibiotic is protected in the core due to the intact PCL (polycaprolactone). As shown in fig. 3, in the presence of lipase inside the bacterial cell, the PCL layer degrades releasing the antibiotic into the cell.

Drug loading and interaction with nanogel

Nanomaterial and nanogel complex possess the ability to interact with many inorganic and organic components. The interaction between these components is mostly through a hydrogen bond, covalent bond, electrostatic and van der Waals forces [38]. These interactions determine the effectiveness of drug entrapment by nanogels. Biological molecules are released from nanogels through various mechanisms, such as diffusion, degradation, pH and environmental stimuli [39]. Following mechanisms explain the nanogel interactions with the drug.

a. Physical entrapment

b. Covalent conjugation

c. Controlled self-assembly

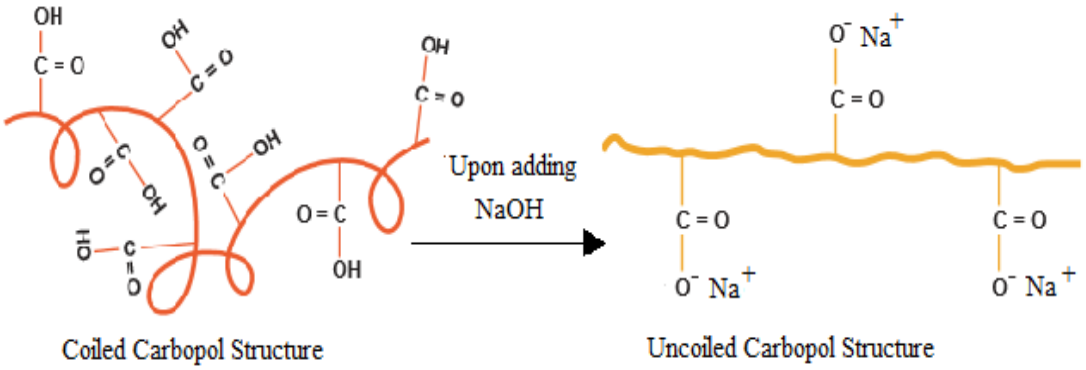

Fig. 2: Structural change of carbomer polymer, reprinted with permission from ref. 32

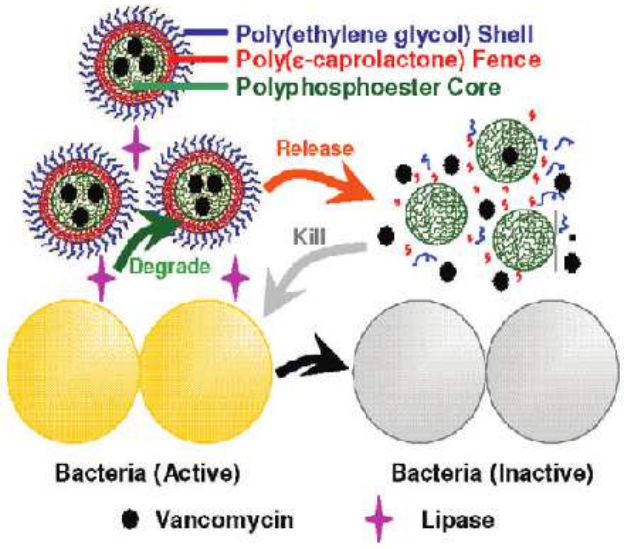

Fig. 3: Delivery of antibiotic by triple-layered nanogel, triggered by lipase enzyme. Reprinted with permission from ref. 33

Physical entrapment

The drug entrapment within nanogels can be achieved through non-covalent interactions, such as ionic, lipophilic and hydrogen bonding [34]. An example would be the self-assembly of cholesterol-containing hyaluronic acid into nanogels for protein delivery. Injection of this gel incorporating a recombinant human growth hormone (rhGH) into rats, has shown sustained release for over a week [35]. Encapsulation of curcumin into chitin nanogel for skin cancer treatment is a good example of hydrogen bonding. Chitin is mostly preferred for nanogel synthesis because of its high biocompatibility, biodegradability, skin non-irritability, easy availability, and cost-effectiveness. It can form polyelectrolyte complexes due to the large number of-OH and-$NHCOCH_3$ reactive groups. The cationic charge of chitin and the lipophilic nature of both chitin and curcumin facilitate skin penetration. However, nanogels are hydrophilic, and thus the hydrophilic-lipophilic balance of chitin-curcumin nanogel is beneficial. As shown in fig. 4, the end to end interaction of curcumin is through its terminal-OH group with the-OH and-$NHCOCH_3$ of chitin [36].

Covalent conjugation

Nanosystems provide a platform for convenient drug delivery. This is a result of their inherent functional groups that are involved in determining the structure and properties of the nanogel [40]. Covalent conjugation of the drug with cross-linked nanogels provides additional stability to the encapsulated drug. Polysaccharides contain hydroxyl groups that readily interact with the carboxyl group in the drug by forming esters linkages [37]. In such instances, premature drug release can occur due to cleavage of functional group bonds by enzymes like esterases [40]. In addition, by introducing easily cleavable linkers, degradable nanogels can be synthesized for a variety of applications [37].

Controlled self-assembly

Controlled self-assembly essentially contains non-covalent conjugation of drugs. Polyelectrolyte based nanogels have the tendency to self-assemble in the presence of oppositely charged solutes, such as surfactants, polynucleotides, proteins and synthetic polyions [39].

The strategy followed in non-covalent drug conjugation is like that of covalent conjugation functionalities like triggering of drug release stimulated by external factors. Non-covalent drug conjugation is potentially supported by disulfide bonds which help drugs to interact with nanogels, at times induced by the stimulus to release the drug. Disulphide cross-linked nanogels have the highest drug loading capacity of Doxorubicin and Paclitaxel are sensitive to temperature and pH [40]. Amphiphilic molecules instantaneously form self-assembled nanoparticles in an aqueous environment which facilitate better drug interaction and release from the nanogel. The drug molecule's orientation is such that, the hydrophilic moieties are exposed to the polar or aqueous medium, and the hydrophobic regions are secured within the core of the assembly [25].

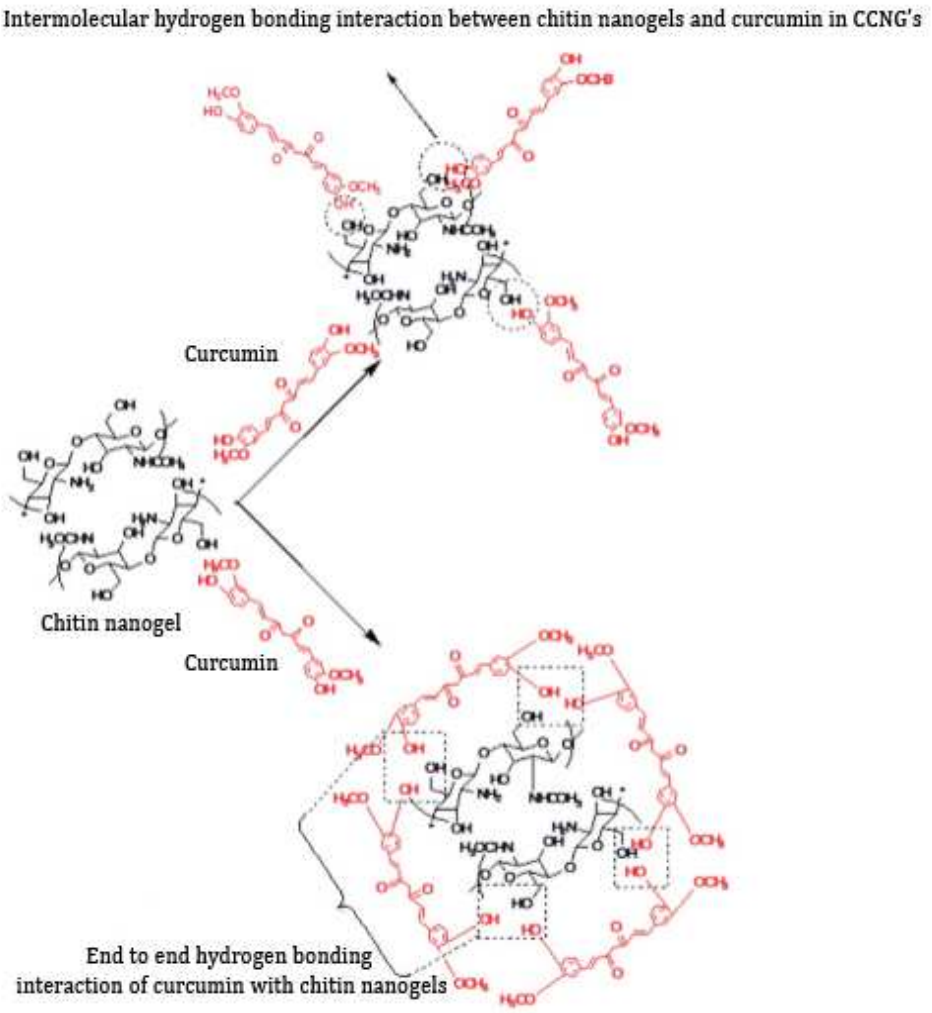

Fig. 4: **Structure of chitin-curcumin nanogel, reprinted with permission from ref. 39**

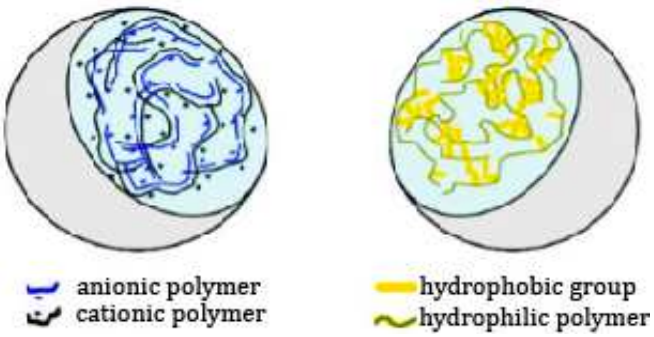

Fig. 5: Structure of self-assembled nanogels, reprinted with permission from ref. 28

Oral application of herbal nanogels

The oral route of delivery is the most common route of administration for many clinical drugs. However technical difficulties of the oral route of administration have some limitations such as first-pass metabolism, gastrointestinal degradation, and poor bioavailability. The present market potential of oral route of delivery is huge, but the limitation is at par for many chronic disorders due to ill effects of oral drugs. Nanogels has achieved obvious milestones in oral herbal formulation due to their non-toxic effect, high bioavailability and better release rate in the system. Curcumin is the most widely used herbal compound which has been studied extensively in cancer research. Alginate aldehyde gelatin nanogels is prepared by inverse miniemulsion technique has better entrapment of curcumin.

Precipitation of nanogels with acetone containing curcumin renders better encapsulation in the cross-linked polymer network. Better encapsulation formed by interaction between-OH terminal group of curcumin and unreacted-OH functionalities in the Alginate aldehyde interacts through end-end hydrogen bonding [40] (fig. 6).

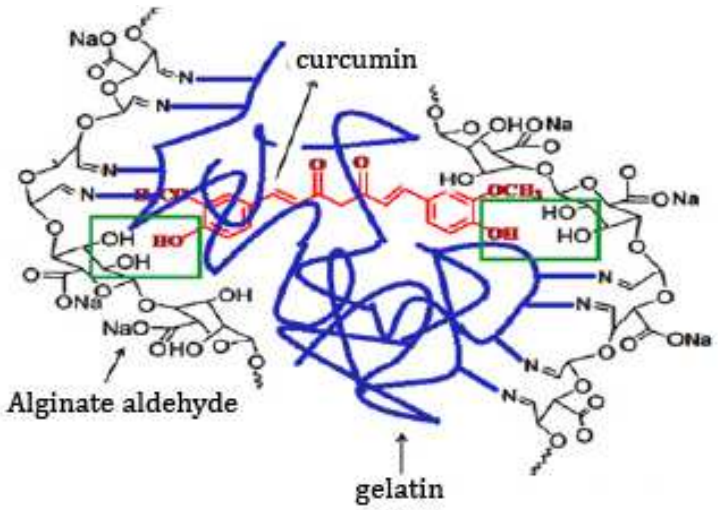

Fig. 6: A possible interaction mechanism between alginate aldehyde nanogel. Reprinted with permission from ref. 40

Encapsulation of curcumin in nanogel increases its solubility, thus increasing the drug loading efficiency to reach the level of therapeutic index for oral administration. It is realized that high drug loading does not influence the encapsulation stability of the herbal nanogel. Another important aspect of the good delivery vehicle system is the potential of nanogel to remain stable in the blood circulation. Studies reveal that cross-linked polymeric nanogels establish the stable properties when compared to the non-cross-linked nanogels. Disulphide cross-linked nanogels based on oligo (ethylene glycol) acrylate (OEGA) and 2-(5,5-dimethyl-1,3-dioxan-2-yloxy) ethyl acrylate (DMDEA) have the highest drug loading capacity of Doxorubicin and Paclitaxel [41]. Oral delivery of this nanogel herbal formulation produces better release and permeability through the gastrointestinal tract.

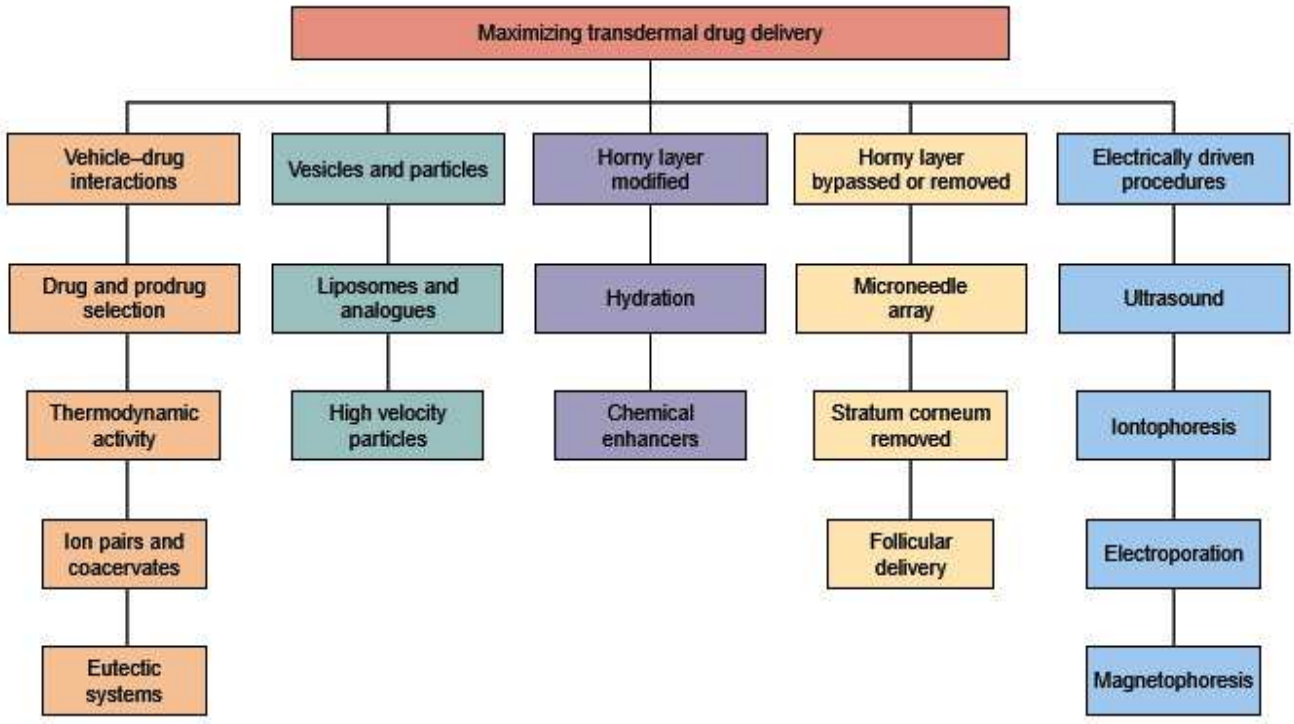

Fig. 7: Maximizing transdermal drug delivery, reprinted with permission from ref. 47

Transdermal application of herbal nanogel formulations

Transdermal drug delivery system has various advantages over the other conventional methods in having good patient compatibility, slow and continuous release of the drug/controlled release, and circumventing first-pass metabolism effect of the drug [42]. Low absorption property of drug through the skin is itself a challenge to be contested by any other delivery methods. On that account, nanogels are being investigated to achieve the best penetration capability through the skin with additional functions [43], such as drug release response to environmental stimulus, pH and other factors [44]. Curcumin-loaded chitin nanogels have excellent skin permeability property and certainly increased the cellular intake in the target cancer cells [36]. Reeves, Anna *et al.* also discussed about the curcumin nanogel formulation with high potential in cancer therapies and demonstrated significant efficiency [45]. Certainly, there are more

limitations for large drug molecules which have comparatively high molecular weight and are less permeable across skin because of several barrier factors. Many alternative methods have been tested to achieve the best transdermal drug delivery system. The vehicle systems, physical enhancers and chemical enhancers that are used to maximize the rate of drug absorption have been explained in fig. 7. Upon applying a drug formulation on to the skin, several physical and chemical gradients are established. Out of these, the water gradient plays an important role in enabling the drug to infiltrate the stratum corneum [46]. For a drug to penetrate transdermal, there are two routes: transepidermal and trans appendageal routes [47].

Transepidermal or trans corneal penetration can be further divided into two categories namely intracellular and intercellular penetration. In intracellular penetration, the hydrophilic drug passes through the immobilized water molecules on the outer surface of protein filaments of the stratum corneum. In intercellular penetration, the hydrophobic/non-polar drug diffuses and dissolves through the lipid matrix imbedded between the protein filaments [48]. There are three possible trans-appendageal routes for drug delivery namely hair follicles, sebaceous and sweat glands. Non-polar drugs penetrate through this route; however, these appendages cover less than 0.1% of the skin surface [49].

The efficacy of many herbal drugs is limited by its inability to reach the target site [50], the requirement of high drug concentration to produce the desired effect, low bioavailability and absorption [51]. The enhanced permeability, bioavailability, high drug loading capacity, biocompatibility and ability to load both hydrophilic and hydrophobic drugs, make nanogels an ideal delivery system for herbal drugs.

Targeting nanogels is of great interest in combating the need for improving the transdermal drug delivery systems. The delivery system of nanogels is a smart carrier option for a wide range of drugs that can be either passive or active permeation. Passive targeting involves passive diffusion and accumulation by enhanced permeability and retention (EPR) effect. Active targeting includes the selective interaction of nanogel with certain cells, mediated by the surface coating of the gel. Nanogel made of polyNIPAM has shown good migration across the epidermis of skin within the range of body temperature [52].

The release of drug from nanogels

The release of the drug from nanogels in the site of the action occurs by following ways [39]

a. Simple diffusion of the drug from the nanogel

b. Degradation of nanogel

c. pH stimulus

d. Ionic exchange with the environment

e. External energy source

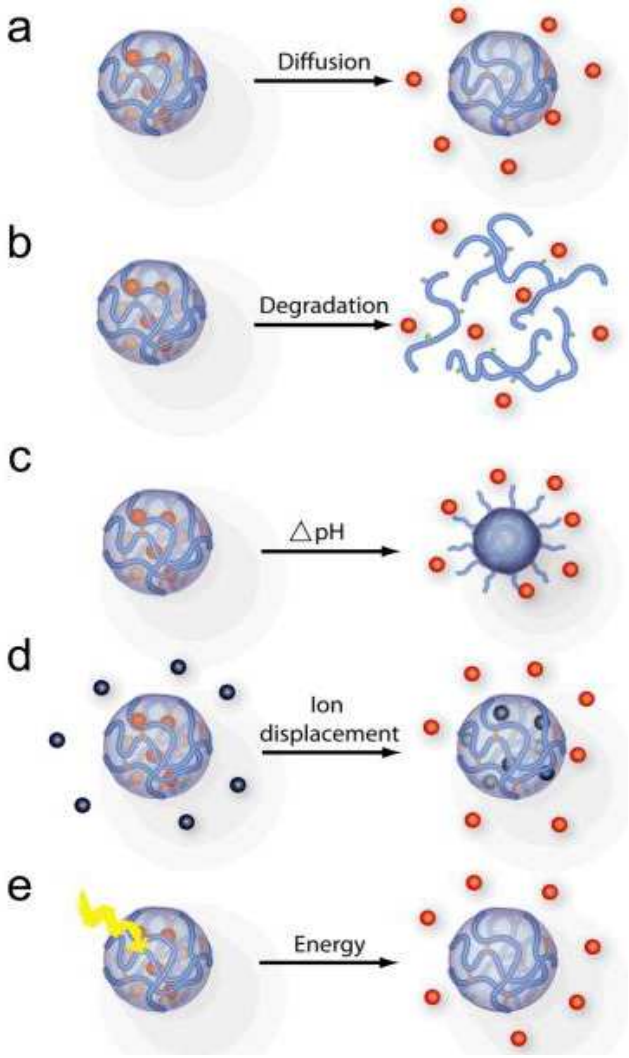

Fig. 8: Drug release from nanogel, reprinted with permission from ref. 39, a) Simple diffusion of the drug from the nanogel, b) Degradation of nanogel, c) pH stimulus, d.) Ionic exchange with the environment, e) External energy source

The diffusive release of the drug from the gel is a consequence of the concentration difference with the environment. The drug moves from a region of higher concentration (inside the gel) to a region of lower concentration (surrounding). Polymeric nanogel composed of poly (ethylene glycol) and poloxamer releases its encapsulated drug, doxorubicin, and a hydrophobic anticancer drug through sustained diffusion for over 1 w. The encapsulation by hydrophobic interaction has reduced the rate of drug degradation [53]. Degradable nature of nanogels promises lower toxicity and prevents unwanted accumulation upon repeated administration. Easily cleavable bonds can be introduced into the polymer backbone. The degradation is in response to specific reducing compounds, pH or even enzymatic activity. The pH stimulated release from the gel is a result of ionization of pendant groups. Nanogel polymer consists of pendant anionic or cationic groups. In an aqueous environment, these groups undergo ionization at the appropriate pH and ionic strength. This produces a fixed charge on the polymer causing electrostatic repulsion and thereby enlarges the pores of the gel.

Hence, there is an enhanced influx of water into the gel, leading to nanogel swelling and drug release. Thermosensitive nanogels poly-(N-isopropyl acrylamide) in aqueous medium has Lower Critical Solution Temperature (LCST) of 32 °C. At temperatures below LCST, the amide group of the polymer is in interaction with the hydrogen of water, and thus the polymer gets hydrated. When the temperature is increased, the hydrophobic-hydrophobic interactions of the polymer become apparent. The hydrogen bonds with water get cleaved and separation of the aqueous phase and the nanogel aggregates occurs; thereby, releasing the entrapped drug into the environment [54]. Another way for the drug release is through displacement with counterions. When a cationic nanogel containing a negatively charged drug is in interaction with the negatively charged particles in the environment/cell surface, the drug is exchanged for the negatively charged particle [22]. Photosensitive molecules or chromophores undergo cis-trans isomerization when induced with UV light. In the cis form, there is an increased dipole moment, making the molecule highly hydrophilic. The alteration can be inversed in the presence of light or by temperature. The energy triggered drug release involves a chromophore molecule attached to the polymer backbone and photothermal effect. When the chromophore-containing nanogel is irradiated with light at its resonance wavelength, the light energy is converted to heat energy by non-irradiative relaxation. The increase in temperature causes volume phase transition, releasing the drug into the surroundings [55].

Other herbal nanogels

The effectiveness of herbal medicine is dependent on the synergistic activity of all its active compounds. Most the herbal drugs have insoluble components that result in low bioavailability and increased systemic clearance [55]. Nanogel formulation of these drugs helps to combat these limitations. Sundry of nanogels that incorporates herbal drugs are given below.

In Ayurveda, leaves of *Eupatorium adenophorum* (asteraceae) are used as antimicrobial, analgesic and in wound treatment. Negi *et al.* studied the anti-inflammatory activity of the ethanolic extracts of asteraceae. The greenish translucent carbopol 934 gel prepared with 1% of this extract had significant anti-inflammatory activity against carrageenan induced rat paw edema [57].

Leaf extracts of Cleodendron infortunatum linn. are traditionally used for the treatment of bronchitis, asthma, fever, skin infections and epilepsy. Das et al. formulated the leaf extract into a nanogel using a synthetic polymer carbopol 940. The gel with 2.5% extract had shown good anti-inflammatory activity and had no skin irritation [58].

Rajesh *et al.* reported the anti-inflammatory and analgesic activity of a gel containing the methanolic extracts of *Albizia lebbeck*. The nanogel made using sodium alginate, and carboxymethyl cellulose (CMC) had shown better permeation than with carbopol 934 and various other combinations [8].

The roots of *Millettia pinnata* (*pongamia pinnata*) have anti-inflammatory and angiogenesis potential. The roots are also being used as a toothbrush to improve oral hygiene, to treat vaginal and skin infections, gonorrhea and to kill parasitic worms. Paul *et al.* studied the anti-inflammatory activity of the nanogel containing the root extract. Aqueous extract of the root was first entrapped with silver nanoparticles and then made into a gel using paraffin wax base. The gel had significant activity and inhibited the heat-induced denaturation of bovine serum albumin [29].

Per Dwivedi and Gupta**,** the non-irritant nanogel containing leaf ethyl acetate extracts of *Sesbania grandiflora*, Carbopol 934 and sodium CMC can be used against various skin inflammations. The leaves of *Sesbania grandiflora* have anti-ulcer, anti-oxidant, analgesic, antipyretic, antimicrobial, anti-cancer, anticonvulsant, anxiolytic and hepatoprotective properties [59].

The leaves of *Lantana camara* have anti-hemorrhoid and anti-inflammatory activities. The two concentrations of the extracts (2.5% and 5%) were made into gels using Carbopol 934. As documented by Pawar and Shamkuwar**,** the gel with 2.5% extract had better characteristics than the 5% gel [42].

The stem bark ethanolic extracts of *Butea frondosa* have analgesic and anti-inflammatory activities. The optimized gel formulation with carbopol 934 and DMSO, performed by Shankar *et al.* showed a diffusion and permeation percentage after 8 h as 92.37 and 98.29 [28].

Goyal *et al.* deliberate the possibility of formulating a gel containing extracts of *Boswellia serrata* (kunduru) and *Withania somnifera* (ashwagandha). *Boswellia serrata* (pentacyclic triterpenes) has anti-inflammatory and anti-arthritic activities due to its ability to inhibit 5-lipoxygenase. Withaferin A, a cell-permeable steroidal lactone present in *withania somnifera,* confers to it its anti-inflammatory and anti-arthritic activities [60].

A comparative study on the antibacterial activity of the glycolic extracts of pomegranate, apricot and green tea was done by Giovana *et al.* Pomegranate is used for its astringent and antiseptic activity accounted by its alkaloids and gallic tannins. Apricot, in addition to having the same activity also has muco protective and remineralising potential. The various benefits of green tea include chemo protectant, sunscreen, anti-inflammatory, and anti-oxidative activities. Against *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli*, green tea gallic acid extract gel proved to be a potent antibacterial agent. This activity is attributed to the presence of catechins in green tea [61].

The antibacterial activity of the ethanolic extracts of *Tridax procumbens* against *Staphylococcus aureus* was performed by Jadhav *et al.* Carbopol 940 gel with 1% extract was found to have strong antimicrobial activity [4].

Chewing the leaves and flowers of *Spilanthus acmella*, commonly known as Akkalkara, causes numbness of tongue and gums. It is also being used to relieves a toothache and as an anti-inflammatory agent. Gupta *et al.* explored the benefits of formulating ethanosomes containing the plant extracts into a mucoadhesive oral gel, for treating toothache, tooth decay and mouth ulcer [9].

Aloe vera is commonly used to speed up the wound healing process (different stages of healing: wound contraction, wound closure and restoration of functional barriers), to stimulate immunity (by activating macrophages) and considered as an antifungal agent. A*loe vera*-carbopol 934 nanogel formulation performed by Khan *et al.* had increased the rate of wound contraction in skin excision wounds in rats. This ability is a consequence of the presence of mannose-6-phosphate in the leaf extracts. Mannose can stimulate the fibroblast activity and collagen synthesis [62].

Misal *et al.* formulated a nanogel with *Cassia alata* linn. *Cassia tora* linn. and *Cynodon dactylon* Pers. *Cassia alata* linn. and *Cassia tora* linn. are used for their anticancer, oral anti-inflammatory, antibacterial, anti-oxidant, skin disorder and wound healing properties. Apart from having wound healing anti-oxidative activity, *Cynodan dactylon* Pers. also has antiviral, antidiabetic, antifungal, antibacterial and antiulcer activities. Carbopol 940 gel with 4% *Cassia alata* linn. had shown better anti-inflammatory activity than the other gels, against carrageenan-induced rat paw edema [63].

Challenges and opportunities

Nanogels formulated with herbal drugs opens a multi-billion-dollar market for the growing pharmaceutical industry. However, there remain significant challenges for implementation of herbal drugs in the clinical trials. As per a report by the World health organization (WHO), 80% of the world population will highly rely on herbal-based drugs to meet their health needs [41]. Despite the market potential of allopathic drugs, people continue looking for alternative medicine as a complimentary medicinal practice. Therapeutic application of the herbal drug is highly diminished due to the significant changes in the social, political and economic values of the people [64]. Nanogels can significantly help herbal medicines to come into much applicable clinical practice through effective research programmes. New opportunities always exist for nanogel due to its fascinating properties such as biocompatibility and degradability, swelling property in aqueous media, higher drug loading capacity, permeability and particle size, Non-immunologic response, and colloidal stability [65]. Nanogel facilitates in designing the delivery system responding to the external stimuli factor that controls the drug release rate at the site of action. This enables the herbal drugs to play a multi-functional role by increasing its efficiency [67, 68].

CONCLUSION

Nanogel formulation is a versatile platform for augmenting herbal drug properties. Due to its flexibility and versatility nanogels have several opportunities in herbal formulations as a drug carrier. Di-sulfide cross-linked polymeric nanogels have excellent features to be developed as bio-responsive delivery systems. Perhaps herbal nanogel convert the natural product into a most applicable medication for the treatment of various diseases like cancer, skin diseases, diabetes, etc. Polymers such as chitin, chitosan, PLGA, PEG are widely used in the synthesis of cross-linked herbal nanogels. These cross-linked nanogels have excellent potential in delivering the drugs through the transdermal route, and this influences the patient compliance of the herbal drugs with little side effects compared to that of oral drug administration. Consequently, there is a better drug bioavailability and an increased penetration capacity in transdermal delivery. The non-toxic and biocompatible herbal nanogels can be further modified to possess multiple therapeutic properties with different herbal formulations.

Though many natural medicinal products have been developed, but not all of them are safe; some are highly toxic, can interact with conventional drugs and have adverse side effects. For an herbal product to be accepted in the modern system of medicine, the quality of the herbal product needs to be assessed. The lack of quality control profiles for Phyto materials and their formulations acts as an obstacle in product development. The department of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy) is an initiative by the Indian Government to develop a pharmaceutical standard and to regulate Ayurveda preparations through modern technologies like nanotechnology. Herbal nanogel formulations are the prospective scope of the current pharmaceutical industry which can provide the desired synergistic effect at low drug concentrations and with little side effects. Overall, the herbal nanogel product can be a novel drug carrier system for practical use.

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CONFLICT OF INTERESTS

All authors declare that there is no conflict of interest associated with this article

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