

Herbal Nanogels for Topical Drug Delivery: A Review with Special Reference to Curcumin-Loaded Chitosan Nanoparticles

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Abstract: *The skin is the largest organ of the human body, and topical application of drugs on the skin is a very old and convenient way to treat local skin conditions such as inflammation, infection, wounds, burns, acne and psoriasis. Topical drug delivery avoids the first-pass metabolism and the gastrointestinal side effects of oral drugs, gives a high drug concentration at the site of action and is non-invasive and painless, so patient compliance is good [1,2].*

Keywords: *human body*

I. INTRODUCTION

The skin is the largest organ of the human body, and topical application of drugs on the skin is a very old and convenient way to treat local skin conditions such as inflammation, infection, wounds, burns, acne and psoriasis. Topical drug delivery avoids the first-pass metabolism and the gastrointestinal side effects of oral drugs, gives a high drug concentration at the site of action and is non-invasive and painless, so patient compliance is good [1,2].

Herbal drugs have been used on the skin in India since ancient times, and they are widely accepted by patients because they are easily available, relatively cheap and generally considered to have fewer side effects. Many active constituents of plants, however, such as curcumin, are poorly soluble in water, are unstable in light and at alkaline pH, and penetrate poorly through the skin. Conventional herbal creams and gels therefore give a low and variable drug concentration in the skin [3,4,5].

Nanotechnology has opened new possibilities for overcoming these problems. Drugs entrapped in nanosized carriers show better stability, a higher surface area, a controlled release and better contact with and retention in the skin. A nanogel combines the advantages of nanoparticles and gels: the drug is entrapped in nanosized polymeric particles, which are then dispersed in a gel base so that the preparation is easy to apply and spread on the skin [6,7,8].

Structure of the Skin and Topical Absorption

The skin consists of three layers: the epidermis, the dermis and the hypodermis. The outermost layer of the epidermis, the stratum corneum, is only about 10 to 20 μm thick, but it is the main barrier to the entry of drugs because it is made of dead, flattened keratin-rich cells embedded in a lipid matrix. A drug applied on the skin must diffuse through this layer, mostly by the intercellular route, before it reaches the viable epidermis and dermis. Drugs of small size, moderate lipophilicity and low dose pass more readily, and penetration can be improved by hydration of the skin, by penetration enhancers and by nanosized carriers that adhere to the skin and release the drug slowly [1,2].

Concept of Nanogel

Nanogels are three-dimensional, cross-linked hydrophilic polymer networks of nanometre size (generally 10 to 200 nm) that can absorb large amounts of water or biological fluids without dissolving and can hold drugs inside their network [6,7]. They may be formed from natural polymers such as chitosan, alginate and hyaluronic acid or from synthetic polymers. In the pharmaceutical literature the term is also used for a hybrid system, in which drug-loaded polymeric



nanoparticles are dispersed in a hydrogel (gel) base. This hybrid nanogel is easy to prepare, and the gel base gives the preparation the viscosity and spreadability needed for application on the skin.

Advantages of Nanogels for Topical Delivery

- Poorly soluble herbal drugs can be entrapped and dispersed uniformly in an aqueous gel.
- Protection of unstable drugs from light, oxygen and pH changes by the polymer matrix.
- Controlled, prolonged release of the drug, which reduces the frequency of application.
- Better adhesion to and retention on the skin, and improved penetration because of the small particle size.
- Non-greasy, easily washable and cooling, with good spreadability and patient acceptability.
- Biocompatible and biodegradable carriers such as chitosan can be used.
- Suitable for inflamed and wounded skin because the gel is soothing and moist.
- Simple and low-cost preparation with common laboratory equipment.

Limitations of Nanogels

- Particle size, drug loading and stability must be carefully controlled and checked.
- Nanoparticles may aggregate on storage if the surface charge is not sufficient.
- Carbopol gels lose viscosity in the presence of electrolytes and alcohol.
- Gels are liable to microbial contamination and need preservatives.
- Special instruments (particle size analyser, electron microscope) are needed for full characterisation.
- The long-term safety of nanocarriers on damaged skin needs to be checked.

Characteristics of an Ideal Topical Nanogel

- Nanosized particles with narrow size distribution and good entrapment of the drug.
- Skin-compatible pH (about 5 to 7) and non-irritant to the skin.
- Suitable viscosity, good spreadability and easy removal from the container.
- Homogeneous, with uniform drug content.
- Controlled release of the drug and good retention in the skin.
- Physically, chemically and microbiologically stable on storage.

Composition of Nanogel

The usual components of a topical nanogel are shown in Table 1 [6,9,10].

Table 1: General composition of a topical nanogel

Component	Typical amount	Examples
Herbal drug	0.5 – 2% w/w	Curcumin, quercetin, aloe extract, neem extract
Nanoparticle polymer	0.1 – 0.5% w/v	Chitosan, sodium alginate, gelatin, PLGA
Cross-linking agent	0.05 – 0.2% w/v	Sodium tripolyphosphate, calcium chloride
Gelling agent	0.5 – 2% w/w	Carbopol 934 / 940, HPMC, sodium CMC
Humectant / penetration enhancer	5 – 15% w/w	Propylene glycol, glycerol, PEG 400
Preservative	0.02 – 0.2% w/w	Methylparaben, propylparaben
Neutralising agent	q.s.	Triethanolamine, sodium hydroxide
Vehicle	q.s. to 100	Purified water

II. DESCRIPTION OF DRUG AND EXCIPIENTS

Curcumin is the principal yellow pigment (curcuminoid) obtained from the rhizome of turmeric (*Curcuma longa* Linn., family Zingiberaceae). Turmeric is used daily in Indian kitchens, in religious ceremonies, and in Ayurvedic medicine for wounds, skin diseases, inflammation, and many other conditions, and it is often called 'Indian solid gold' [3,11].



Table 2: Profile of curcumin

Parameter	Details
Drug name	Curcumin (diferuloylmethane)
Source	Rhizomes of <i>Curcuma longa</i> Linn. (turmeric), family Zingiberaceae
Chemical name	(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
Molecular formula	C ₂₁ H ₂₀ O ₆
Molecular weight	368.38 g/mol
Description	Orange-yellow crystalline powder
Melting point	About 183 °C
Solubility	Practically insoluble in water at acidic and neutral pH; soluble in ethanol, acetone and DMSO
λ_{max}	About 425 nm in ethanol
Stability	Sensitive to light; degrades quickly at alkaline pH
Category	Herbal anti-inflammatory and antioxidant agent
Reported activities	Anti-inflammatory, antioxidant, antimicrobial, wound healing, anticancer

Phytochemistry

Turmeric contains about 2 to 5% of curcuminoids, which are a mixture of curcumin (the major component), demethoxycurcumin and bisdemethoxycurcumin. Besides these, it contains volatile oil with turmerones, carbohydrates, proteins and resins. The activity of the plant is mainly due to the curcuminoids, and the phenolic hydroxyl groups and the β -diketone moiety of curcumin are responsible for its antioxidant and anti-inflammatory action [3,11,12].

Pharmacological Activities Relevant to Topical Use

Anti-inflammatory activity: curcumin inhibits the enzymes cyclooxygenase-2 and lipoxygenase and the transcription factor NF- κ B, and so reduces the production of inflammatory mediators [11,12]. Wound healing: curcumin increases granulation tissue formation, collagen deposition and wound contraction, and reduces oxidative damage at the wound site [13]. Antioxidant activity: it scavenges free radicals and protects the skin from oxidative stress. Antimicrobial activity: it is active against many bacteria and fungi, including *Staphylococcus aureus*, and so it is useful in infected wounds and skin infections [3,11].

Problems with Conventional Curcumin Preparations

Curcumin is practically insoluble in water, it degrades rapidly at neutral and alkaline pH and on exposure to light, and its penetration through the skin is poor, so the effective concentration reached in the skin is low [4,5]. These problems make a conventional curcumin gel less effective.

Profile of Chitosan (Nanoparticle Polymer)

Chitosan is a linear cationic polysaccharide obtained by partial deacetylation of chitin, which is found in the shells of crabs and shrimps. It is biocompatible, biodegradable, non-toxic, mucoadhesive and has antimicrobial and wound-healing properties. It dissolves in dilute acids because its amino groups become protonated, and the positively charged chains can be cross-linked with polyanions such as sodium tripolyphosphate (TPP) to form nanoparticles by ionic gelation [14,15,16].

III. METHODS OF PREPARATION AND RELATED ASPECTS

The preparation of a herbal nanogel generally involves two steps: the preparation of drug-loaded nanoparticles (nanogel particles), and the incorporation of the nanoparticles into a gel base. The methods commonly used are described below [6,7,8].



A. Methods of Preparation of Nanoparticles

1. Ionic gelation (ionotropic gelation) method: this method is based on the electrostatic interaction between the positively charged amino groups of chitosan and the negatively charged groups of a polyanion such as sodium tripolyphosphate. When the TPP solution is added drop by drop to the chitosan solution under stirring, the polymer chains cross-link spontaneously and nanoparticles are formed. The drug is added to the polymer solution before the cross-linker. The method is simple, uses only aqueous conditions and no harmful organic solvents, and is suitable for herbal drugs [14,15].
2. Emulsification and solvent evaporation: the polymer and drug are dissolved in a volatile organic solvent, the solution is emulsified in an aqueous phase containing a stabiliser, and the solvent is evaporated to form nanoparticles. It is widely used for hydrophobic polymers such as PLGA, but it needs organic solvents and high-energy homogenisation [6,8].
3. Nanoprecipitation (solvent displacement): the polymer and drug are dissolved in a water-miscible solvent such as acetone or ethanol, and the solution is added to water under stirring. The solvent diffuses out quickly and the polymer precipitates as nanoparticles. It is simple, but the drug loading of hydrophilic drugs is low [8].
4. Emulsion (inverse micro-emulsion) polymerisation and chemical cross-linking: the polymer is cross-linked chemically, for example with glutaraldehyde, in the water droplets of a water-in-oil emulsion. It gives stable nanogels, but the residual cross-linker and organic solvent may be toxic, and so it is not preferred for topical herbal products [6,7].
5. Self-assembly: amphiphilic polymers assemble in water to form nanosized micelle-like particles that swell to form nanogels. The polymers need to be synthesised first, and so the method is more complex [6,7].

Table 3: Comparison of methods of preparation of nanoparticles / nanogels

Method	Main requirement	Advantage	Drawback
Ionic gelation	Chitosan, TPP, stirrer	Simple, aqueous, mild	Size depends on many factors
Emulsification-solvent evaporation	Organic solvent, homogeniser	Suits hydrophobic polymers	Organic solvent residue
Nanoprecipitation	Water-miscible solvent	Simple and quick	Low loading of hydrophilic drugs
Chemical cross-linking	Cross-linker, oil phase	Stable particles	Toxic residues
Self-assembly	Amphiphilic polymers	No cross-linker	Polymer synthesis needed

B. Incorporation of Nanoparticles into the Gel Base

The gelling agent, for example Carbopol 940, is dispersed in water and kept for several hours to swell. The preservatives and humectant are added, and the nanoparticle dispersion is added slowly with gentle stirring. The dispersion is then neutralised with triethanolamine, so that the carboxylic acid groups of Carbopol ionise, the polymer chains uncoil and a clear viscous gel is formed, in which the nanoparticles are dispersed uniformly. Gentle stirring is necessary to avoid damaging the nanoparticles and to avoid air bubbles [9,10,17].

C. Polymers Used for Nanogels

Table 4: Commonly used polymers for nanogels

Polymer	Important features
Chitosan	Natural cationic polysaccharide; biocompatible, mucoadhesive, antimicrobial; cross-linked with TPP
Sodium alginate	Anionic polysaccharide; cross-linked with calcium ions; biodegradable



Gelatin	Protein-based polymer; biocompatible; cross-linked by temperature or chemicals
Hyaluronic acid	Natural, skin-friendly polymer with high water-holding capacity; costly
PLGA	Synthetic biodegradable polyester; prepared with organic solvents
Pluronic F127 / poloxamer	Thermoreversible gelling polymer; self-assembling micelles

D. Factors Affecting Particle Size and Quality

In the ionic gelation method the concentration of chitosan and of TPP and the chitosan to TPP ratio are the most important factors: a high polymer concentration gives larger and more viscous particles, and an excess of TPP causes aggregation. The pH of the chitosan solution decides the degree of protonation of the amino groups and thus the charge of the particles. The stirring speed and time and the rate of addition of TPP also affect the size and size distribution. The drug to polymer ratio influences the entrapment efficiency [14,15,18].

IV. EVALUATION PARAMETERS

A herbal nanogel is evaluated at two levels: the nanoparticles (particle size, polydispersity index, zeta potential, entrapment efficiency and morphology) and the final gel (appearance, pH, viscosity, spreadability, extrudability, drug content, drug release and stability). The important parameters and the usual criteria are given in Table 5.

Table 5: Evaluation parameters and expected criteria

Parameter	Method / instrument	Expected criteria
Particle size / PDI / zeta potential	Dynamic light scattering	Nanometre range; PDI below 0.3; above +20 mV
Entrapment efficiency	UV spectrophotometry	High (preferably above 70%)
Appearance / homogeneity	Visual inspection	Uniform, smooth, no lumps
pH	Digital pH meter	About 5.5 – 7.0
Spreadability	Parallel plate method	Good (short spreading time)
Drug content	UV spectrophotometry	90 – 110% of label claim
In vitro diffusion	Franz diffusion cell	Sustained release over 8 hours
Antimicrobial activity	Agar well diffusion	Clear zone of inhibition
Irritation	HET-CAM test	Non-irritant

V. REVIEW OF LITERATURE

Aggarwal et al. (2007) and Gupta et al. (2013) reviewed the anti-inflammatory, antioxidant, antimicrobial and wound-healing properties of curcumin, including the results of clinical trials [3,11].

Anand et al. (2007) discussed the problems of curcumin, mainly its poor solubility, poor absorption and rapid metabolism, and Tønnesen and Karlsen (1985) studied the degradation kinetics of curcumin in aqueous solution, which showed that it is unstable, so that a protective carrier system is useful [4,5].

Kabanov and Vinogradov (2009) and Sultana et al. (2013) reviewed nanogels as pharmaceutical carriers, and described how the cross-linked nanosized network can load the drug and give a controlled release [6,8].

Calvo et al. (1997) described the preparation of chitosan nanoparticles by the ionic gelation method with tripolyphosphate, and Fan et al. (2012) studied the mechanism of formation of the chitosan nanoparticles by this method, and the effect of the process variables on the size [14,15].

Rinaudo (2006) reviewed the properties of chitosan, including its biocompatibility, antimicrobial effect and mucoadhesion, and Akbik et al. (2014) reviewed curcumin as a wound-healing agent [13,16].



VI. CONCLUSION AND FUTURE PERSPECTIVES

Nanogels combine the carrier function of nanoparticles with the good skin feel and ease of application of gels, and they are a promising system for topical delivery of poorly soluble and unstable herbal drugs such as curcumin. Chitosan nanoparticles prepared by ionic gelation are simple to make, need no organic solvent and have the added advantages of biocompatibility, antimicrobial effect and mucoadhesion, and their incorporation into a Carbopol gel gives an easy-to-apply product.

The particle size, polydispersity index, zeta potential and entrapment efficiency are the key quality attributes, and they depend on the process variables. Most of the reported work is at the laboratory stage, and further studies on skin penetration, safety, scale-up and stability, and clinical studies, are needed before such nanogels can be used in practice.

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