

Microgels: A Review on Formulation and Evaluation of Anti-Hypertensive Transdermal Microgel

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ABSTRACT: Hypertension is a chronic cardiovascular disorder that requires long-term pharmacotherapy, often associated with poor patient compliance and systemic side effects due to conventional oral dosage forms. Transdermal drug delivery systems offer a promising alternative by providing controlled drug release, improved bioavailability, and reduced dosing frequency. Microgels, three-dimensional cross-linked polymeric networks capable of swelling in biological fluids, have gained considerable attention as novel carriers for transdermal drug delivery. This review focuses on the formulation and evaluation of anti-hypertensive transdermal microgels, highlighting their potential to enhance therapeutic efficacy and patient compliance. Various formulation approaches, including selection of polymers, cross-linking agents, penetration enhancers, and drug loading techniques, are discussed. Additionally, critical evaluation parameters such as particle size, swelling behavior, drug entrapment efficiency, in-vitro drug release, ex-vivo skin permeation, stability studies, and pharmacokinetic performance are reviewed. The role of microgels in overcoming skin barrier limitations and providing sustained antihypertensive drug delivery is emphasized. Overall, transdermal microgels represent a promising and innovative platform for effective management of hypertension.

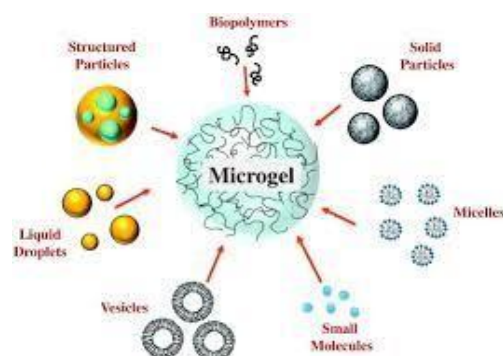
KEYWORDS: Transdermal drug delivery, Microgels, Antihypertensive drugs, Skin permeation enhancement.

I. INTRODUCTION:

Microgels:

Polymer microgels are crosslinked colloidal particles with a network structure that are swollen in a suitable solvent [1]. The vast array of applications that microgels are suitable for arises from their stimulus-responsive nature, that is, their ability to undergo reversible volume phase

transitions in response to external stimuli such as a change in pH, temperature, ionic strength of the surrounding medium and quality of solvent [2].



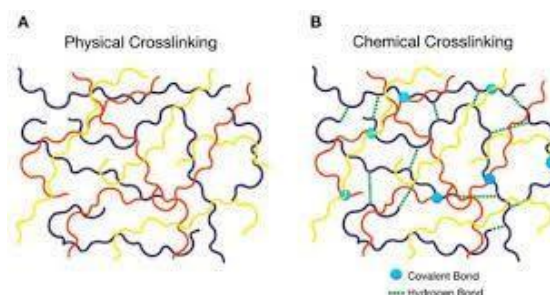
Classification of microgels :

➤ Physically-cross linked microgels

In physically crosslinked microgels, network formation occurs via non covalent attractive forces such as hydrophobic or ionic interactions and are constructed from biopolymers like chitosan particles^[3].

➤ Chemically cross-linked microgels

Covalently crosslinked microgels are typically synthesized by copolymerizing monomers in the presence of a multifunctional crosslinking agent. Microgels (1001000 nm) were obtained^[4].



Classification based on response :

Microgels may also be classified as stimuli-responsive or non-responsive gels^[5]. Non-

responsive microgels simply swell upon absorption of water whereas stimulus-responsive microgels swell or deswell by changes in the environment like temperature, pH, electric field and magnetic field^[6].

Advantages of Transdermal Microgels :

- Bypass first-pass hepatic metabolism, improving bioavailability.
- Provide controlled and sustained drug release.
- Improve patient compliance due to non-invasive application.
- Reduce dosing frequency and plasma drug fluctuations.
- Minimize gastrointestinal side effects and drug–food interactions.
- Enhance skin penetration and reduce dose-related toxicity^[7].

Disadvantages of Transdermal Microgels:

- Limited skin permeability restricts use to selected drugs only.
- Possibility of skin irritation or allergic reactions.
- Not suitable for drugs requiring high doses.
- Slow onset of action compared to oral or injectable dosage forms.
- Variability in drug absorption due to differences in skin condition and site^[8].

Mechanism of action of microgels transdermally:

The drug release in a swelling-controlled system is typically non-Fickian in nature. These models are based on Fick's Law, assuming perfect sink conditions, rapid surface equilibrium between the polymer and water^[9]. Release profile with an initial burst followed by a long period of sustained

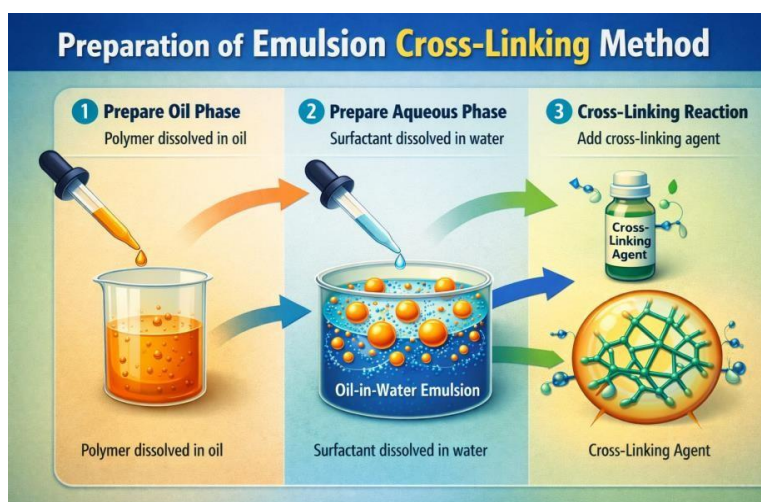
release was observed. The initial burst of drug was attributed to the low-density region of the gel attributed to surface adhesion and desorption while the slow long-term release was from the high-density microgel region. The burst effect is due to enzymatic cleavage causing degradation of polymer matrices and liberation of pools of drug. The solubility of drugs as well as their partition coefficients affect the driving forces for release, and can lead to rapid release due to thermodynamic imbalances^[10].

Methods of Preparation of Transdermal Microgels:

Transdermal microgels are small, cross-linked, hydrophilic polymeric particles capable of entrapping drugs and releasing them in a controlled manner through the skin.^[11] Various preparation methods are employed depending on the drug properties, polymer type, and intended release profile^[12].

II. Emulsion Cross-Linking Method:

Microgels are formed by cross-linking hydrophilic polymers present in the dispersed phase of an emulsion system. The drug is dissolved or dispersed in an aqueous polymer solution (e.g., sodium alginate, gelatin, chitosan)^[13]. This solution is emulsified into an oil phase (liquid paraffin) containing a surfactant (e.g., Span 80) under constant stirring. A cross-linking agent (e.g., calcium chloride, glutaraldehyde) is added slowly. Cross-linking leads to the formation of spherical microgels. Microgels are separated by filtration, washed, and dried^[14].

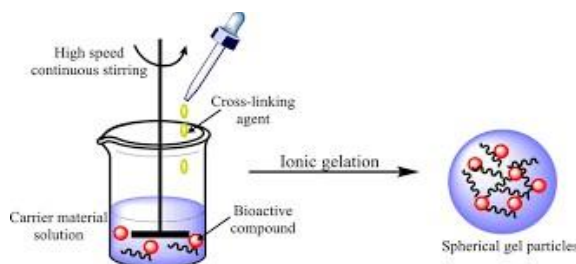


Advantages:

- Simple and economical
- Produces uniform microgels
- Suitable for hydrophilic drugs

Disadvantages:

- Use of oil phase
- Removal of residual oil may be difficult



III. Ionic Gelation Method:

Microgels are formed due to ionic interaction between oppositely charged polymers and cross-linking ions[15]. The drug is dissolved in a polymer solution (e.g., sodium alginate). This solution is added dropwise into a solution containing multivalent ions (e.g., Ca²⁺). Instant gelation occurs due to ionic cross-linking. The formed microgels are collected, washed, and dried[16].

Advantages:

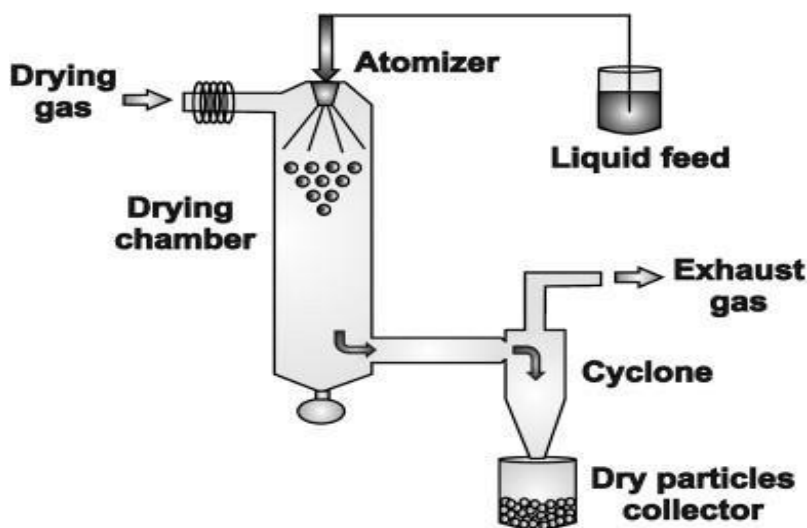
- a. No use of organic solvents
- b. Mild processing conditions
- c. Suitable for thermolabile drugs

Disadvantages:

- d. Lower mechanical strength
- e. Limited control over particle size[17].

IV. Spray Drying Method:

Microgels are formed by rapid solvent evaporation from polymer droplets. Drug and polymer are dissolved in a suitable solvent. The solution is sprayed into a heated chamber. Solvent evaporates instantly, forming dry microgels. The particles are collected using a cyclone separator[18].



Advantages:

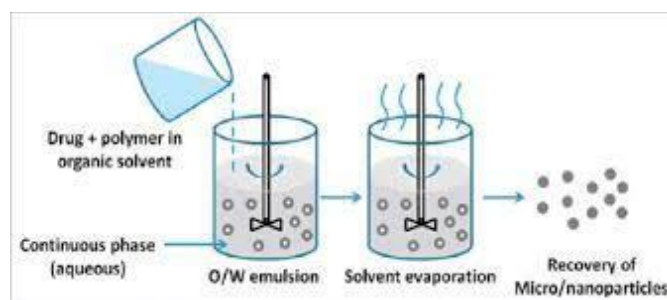
- a. Rapid and continuous process
- b. Good control over particle size
- c. Suitable for large-scale production

Disadvantages:

- d. High temperature may degrade heat-sensitive drugs
- e. Expensive equipment

V. Solvent Evaporation Method:

Microgels are formed by evaporation of solvent from polymer droplets dispersed in a continuous phase. Drug and polymer are dissolved in a volatile organic solvent[19]. This solution is emulsified into an aqueous phase. Continuous stirring causes solvent evaporation. Hardened microgels are collected and dried[20].



Advantages:

- Good encapsulation efficiency
- Suitable for hydrophobic drugs

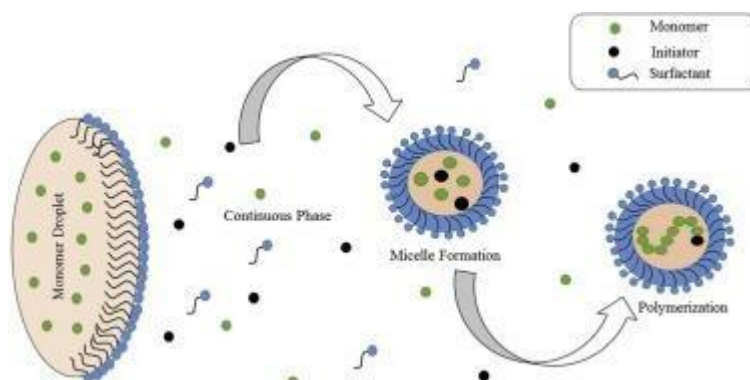
Disadvantages:

- Use of organic solvents
- Possible drug loss during evaporation

Microgels are prepared by polymerization of monomers within an emulsion system. Monomers, drug, and initiator are dispersed in an aqueous medium. Polymerization is initiated by heat or chemical initiators[21].

- Cross-linked microgels are formed.
- Microgels are purified and dried.

VI.Emulsion Polymerization Method:



Advantages:

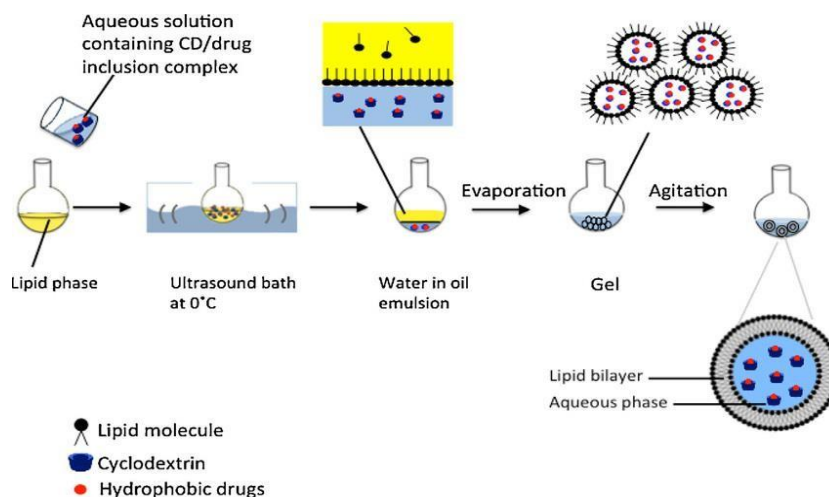
- Strong and stable microgels
- Controlled particle size

Disadvantages:

- Toxic monomers and initiators
- Complex process

VII.Reverse Phase Emulsion Method:

An aqueous polymer phase is dispersed in an oil phase, followed by cross-linking. Polymer and drug are dissolved in water. This aqueous phase is emulsified in oil using surfactants. Cross-linker is added to form microgels[22]. Microgels are recovered and washed.



Advantages:

- Produces small-sized microgels
- Suitable for hydrophilic drugs

Disadvantages:

- Oil removal is difficult
- Multiple washing steps required

Characterization of Transdermal Microgel:

Characterization of transdermal microgel is essential to evaluate its physical, chemical, and biological performance[23]. It ensures stability, uniform drug distribution, skin compatibility, and controlled drug release[24].

1. Physical Appearance:

- Color
- Clarity
- Homogeneity

Presence of aggregates or phase separation

A good microgel should be smooth, uniform, and free from lumps.

2. pH Measurement:

The pH is measured using a digital pH meter.

- Ideal range: 5.5–7, compatible with skin
- Prevents irritation and improves patient compliance

3. Viscosity:

Viscosity is measured using a Brookfield viscometer. Determines flow behavior Affects spreadability and drug release

- Higher viscosity → slower drug diffusion

4. Spreadability:

Spreadability indicates ease of application. It is calculated using:

Where:

$S = \text{Spreadability}$ $M = \text{Weight applied}$

$L = \text{Length moved by slide}$ $T = \text{Time taken}$

Good spreadability ensures uniform application on skin.

5. Drug Content Uniformity:

Drug content is analyzed using UV spectrophotometry or HPLC.

Ensures uniform drug distribution Typically expressed as % drug content Ideal range: 95–105%[25].

6. Particle Size Analysis:

Measured by dynamic light scattering or microscopy. Smaller particle size enhances skin penetration Ensures uniform microgel structure[26].

7. In Vitro Drug Release Study:

Performed using Franz diffusion cell. Determines release rate and mechanism Helps predict therapeutic effectiveness. Data fitted to kinetic models (zero order, first order, Higuchi)[27].

8. Ex Vivo Skin Permeation Study:

Conducted using animal or human cadaver skin. Evaluates permeation through biological membrane Measures flux and permeability coefficient[28].

9. Stability Study:

Microgel stored under different temperature conditions:

- Room temperature
- Refrigerated
- Accelerated conditions[29] Observed for changes in:
 - pH
 - viscosity
 - drug content
 - appearance

10. Skin Irritation Test:

Performed on animal models or reconstructed skin.

- Checks safety
- Confirms non-irritant nature

VIII. Conclusion:

Transdermal microgels are a promising drug delivery system that provides controlled and sustained drug release through the skin. Their stimulus-responsive structure, flexible preparation methods, and favorable physicochemical properties make them suitable for improving bioavailability and patient compliance. Proper characterization ensures stability, safety, and effective performance. Despite certain limitations such as permeability barriers and possible irritation, transdermal microgels offer significant advantages over conventional dosage forms and hold strong potential for future pharmaceutical applications.

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