



## Review Article

# Oral Gels in Drug Delivery: A Patient-Friendly Approach to Enhancing Therapeutic Efficacy

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### ABSTRACT

The aim of this review is to explore and evaluate oral gel formulations, utilizing both natural and synthetic polymers. Oral gels serve as effective drug delivery systems due to their ability to provide precise drug release, enhanced stability, and local therapeutic effects. Various physicochemical parameters of oral gels that influence their properties are discussed. Oral gels are evaluated for their gelling capacity, mechanical strength, bio-adhesion, spread-ability, microbiological safety, and in vitro drug release profiles. The analysis suggests that oral gel formulations offer a promising approach for local treatment in the oral cavity, improving drug bioavailability and enabling rapid action at the target site. They also reduce systemic side effects and avoid challenges related to gastrointestinal degradation or first-pass metabolism. Oral gels thus represent a safe, effective, and patient-friendly dosage form for managing oral conditions and delivering therapeutic agents efficiently. Further research is needed to optimize formulation strategies and fully understand the mechanisms of drug release and action in the oral cavity.

### INTRODUCTION

Oral gels are semi-solid dosage forms specifically designed to improve drug delivery within the oral cavity and gastrointestinal tract. They are characterized as semi-rigid systems in which the mobility of a liquid medium is restricted by a three-dimensional network of polymers or colloidal particles, resulting in desirable properties

such as muco-adhesion, spread-ability, and localized or systemic drug delivery potential. The term *gel*, derived from “gelatin” and rooted in the Latin *gelu* (frost) and *gelare* (to freeze), reflects their transformation from a liquid to an elastic, solid-like matrix capable of entrapping fluids. Historically, gels were recognized as a distinct pharmaceutical system in the late 19th century,

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when formulations were classified based on their physical and phenomenological characteristics.[1]

According to the United States Pharmacopeia (USP), gels are defined as semisolid systems containing either suspensions of small inorganic particles or dispersions of large organic macromolecules in a liquid medium. They may exist as two-phase systems, where discrete particles form a colloidal network or as single-phase systems, in which polymers are uniformly distributed without visible boundaries. For oral gels, water and hydroalcoholic solutions are the most widely used dispersion media.[2]

From a pharmaceutical standpoint, oral gels offer distinct advantages over conventional dosage forms. Their viscosity and mucoadhesive properties prolong residence time in the oral cavity, improve drug absorption, sustain therapeutic action, and enhance patient compliance. Many formulations exhibit reversible sol–gel transitions, allowing a switch between liquid and semisolid states under specific physiological conditions, while others form irreversible networks that improve stability. The physical appearance of oral gels may vary from transparent to turbid depending on the drug and excipients, with gelling agents typically employed in concentrations of 0.5–2.0%. Despite such small quantities, these agents impart a broad range of rheological and mechanical properties, making gels highly versatile carriers for drugs including antifungal, antimicrobial, analgesic, anti-inflammatory, and more recently, antidiabetic agents.[3]

### Evolution of Oral Gels in Drug Delivery

The development of oral gels as pharmaceutical systems has undergone significant transformation over the last century. Originally, gels were limited to topical, dental, and cosmetic applications,

where their semi-solid consistency, spreadability, and ease of local application were valued. With advances in polymer science and colloidal chemistry, their potential as carriers for oral and systemic drug delivery gradually emerged. [4,5]

- 1) **Early Stage (Topical & Dental Applications):** Oral gels were initially used for local treatment of infections, inflammation, and pain within the oral cavity, such as antifungal (clotrimazole gels) or analgesic gels. [6,7]
- 2) **Expansion to Systemic Delivery:** The introduction of biocompatible polymers (e.g., carbopol, hydroxypropyl methylcellulose) allowed gels to be adapted for oral administration of drugs intended for systemic absorption. [8,9]
- 3) **Mucoadhesive Gels:** By the late 20th century, research shifted toward mucoadhesive formulations that adhered to oral or gastrointestinal mucosa, improving residence time and bioavailability. This was especially valuable for drugs with poor solubility or rapid degradation.[10]
- 4) **In-situ Gelling Systems:** The next step was in-situ gels, which are administered as liquids but transform into gels under physiological triggers such as pH, ionic strength, or temperature. These systems offered better patient compliance and controlled release.[11]
- 5) **Smart/Stimuli-Responsive Gels:** Recent innovations focus on responsive gels that can react to external or internal stimuli (e.g., pH-sensitive, temperature-sensitive, enzyme-sensitive, or glucose-sensitive). These systems have opened opportunities for precision medicine, particularly in chronic conditions such as diabetes. [12,13]



**Table 1 : Routes of Administration and Delivery Pathways for Oral Gels [14,15,16]**

Route of Administration	Description	Advantages
<b>Buccal Route (Via Oral Mucosa)</b>	Oral gels are applied to the buccal cavity where drugs penetrate the mucosal lining.	Bypasses gastrointestinal degradation and hepatic first-pass metabolism, improves systemic bioavailability.
<b>Sublingual Route</b>	Gel placed beneath the tongue, enabling rapid diffusion through sublingual mucosa.	Provides rapid onset of action due to high vascularization.
<b>Gastrointestinal Route (Swallowed Gels)</b>	Oral gels are swallowed and act in the GI tract, releasing drug locally or systemically.	Useful for gastric/intestinal disorders, systemic absorption; mucoadhesive polymers prolong GI residence.
<b>Mucoadhesive/ Periodontal Route</b>	Applied to gingival or periodontal pockets for sustained local release.	Effective for dental/periodontal infections and inflammation.
<b>Targeted/Modified Release (In-situ &amp; Stimuli-Responsive Gels)</b>	Gels undergo sol-to-gel transition under triggers like pH, ionic strength, or temperature.	Improves patient compliance, provides controlled or site-specific drug release.

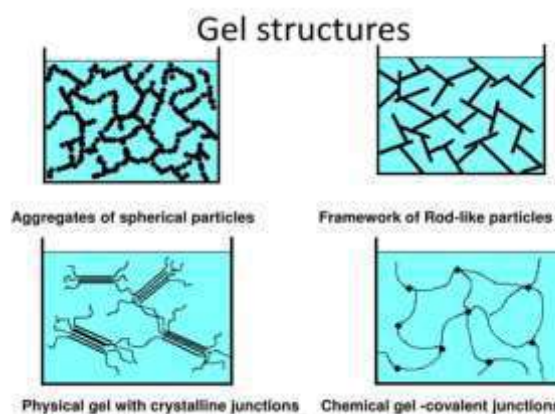
### Gel structure and Network Formation:

The rigidity and stability of oral gels are primarily derived from the three-dimensional network formed by gelling agents. This network results from the interconnection of particles, and its structural characteristics depend on both the nature of the gelling agent and the type of intermolecular forces involved.[17]

In oral gels, hydrophilic colloids can exist either as spherical units, aggregates of smaller molecules, or as long polymeric chains. These components interconnect to create a gel matrix through different arrangements, such as entangled polymer chains or ordered crystalline alignments. The degree of cross-linking and organization directly influences the viscosity, spreadability, and drug release properties of the formulation.[18]

The interactions that stabilize the gel framework vary in strength, ranging from strong covalent linkages (as in certain inorganic gels like silica-based systems) to weaker forces such as hydrogen bonding, ionic interactions, or van der Waals attractions. In gels dominated by weaker interactions, a minor increase in temperature can

disrupt the structure and lead to liquefaction. This property is particularly important in designing oral gels, as it determines their thermal stability, shelf-life, and patient acceptability.[19]



**Figure 1:** shows different types of gel network structures, including spherical particle aggregates, rod-like frameworks, crystalline junctions, and covalent junctions.

### Advantages of Gels: [20,21,22]

1. Improved Patient Compliance easy to administer, especially for pediatric, geriatric, and dysphagic patients.
2. Controlled Drug Release can sustain or localize drug release depending on the gel matrix (physical or chemical network).

3. High Stability of API protects sensitive drugs (e.g., peptides, proteins) from degradation in liquid solutions.
4. Better Bioavailability enhances solubility and absorption of poorly water-soluble drugs.
5. Ease of Formulation simple preparation with biopolymers (e.g., polysaccharides, cellulose derivatives).
6. Non-greasy & Pleasant Texture preferred over ointments and creams in topical use.
7. Targeted Delivery can adhere to mucosal surfaces (buccal, oral, vaginal) and provide site-specific action.
8. Reduced Side Effects lower systemic absorption in topical/oral gels compared to oral solid dosage forms.
8. Not suitable for all drugs poor choice for lipophilic drugs unless modified with surfactants or cosolvents.

### **Key Properties of Gels:** [26,27,28]

#### **1. Network Structure**

The firmness and rigidity of gels arise from the three-dimensional network formed by interconnected particles of the gelling agent. The type of particles and the forces linking them whether physical (hydrogen bonding, van der Waals) or chemical (covalent cross-links) determine the mechanical strength, elasticity, and overall properties of the gel.

#### **2. Swelling Behavior**

Gels can absorb liquids and expand in volume, which represents the initial stage of gel-solvent interaction. When a solvent penetrates the gel matrix, the original gel-gel interactions are replaced by gel-solvent interactions. The extent of swelling is often restricted by cross-linking within the gel network, which prevents complete dissolution. Swelling is maximized when the solvent's properties closely match the gelling agent's solubility characteristics.

#### **3. Syneresis (Contraction of Gel)**

Over time, gels may undergo shrinkage, releasing interstitial fluid to the surface a phenomenon known as syneresis. This occurs in hydrogels, organogels, and inorganic gels. The process is influenced by polymer concentration, pH, electrolyte levels, and relaxation of elastic stresses formed during gel setting, which reduces the available space for solvent, forcing its expulsion.

#### **4. Ageing**

### **Disadvantages of Gels:** [23,24,25]

1. Limited drug loading not suitable for drugs requiring high doses due to solubility and viscosity constraints.
2. Physical instability prone to dehydration, shrinkage (syneresis), or microbial contamination during storage.
3. Chemical instability some gels are sensitive to pH, temperature, or ionic strength, altering drug release.
4. Short residence time in oral gels, rapid dilution or swallowing may reduce contact time with mucosa.
5. Irritation potential certain gelling agents or preservatives may cause irritation/allergic reactions.
6. Sterility issues aqueous gels can support microbial growth, requiring preservatives or sterile handling.
7. Viscosity variation environmental conditions (temperature, ionic content) can alter gel consistency.



Gels are dynamic systems and may continue to change after initial formation. Ageing refers to slow, spontaneous structural rearrangements in the gel, resulting in a denser network of gelling agent over time. This process resembles the initial gelation and can lead to gradual loss of free fluid from the gel matrix.

### 5. Rheological Properties

Gels typically show non-Newtonian, pseudoplastic flow behavior, where viscosity decreases under increasing shear stress. In particulate gels, applied stress disrupts interparticle associations, while in polymer-based gels, macromolecules align along the direction of flow, reducing internal resistance. This property is

crucial for processing, application, and ease of administration.

### 6. Transparency

Many gels exhibit optical clarity due to uniform dispersion of gelling agents and solvents, which can enhance patient acceptability and allow visual assessment of homogeneity or phase separation.

### 7. Adhesiveness

Gels often possess mucoadhesive or surface-adhesive properties, allowing them to adhere to mucosal membranes (oral, buccal, vaginal) or skin, which facilitates localized drug delivery and prolongs residence time.

### Classification of Gel:[29,30]

**Table 2: Classification of Gels Based on Composition, Cross-linking, and Application.**

Classification Basis	Type of Gel	Description
Nature of Solvent	Hydrogel	Water is the dispersion medium; e.g., gelatin, alginate gels
	Organo-gel	Organic solvent as medium; e.g., sorbitol organo-gel
Type of Cross-linking	Physical Gel	Non-covalent interactions like hydrogen bonds, ionic interactions; reversible
	Chemical Gel	Covalent cross-linking; permanent network; e.g., polyacrylamide gel
Nature of Particles	Inorganic Gel	Formed by inorganic particles; e.g., silica gel, aluminum hydroxide
	Organic Gel	Formed by organic macromolecules; e.g., polysaccharides, proteins, synthetic polymers
Swelling Behavior	Superabsorbent Gel	High liquid uptake capacity; used for wound dressings, diapers
	Non-absorbent Gel	Limited swelling; maintains structure without much liquid uptake
Application / Route	Topical Gel	Applied to skin; e.g., antiseptic gels, anti-inflammatory gels
	Oral / Buccal Gel	For drug delivery in the oral cavity; e.g., mucoadhesive gels
	Vaginal / Rectal Gel	Localized drug delivery to mucosal surfaces; e.g., antifungal gels

### Gel-Forming Agents in Oral Gels:

In oral gel formulations, gel-forming agents play a crucial role in establishing a stable semisolid

structure when dispersed in a liquid medium. These agents can be hydrophilic natural hydrocolloids or synthetic polymers, which form a three-dimensional network that provides viscosity



and consistency without making the gel overly stiff. Natural polymers like fenugreek gum, xanthan gum, and tragacanth are widely used for their biocompatibility, mucoadhesive properties, and ability to control drug release in the oral cavity.

Synthetic polymers such as carbomers (cross-linked acrylic acid derivatives) and hydroxypropyl methylcellulose (HPMC) are frequently employed due to their excellent thickening efficiency across

a broad pH range, ease of formulation, and reproducible gel properties. Even at low concentrations, these polymers impart a smooth semisolid texture, improving the gel's residence time on oral mucosa and enhancing patient compliance. Additionally, gelling agents help maintain uniform dispersion of the active pharmaceutical ingredient, prevent sedimentation, and contribute to controlled or sustained release of the drug at the site of action.

**Table 3: Natural gelling agents used in pharmaceutical formulations.**

Polymer Name	Chemical Nature	Pharmaceutical Applications	References
<b>Agar (Agarobiose)</b>	Composed of agarose and agaropectin (D-galactose units)	Used in gelling suppositories, tablet disintegrants, suspending agents, emulsifying agents, laxatives, bacterial cultures, and surgical lubricants	Kulkarni et al., 2012 [31]
<b>Aloe Gel</b>	Natural plant gel containing polysaccharides and mucilaginous substances	Used in gelling suppositories, sustained-release matrices, suspending agents, emulsifying agents, and direct compressible tablets	Alonso et al., 2009; Hamman et al., 2008; Ahad et al., 2010 [32]
<b>Albumin</b>	Plasma protein with three homologous domains and 585 amino acids (human serum albumin)	Used for gene delivery, injectable formulations, nanoparticle preparation, and peptide/protein-based drug delivery	Langer et al., 2003 [33]
<b>Alginic Acid</b>	Edible polysaccharide from brown algae	Used as stabilizer for oil-in-water emulsions, thickening agent, suspending agent, and for pastes, creams, and gels	Suhail et al., 2021 [34]
<b>Arginine</b>	Amino acid essential for protein synthesis	Used in formulations to support immune function and protein-based therapies	IUPAC-IUB Joint Commission [35]
<b>Guar Gum</b>	Galactomannan polysaccharide from guar beans	Used as a binder or disintegrator in tablets; main ingredient in some bulk-forming laxatives	Thombare et al., 2016 [36]
<b>Gellan Gum</b>	Anionic polysaccharide produced by <i>Sphingomonas elodea</i>	Used in controlled-release drug delivery systems, suspensions, emulsions, gels, and as a binder in tablet formulations	ScienceDirect, 2023 [37]
<b>Gelatin</b>	Protein derived from collagen of animal origin	Used in gelling agents, capsule shells, stabilizers in emulsions, tablet binders, and sustained-release matrices	Singh et al., 2020 [38]

### Semi-synthetic polymers:



Semi-synthetic polymers, particularly **cellulose derivatives**, are extensively utilized in pharmaceutical and cosmetic formulations due to their versatile physicochemical and mechanical properties. These derivatives are primarily classified into **cellulose ethers** and **cellulose esters**, each exhibiting distinct solubility and functional characteristics. Cellulose derivatives are valued for their uniform molecular arrangement, surface activity, film-forming ability, and resistance to oxidation, biodegradation, and hydrolysis. **Cellulose ethers**, such as methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose, and sodium carboxymethyl cellulose,

are water-soluble and widely applied as gelling agents, bioadhesives, stabilizers, and thickeners. In contrast, **cellulose esters**, including cellulose acetate, cellulose acetate phthalate, and cellulose acetate butyrate, have limited water solubility and are mainly used for controlled-release coatings and protective films. Compared to natural gelling agents like starch, acacia, sodium alginate, agar, and gelatin, cellulose derivatives are less susceptible to microbial contamination, making them ideal for semisolid preparations such as gels, creams, ointments, and shampoos. Their stability, adaptability, and broad applicability have established them as essential excipients in both pharmaceutical and cosmetic industries.[39]

**Table 4: Semi-synthetic polymer used in pharmaceutical formulation**

Polymer Name	Applications	References
<b>Hydroxypropyl methylcellulose (HPMC)</b>	Film formation and prolonged product wear	Silva, A., et al. (2005). <i>Journal of Pharmaceutical Sciences</i> , 94(9), 2005. [40]
<b>Polyacrylic acid</b>	Prolonged shelf life of the product	Ohara, K., et al. (2021). <i>International Journal of Pharmaceutics</i> , 602, 120678. [41]
<b>Cellulose acetates</b>	Thermoplastic film formation and heat resistance	Mohite, P., et al. (2014). <i>International Journal of Polymer Science</i> , 2014, 1–8. [42]
<b>Polyamides</b>	Extended product wear, improved shelf life, rheological control, and easy application	Patil, R., et al. (2013). <i>Journal of Applied Polymer Science</i> , 128(6), 4076–4085. [43]
<b>Nitrocellulose</b>	Film development and prolonged product wear	Tafuro, M., et al. (2019). <i>International Journal of Cosmetic Science</i> , 41(5), 457–464. [44]
<b>Hydroxyethyl cellulose</b>	Rheological control and ease of use	National Center for Biotechnology Information. (n.d.). <i>Hydroxyethyl cellulose</i> . [45]
<b>Cellulose nitrates</b>	Biodegradation, hydrolysis, and oxidation	Costa, P., et al. (2019). <i>Journal of Applied Polymer Science</i> , 136(12), 47126. [46]
<b>Acrylate copolymers</b>	Enhanced product design and formulation improvement	Penzel, R., et al. (2000). <i>Journal of Cosmetic Science</i> , 51(3), 123–132. [47]
<b>Cellulose derivatives</b>	Solution viscosity control and surface performance	Iunchedii, T., et al. (2002). <i>European Journal of Pharmaceutics and Biopharmaceutics</i> , 53(1), 1–9. [48]

### Synthetic polymer:

Carbomer, a member of the Carbopol family, is one of the most widely used synthetic polymers in



gel formulations. Introduced in the 1950s, carbomers are available as powdered substances with high bulk density and are typically used to prepare aqueous gels with an acidic pH of around 3. When the pH is increased to 5–6, carbomer dispersions swell significantly and achieve high viscosity, ranging from 0 to 80,000 centipoise, depending on concentration and polymer grade.

These polymers can expand several times their original volume upon hydration, providing efficient gel formation and stability. Other commonly used synthetic gelling agents include poloxamers, polyacrylamides, and surfactant-based polymers, which contribute to the rheological control, spreadability, and structural integrity of gel products.[50]

**Table 5: Synthetic polymer used in pharmaceutical formulation.**

Polymer Name	Key Properties / Applications	Reference
Carbomer (Carbopol)	Swelling and gel formation; controllable viscosity; high stability; pH-responsive thickening; 0–80,000 cP viscosity	ScienceDirect (n.d.) [51]
Poloxamers	Thermoresponsive gel formation; sol–gel transition; improved drug release and spreadability	ScienceDirect (n.d.) [52]
Polyacrylamides	Rheological control; structural integrity; thickening agent; stabilizer in gels	PubChem (n.d.) [53]
Surfactant-based polymers	Enhances solubilization, spreadability, and gel consistency; stabilizes formulations	NCBI (n.d.) [54]
Polyvinyl alcohol (PVA)	Film-forming, thickening, and stabilizing properties; biocompatible; used in ophthalmic and topical gels	PubChem (n.d.) [55]
Polyvinylpyrrolidone (PVP)	Solubilizing agent; viscosity enhancer; adhesive properties; improves gel clarity and consistency	ScienceDirect (n.d.) [56]
Hydroxypropyl cellulose (HPC)	Water-soluble polymer; film-forming, thickening, and rheology control; improves gel stability and drug release	PubChem (n.d.) [57]

## Types of Gels:

### Hydrogels:

Hydrogels are three-dimensional polymeric networks capable of absorbing and retaining large amounts of water while remaining insoluble in aqueous solutions due to physical or chemical cross-linking between polymer chains. Hydrophilic hydrogels possess unique physicochemical properties that make them highly suitable for biomedical applications and drug delivery systems, unlike hydrophobic polymers such as poly(lactic acid) (PLA) or poly(lactide-co-glycolide) (PLGA), which exhibit limited water absorption. Hydrogel formation usually occurs at room temperature without the need for organic solvents. They are further distinguished by their ability to undergo in situ gelation and encapsulate

cells or therapeutic agents. Depending on the source of the polymer, hydrogels can be derived from either natural or synthetic materials.[58]

### Organo gels

Organo-gels are semisolid systems in which the continuous phase is a non-aqueous solvent. Examples include Plastibase (a formulation of low molecular weight polyethylene dissolved in mineral oil and cooled) and dispersions of metallic stearates in oils. Structurally, organo-gels are thermo-reversible, non-crystalline materials composed of an interconnected organic liquid phase, which may include mineral oil, vegetable oil, or other organic solvents. Their rheological and stability properties largely depend on the solubility and molecular interactions of the gelators. Organo-gels are widely explored for



applications in pharmaceuticals, cosmetics, food, and industrial products. In some cases, undesirable thermo-reversible gels may form, such as wax crystallization in crude petroleum.[59]

### **Xerogels:**

Xerogels are solid forms of gels obtained after the removal of solvent from the gel matrix, usually through evaporation or heating. They possess small pore sizes (1–10 nm), high surface areas (150–900 m<sup>2</sup>/g), and moderate porosity (~25%). Common examples include dried gelatin, acacia, tragacanth, cellulose derivatives, and polystyrene. Although xerogels generally retain their overall structure, they often undergo significant shrinkage during drying, which can lead to cracking and brittleness. When exposed to higher drying temperatures, the porous network collapses further, converting the gel structure into a dense, glass-like material.[60]

### **Aerogels:**

Aerogels are lightweight, highly porous materials formed when the liquid component of a gel is replaced with gas under supercritical drying, preventing network shrinkage. They exhibit high porosity, large surface area, and excellent thermal insulation properties, making them useful in pharmaceuticals, catalysis, and biomedical applications.[61]

### **Methods of Gel Preparation:**

Gels can be produced by a variety of techniques, depending on the type of polymer, solvent system, and desired final properties. While many gels are prepared at room temperature, some polymers require specific conditions such as thermal treatment, cross-linking, or solvent exchange. The major methods include thermal variation,

flocculation, chemical reaction, solvent exchange, diffusion, irradiation, and enzymatic cross-linking.

## **1. Thermal-Induced Gelation**

Temperature plays a critical role in the solubility and hydration of certain polymers. Many hydrogen-bond-forming colloids are more soluble in hot water than in cold. On cooling, hydration decreases, causing the polymer chains to associate and form a three-dimensional gel matrix. Examples include gelatin, agar, sodium oleate, guar gum, and cellulose derivatives. Conversely, some polymers like cellulose ethers undergo gelation upon heating due to the disruption of hydrogen bonds with water, which reduces solubility and promotes network formation.[62]

## **2. Flocculation-Induced Gelation**

This method relies on partial precipitation by adding controlled amounts of salts or non-solvents. The precipitant concentration is carefully maintained to avoid complete precipitation, allowing only a loose network structure to form. Quick and uniform mixing is essential. For instance, ethyl cellulose or polystyrene dissolved in benzene can be gelled using petroleum ether as a non-solvent. Such gels often display thixotropy, meaning they liquefy upon agitation and regain their gel structure when allowed to rest.[63]

## **3. Chemically-Induced Gelation**

Here, gelation is achieved through chemical reactions that cross-link the polymer chains, producing stable three-dimensional structures. A common example is aluminum hydroxide gel, formed by the reaction of aluminum salts with sodium carbonate in aqueous solution. Additionally, polymers such as polyvinyl alcohol (PVA) and cyanoacrylates can be cross-linked with agents like glycidyl ethers, toluene



diisocyanate (TDI), or methylene diphenyl diisocyanate (MDI) to generate durable gels with enhanced mechanical strength.[64]

#### 4. Solvent Exchange Method

In this process, the solvent in a polymer solution is gradually replaced with a non-solvent, leading to phase separation and gel formation. This technique is particularly useful in preparing hydrogels and organo-gels, where the solvent exchange drives the polymer chains to aggregate into a network structure.[65]

#### 5. Diffusion Method

Gelation can also occur by controlled diffusion of a gelling agent into a polymer solution. The slow penetration of ions, solvents, or reactants promotes a gradual network formation. This approach is commonly used in the preparation of ionotropic gels such as calcium alginate beads, where calcium ions diffuse into a sodium alginate solution and induce cross-linking.[66]

#### 6. Irradiation-Induced Gelation

High-energy radiation such as gamma rays, electron beams, or UV light can induce cross-linking in polymeric materials, leading to gel formation without requiring additional chemical cross-linkers. This method is especially valuable for producing sterile biomedical hydrogels and drug delivery matrices.[67]

#### 7. Enzymatic Cross-Linking

Enzymes such as transglutaminase, peroxidases, or laccases can be used to catalyze the cross-linking of natural polymers like proteins and polysaccharides, resulting in biocompatible gels. This method is particularly attractive in

pharmaceutical and food applications because it avoids toxic reagents and allows mild processing conditions.[68]

#### Formulation Considerations for Oral and Topical Gels:

The successful development of pharmaceutical gels relies on the careful selection of excipients to ensure stability, safety, and therapeutic effectiveness. A critical factor in gel formulation is the choice of vehicle or solvent, with purified water being the most commonly used base. Co-solvents such as glycerol, propylene glycol, polyethylene glycol (PEG 400), or alcohol are often included to enhance drug solubility and facilitate permeation across biological membranes. Buffers, including phosphate and citrate, help maintain the pH within an optimal range for both drug stability and patient comfort, though their solubility may be reduced in hydroalcoholic gels. Preservatives are incorporated to prevent microbial growth; since they can interact with hydrophilic polymers and reduce their active concentration, slightly higher amounts of parabens or phenolic compounds are often necessary. Antioxidants, such as sodium metabisulfite or sodium formaldehyde sulfoxylate, are added when the active ingredient is prone to oxidation, with the choice depending on the nature of the gel vehicle. For oral formulations, flavoring and sweetening agents are included to improve palatability and patient compliance, particularly in gels intended for conditions like infections, inflammation, or ulcers. Sweeteners such as sucrose, sorbitol, glycerol, saccharin sodium, and aspartame, and flavors like mint, cherry, citrus, butterscotch, or vanilla, enhance taste and mouthfeel, directly influencing patient acceptability and adherence to therapy. [69,70]



**Table 6: Formulation consideration for oral and topical gel.**

Formulation Aspect	Purpose	Examples	Reference
<b>Vehicle/Solvent</b>	Provides the main base for the gel; enhances solubility and drug permeation when co-solvents are used	Purified water, glycerol, alcohol, propylene glycol, PEG-400	[Gowda et al., 2020] [71]
<b>Buffers</b>	Maintains pH for drug stability and reduces irritation; helps optimize solubility	Phosphate buffer, citrate buffer	[Tadros, 2010] [72]
<b>Preservatives</b>	Prevents microbial growth; compensates for binding with polymers by increasing initial concentration	Parabens, phenolic compounds	[Barry, 2001] [73]
<b>Antioxidants</b>	Protects drugs sensitive to oxidation; choice depends on vehicle type	Sodium metabisulfite, sodium formaldehyde sulfoxylate	[Lachman et al., 2019] [74]
<b>Flavors &amp; Sweeteners</b>	Improves taste and palatability for oral gels; enhances patient compliance	Sweeteners: sucrose, sorbitol, glycerol, saccharin sodium, aspartame. Flavors: mint, citrus, cherry, vanilla, butterscotch	[Raghavendra & Singh, 2020] [75]
<b>Viscosity Modifiers</b>	Controls gel consistency, spreadability, and stability; ensures desired rheological properties	Carbomers, HPMC, xanthan gum, guar gum	[Peppas & Merrill, 1977] [76]
<b>Permeation Enhancers</b>	Improves drug absorption across mucosal or skin barriers	Ethanol, oleic acid, dimethyl sulfoxide (DMSO), propylene glycol	[Prausnitz & Langer, 2008] [77]

### Key Factors Influencing Topical and Oral Gel Drug Delivery:

The effectiveness of drug delivery via topical or mucosal gels depends on multiple interrelated factors:

#### 1. Physiological Factors

- Skin or mucosal properties such as thickness, hydration level, and hair follicle density.
- Variability due to age, gender, race, anatomical site, general health, and environmental conditions (temperature, humidity).

- To minimize variability, the rate-limiting step should be within the formulation rather than the biological barrier.[78]

#### 2. Drug Physicochemical Properties

- Molecular weight and size, which affect diffusion.
- Partition coefficient between vehicle and application site.
- Melting point, stability, and chemical functionality (influences ionization potential, binding affinity, solubility).
- These properties determine the drug's ability to diffuse through the vehicle and permeate the skin or mucosa.[79]



### 3. Formulation Components and Vehicle Factors

- **Effect on drug:** Influences drug diffusion, thermodynamic activity, stability, and ionization.
- **Effect on site of application:** Alters barrier properties via chemical or physical changes, promoting hydration or increased penetration.
- **Vehicle consistency and viscosity:** Determines adhesion, retention, and duration of contact at the application site.[80]

### 4. Topical Vehicle Classification

- Vehicles can be liquid, semisolid, or solid.
- Semisolid forms (gels, creams, ointments) are the most widely used due to their ease of application, retention, and controlled drug release.[81]

The evaluation of gels involves key parameters to ensure stability, effectiveness, and suitability for their intended use. pH is measured using a digital pH meter after dispersing the gel in distilled water. Drug content is assessed by dissolving the gel in a suitable solvent, filtering, and quantifying via spectrophotometry using calibration curves. Viscosity and rheology are evaluated with rotational viscometers, influencing spreadability, retention, and patient acceptability. Spreadability is determined by measuring the ease with which a gel moves between slides, while extrudability assesses the force required to dispense the gel from containers. For topical or mucosal gels, irritation studies are conducted to ensure safety. Collectively, these evaluations provide a comprehensive understanding of the gel's physicochemical properties and therapeutic potential across oral, topical, and specialized applications.[82]

### Evaluation of Formulated Gel:

**Table 6: Evaluation parameter of gel**

Parameter	Method	Significance	Example / Notes	Ref.
pH	Digital pH meter; gel dispersed in distilled water, equilibrated, measured in triplicate	Ensures stability, safety, and patient compatibility	All topical, oral, mucosal gels	Rowe et al., 2009 [83]
Drug Content / Assay	Dissolve gel in suitable solvent, filter, measure by UV/HPLC	Ensures uniformity and correct dose	Herbal, synthetic, combination gels	Lachman et al., 2013 [84]
Viscosity / Rheology	Rotational viscometer at multiple shear rates	Determines flow, spreadability, retention	Semisolids: hydrogel, organogel, carbomer gels	Bogdan & Zupančič, 2018 [85]
Spreadability	Gel placed between slides; measure time or force for slide movement	Indicates application ease & therapeutic coverage	Topical, oral cavity, vaginal gels	Kaur et al., 2015 [86]
Extrudability	Gel packed in tubes/syringes; force to extrude defined ribbon/volume	Assesses dispensing efficiency	Topical gels, oral gels in tubes	Gupta & Aggarwal, 2017 [87]
Skin / Mucosal Irritation	Apply gel to shaved area/patch test; observe for reactions	Safety & tolerability	Topical, mucosal gels	Draize et al., 1944 [88]
Homogeneity	Visual/microscopic inspection	Detects uniform dispersion of drug/excipients	All gel types	Lachman et al., 2013 [89]

Syneresis / Phase Separation	Store gel; observe for liquid separation/contraction	Physical stability	Hydrogels, organogels	Swarbrick & Boylan, 2012 [90]
Thermal / Temperature Stability	Expose gel to varying temps; check viscosity, pH, phase changes	Stability during storage & transport	All semisolid gels	Jain, 2015 [91]
Drug Release / In-vitro Diffusion	Franz diffusion cell/membrane-based studies	Evaluates drug availability & release profile	Hydrogels, organogels, oral gels	Franz, 1975 [92]
Microbial Load / Sterility	Plate count, microbial limit, sterility tests	Product safety & shelf life	Aqueous/natural gels	USP, 2023 [93]
Appearance / Color / Odor	Visual inspection	Patient acceptability & batch consistency	All gel types	Banker & Rhodes, 2002 [94]
Content Uniformity	Sampling multiple points in batch; assay for drug	Consistent dose per unit	Oral, topical, vaginal gels	Aulton & Taylor, 2017 [95]

**Table 7: Examples of commercial gel formulations with their active ingredients, gelling agents, and routes of administration.**

Sr. No.	Active Ingredient	Proprietary Name	Gelling Agent	Route & Use
1	Clindamycin	Cleocin T Gel	Carbomer	Acne Vulgaris
2	Acetic acid	Aci-jel	Tragacanth, Acacia	Vaginal: restoration and maintenance of acidity
3	Benzoyl peroxide	Desquam-X Gel	Carbomer 940	Acne vulgaris
4	Tretinoin	Retin-A	Hydroxypropyl Cellulose	Acne Vulgaris
5	Metronidazole	Metro-Gel	Carbomer	Vaginal: Bacteria
6	Desoximetasone	Topicort Gel	Carbomer 940	Anti-inflammatory; antipruritic
7	Cyanocobalamin	Nascobal	Methyl Cellulose	Nasal: Hematologic
8	Progesterone Supplement	Crinone-Gel	Carbomer	Progesterone
9	Clobetasol	Termovate Gel	Carbomer 934	Antipruritic
10	Becaplermin	Regranex Gel	Na CMC	Dermatologic

## CONCLUSION:

Oral gels are gaining increasing attention due to their enhanced stability and ability to provide controlled drug release compared to other semisolid oral preparations such as pastes or suspensions. Oral gel formulations can improve drug absorption in the oral cavity, thereby increasing the bioavailability of the active ingredient. A thorough evaluation of the stability and physicochemical properties of oral gels over time can support their therapeutic application.

Since many gelling agents are water-soluble, they form easily washable gels, offering greater patient compliance and comfort. The key advantage of oral gel delivery lies in targeting the drug locally within the oral cavity, allowing higher concentrations at the site of action, which is particularly beneficial for drugs with short biological half-lives or narrow therapeutic windows. Clinical evidence indicates that oral gels are a safe and effective dosage form for managing oral diseases and conditions, enhancing both therapeutic efficacy and patient convenience.

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