

Thermosensitive Hydrogel for Drug Delivery: Mechanism and Application

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ABSTRACT: Thermosensitive hydrogels are highly valuable biomaterials in drug delivery systems (DDSs) due to their ability to undergo sol-to-gel phase transitions in response to temperature changes. This unique property has attracted increasing attention from researchers. Additionally, thermosensitive hydrogels can rapidly form a gel at the application site with just a slight temperature change, eliminating the need for organic solvents, cross-linking agents, or external equipment. This allows the loaded drugs to remain localized, enhancing drug concentration at the target site while reducing the risk of systemic toxicity or side effects. These advantages make thermosensitive hydrogels one of the most promising and effective drug delivery systems in modern biomedical applications. This review article explores the background of thermosensitive hydrogels, highlighting their unique properties and diverse applications in drug delivery. It covers their use in transdermal, oral, ophthalmic, intravaginal, nasal, and rectal drug delivery, as well as their role in cancer therapy and cell-loaded drug delivery systems.

Thermosensitive hydrogels have gained significant attention as intelligent biomaterials in biochemistry and biomedicine. They offer several advantages, including ease of formulation for delivering both hydrophilic and hydrophobic drugs, high drug loading capacity, convenient administration, and sustained drug release. Additionally, their ability to provide targeted drug delivery through injections reduces the need for surgical interventions, enhancing patient compliance and therapeutic effectiveness.

KEYWORDS: Drug Delivery System; Thermosensitive hydrogels; Drug release mechanism.

I. INTRODUCTION

Intelligent hydrogels are a type of stimuli-sensitive hydrogel that undergo a sol-to-gel transition in response to various external factors such as pH^[1], temperature, light^[2], electrical fields^[3], and magnetic fields^[4]. Among these, thermosensitive hydrogels specifically transition from a liquid to a gel state as the environmental temperature changes^[5]. These hydrogels, synthesized using thermo-sensitive polymers, are widely recognized for their sustained-release properties and have emerged as promising drug delivery vehicles in recent years.

Hydrogels are aqueous, viscous, semisolid preparations composed of a gel matrix and a drug. They are widely preferred for local drug administration due to their ability to provide sustained release at a targeted site. Additionally, hydrogels have diverse applications in drug delivery, tissue engineering, and biosensors, among other fields^[6]. In recent years, thermosensitive hydrogels have emerged as promising drug carriers due to their biodegradability, low toxicity, high drug-loading capacity, site specificity, and sustained drug release^[7]. Thermosensitive hydrogels are a type of smart hydrogel that responds to temperature stimuli, undergoing a sol-to-gel transition within a specific temperature range. Typically, these hydrogels are synthesized from natural and derived thermosensitive polymers using conventional methods such as crosslinking and polymerization^[8]. Due to their desirable properties, including good mechanical stability, excellent biocompatibility, thermoresponsive behavior, and ease of formulation, thermosensitive hydrogels hold great promise for drug delivery applications^[9-11].

Thermosensitive hydrogels have gained significant attention from researchers worldwide due to their exceptional properties and biocompatibility. This review article explores the background of thermosensitive hydrogels, their key properties, and their applications in various drug delivery systems,

including transdermal, oral, ophthalmic, cancer therapy, intravaginal, and cell-loaded formulations. Additionally, it highlights recent advancements in the use of thermosensitive hydrogels for drug delivery applications.

II. THERMOSENSITIVE HYDROGEL: A BRIEF OVERVIEW

Thermosensitive hydrogel: polymer material and characteristics

Naturally derived and synthetic polymers can be utilized as thermosensitive materials, either individually or in combination (Table 1.). However, naturally derived polymers are generally less

versatile than synthetic polymers due to their limited potential for chemical modification. Most natural polymers consist of polypeptides or sugar rings, which restrict their adaptability.

In contrast, synthetic polymers offer greater flexibility in molecular design and chemical modification, making them more adaptable for various applications. Hydrogels can be composed of natural or synthetic polymers, depending on their intended use. However, thermosensitive hydrogels specifically consist of thermosensitive polymers, which may be either naturally derived or synthetically modified^[12, 14].

Table 1. Polymer Material and Characteristics

Sources	Name	Characteristics
Naturally derived polymers	Chitosan ^[15, 17]	the second most abundant naturally derived polymer, does not possess thermosensitive properties
	Cellulose ^[18]	the most abundant naturally derived polymer, does not exhibit thermosensitive properties.
	Gelatin ^[19] Agarose ^[20] Collagen ^[21]	Negative Thermosensitivity
	Matrigel ^[22]	Positive Thermosensitivity
	Hyaluronic acid ^[23]	does not possess thermosensitive properties.
Synthetic polymers	Pluronic ^[24]	A thermosensitive, biocompatible material with a fast dissolution rate, low mechanical strength, and non-degradability can sensitize tumors.
	Polyphosphazene ^[25]	Biocompatible and biodegradable materials with nontoxic degradation products are emerging as potential candidates for anti-cancer drug delivery.
	Poly(lactide-polyethylene glycol)-Poly(lactide) (PEGLA-PEG) ^[26]	A thermosensitive and biodegradable material; however, its acidic degradation products can trigger a severe inflammatory response in vivo.
	Poly(N-isopropylacrylamide) PNIPAAm ^[27]	A thermosensitive, non-degradable material with a gelation temperature of around 32°C.
	Poly (oligo (ethylene glycol) methacrylate) (POEGMA) ^[28]	A biocompatible, thermosensitive material with low protein adsorption properties.

Classification of thermosensitive hydrogel

The thermosensitive hydrogel can be classified based on various factors, including physical structure, response type, and crosslinking (fig. 1)^[29]. Depending on their physical structure,

thermosensitive hydrogels can be categorized as amorphous, semi-crystalline, or crystalline.

Thermosensitive hydrogels can be classified based on their response type, source, polymeric charge, and crosslinking mechanism. The response type includes physical responses triggered

by external environmental factors, biological responses originating from internal body stimuli, and chemical responses caused by chemical reactions within the body [30, 31]. Based on their source, thermosensitive hydrogels can be natural, derived, or hybrid, depending on their composition. Additionally, they can be categorized as anionic, cationic, or neutral according to their polymeric charge and synthesis mechanism. Crosslinking

further distinguishes thermosensitive hydrogels into physically crosslinked, chemically crosslinked, and hybrid crosslinked hydrogels, depending on the bonding interactions involved [32]. Moreover, thermosensitive hydrogels are classified based on their material composition, which is essential in selecting suitable hydrogels for specific drug delivery applications [33].

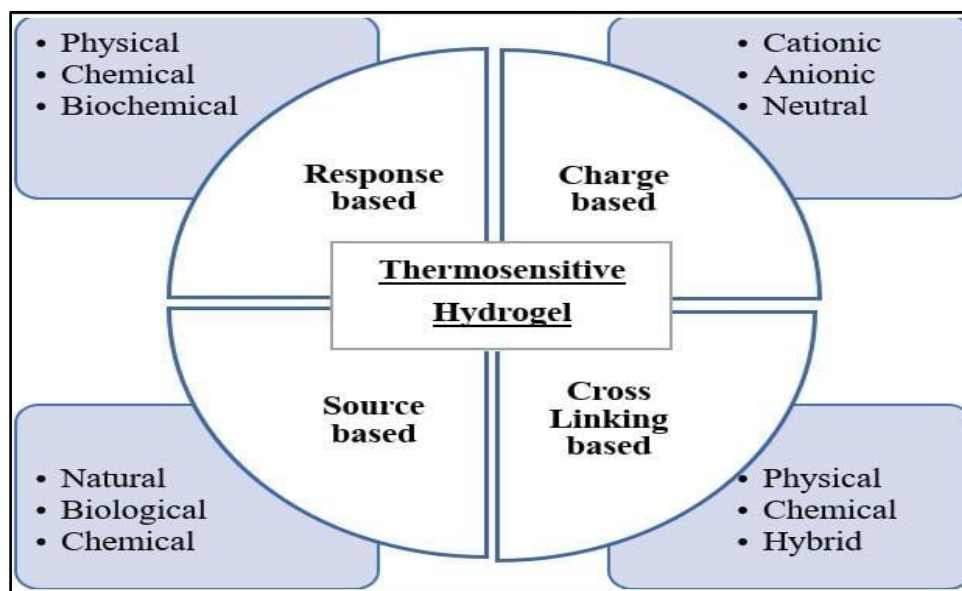


Fig. 1. Classification of Thermosensitive hydrogel

Drug release mechanism of thermosensitive hydrogel:

The drug release mechanisms of thermosensitive hydrogels generally include diffusion control, swelling control, and erosion control [34].

Diffusion-controlled release: based on Fick's first law of diffusion, is the most common mechanism in hydrogel drug delivery systems, categorized as either a reservoir or matrix system [35](Fig.2). The

diffusion of drugs from hydrogels primarily depends on the mesh size of the gel matrix and the hydrated molecular radius of the drug. Several factors influence diffusion, including the degree of crosslinking, which determines the chemical structure and porosity of the hydrogel, as well as the type and strength of external stimuli when applicable.

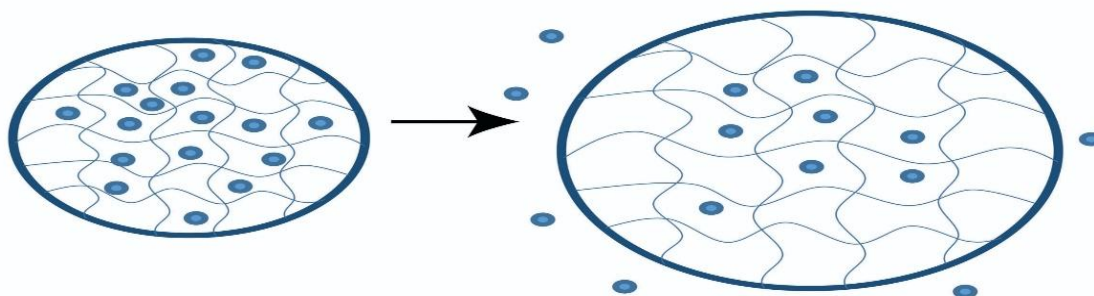


Fig.2. The osmotic pressure difference between the saturated drug within the hydrogel and the surrounding medium drives drug release, allowing the drug to diffuse freely into the external medium

Additionally, the physical properties of hydrogels, such as mechanical strength, degradability, and diffusion characteristics, are largely governed by their network structure. In their swollen state, hydrogels typically exhibit a mesh size of 5–100 nm, which is larger than most small-molecule drugs, allowing their rapid diffusion. However, macromolecular drugs, such as oligonucleotides and proteins, experience a more controlled and sustained release due to size constraints within the hydrogel matrix^[36].

Swelling-Controlled Release: In the swelling-controlled release mechanism, when the hydrated molecular radius of the drug is larger than the pore size of the hydrogel, the drug diffuses significantly faster than the hydrogel itself, making expansion the controlling factor^[35,36]. As the polymer swells upon

contact with the release medium, the drug is transported through the gel layer, classifying this system as a swelling-controlled (bloating control) release system, rather than a purely diffusion-controlled one (Fig. 3). The swelling force depends on the relaxation and diffusion of the macromolecular chains. When drug release is governed by macromolecular relaxation rather than simple diffusion, it deviates from Fick's law and follows Case II diffusion or non-Fickian diffusion. Initially, the drug is dispersed within a glassy polymer matrix, where diffusion is restricted. However, upon exposure to a thermodynamically compatible release medium such as water, the polymer transitions to a viscoelastic swollen state, enabling the controlled release of the drug^[37].

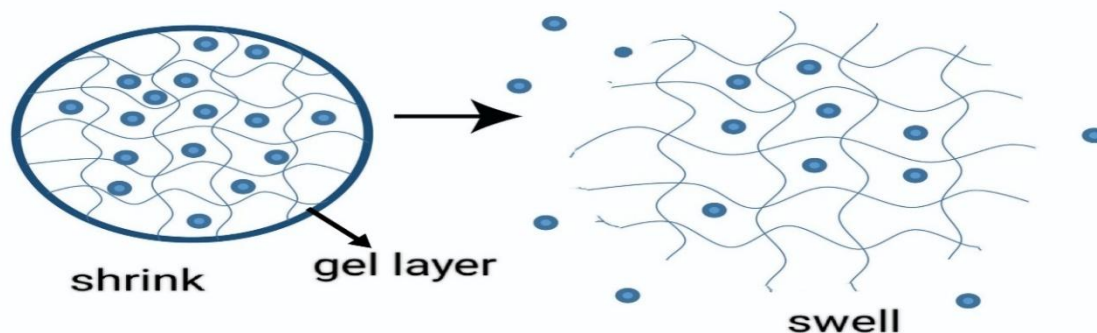


Fig.3: The hydrogel absorbs water, expands, and slowly releases the drug through its gel layer into the surrounding medium

Erosion-Controlled Release: In erosion-controlled drug release, the drug is released as the hydrogel surface erodes or the entire gel degrades. The key process involves the breakdown of molecular chains, leading to drug release (Fig. 4). This occurs through hydrolysis, enzymatic degradation, or reversible/irreversible interactions between the polymer network and the drug. The three main

mechanisms of polymer erosion are^[38]: (1) linking degradation, where polymer chains detach from the substrate; (2) hydrolysis, ionization, or protonation, which dissolves the drug in water; and (3) degradation of unstable molecular bonds, producing low-molecular-weight, water-soluble molecules. These mechanisms can also occur simultaneously, leading to controlled drug release^[39].

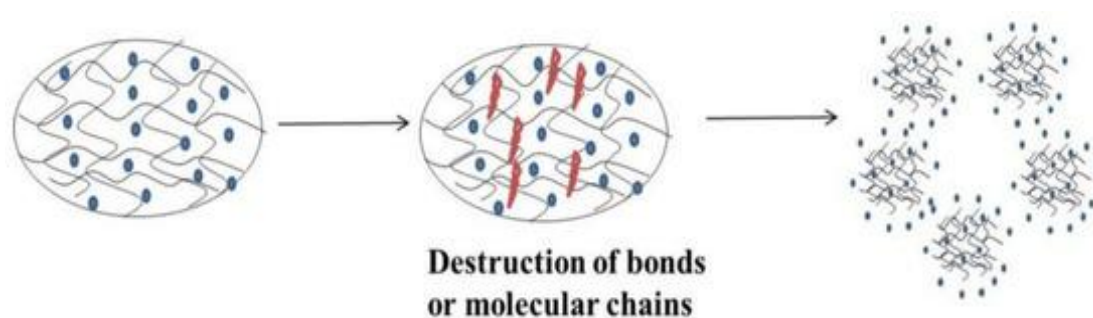


Fig.4: The hydrogel surface gradually erodes in the medium, breaking internal molecular bonds and releasing the drug into the surrounding environment

III. APPLICATION OF THERMOSENSITIVE HYDROGEL

Thermosensitive hydrogels are widely used in biomedical and pharmaceutical fields due to their ability to undergo sol-gel transitions in response to temperature changes.

Thermosensitive hydrogels are widely used in mucosal, transdermal, and local injection drug delivery due to their ability to undergo sol-gel transition at physiological temperatures, enabling controlled and sustained drug release.

1. Thermosensitive Hydrogels for Protein and Growth Factor Delivery:

Thermosensitive hydrogels have been extensively researched for the delivery of proteins and growth factors due to their ability to provide controlled, accurate, sustained, and localized treatment, ensuring optimal doses at target sites for effective tissue regeneration and repair. Protein-based drugs are gaining increasing attention due to their high bioactivity; however, they are highly susceptible to environmental factors such as temperature, pH, and

enzymatic degradation, which can lead to structural changes and loss of activity.

Using temperature-sensitive hydrogels as carriers for protein drug delivery offers several advantages. Firstly, proteins are uniformly dispersed within the hydrogel's three-dimensional network, preventing aggregation and precipitation, which helps maintain their bioactivity. Secondly, hydrogels form a protective barrier, shielding proteins from environmental factors and preventing denaturation during preparation, storage, and delivery. Lastly, these hydrogels enable controlled and sustained protein release, ensuring prolonged therapeutic effects.

In addition to protein delivery, hydrogels facilitate nucleic acid-based drug release through their cross-linked structures. Negatively charged nucleic acids, such as oligonucleotides, siRNA, or DNA, can be easily incorporated into weakly crosslinked polyelectrolyte hydrogels or loaded into nanoscale delivery systems.

Several studies have demonstrated the effectiveness of thermosensitive hydrogels in protein and growth factor delivery^[40,41,42]

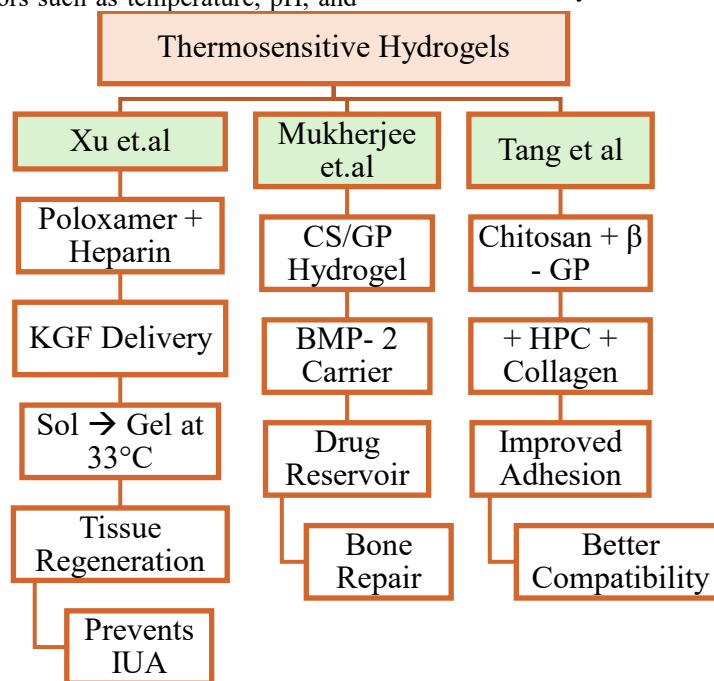


Fig. 5 Several Case Studies of thermosensitive hydrogels in protein and growth factor delivery

2. Oral drug delivery:

A significant challenge in oral drug delivery is the poor bioavailability caused by the liver's first-pass metabolism. Thermo-sensitive hydrogels present a promising approach to protecting drugs from degradation in the gastrointestinal tract. Insulin, a

peptide drug, is primarily administered via the parenteral route due to its susceptibility to deactivation by proteolytic enzymes. Chaturvedi et al. ^[43] reported the development of an insulin-loaded vesicle-chitosan hydrogel as a novel strategy for the

treatment of type II diabetes, potentially enhancing insulin stability and absorption.”

3. Nasal drug delivery:

Nasal administration is often preferred by professionals for delivering proteins and peptides due to the large surface area of the nasal mucosa, which allows for greater drug absorption compared to oral administration. However, challenges such as enzymatic degradation, limited macromolecular absorption, and mucociliary clearance must be addressed for effective nasal drug delivery [44]. Cunha et al. developed a thermo-sensitive in situ nasal hydrogel incorporating an acetylcholinesterase inhibitor (rivastigmine) with nano lipid carriers and nano emulsifiers. The hydrogel demonstrated excellent biocompatibility, prolonged drug release, strong mucoadhesion, and morphological stability. Pharmacokinetic studies indicated that 4% of the drug was successfully delivered to the olfactory region, suggesting that the formulation could be a promising candidate for nasal drug delivery [45]. Chen et al. developed a nano-thermosensitive hydrogel loaded with Albi florin for the treatment of Parkinson's disease. The study demonstrated excellent compatibility of the nanogel with the intranasal administration route, paving the way for further applications of nanogels in intranasal drug delivery systems [46].

4. Transdermal drug delivery:

Thermo-sensitive hydrogels offer superior advantages over conventional formulations for treating superficial disorders such as fungal infections and atopic dermatitis. They are characterized by good stability, ease of use for patients, improved local bioavailability, efficacy at low doses, simple preparation, and low cost [47]. Thermosensitive hydrogels play a significant role in transdermal drug delivery systems due to their excellent biocompatibility, enhanced mechanical properties, simple formulation, and ability to provide sustained drug release. Many researchers have explored their application in smart patches and creams for treating dermal infections [48, 49]. Huang et al. [50] developed a thermo-sensitive hydrogel composed of chitosan, β -glycerophosphate, and glycerol. This hydrogel exhibited rapid and noticeable color changes at higher temperatures, making it a potential tool for preventing overheating-related side effects in focused ultrasound therapy.

Nirmayanti et al. reported a thermoresponsive hydrogel designed for the sustained release of valsartan in the treatment of hypertension via a

transdermal drug delivery system. The proposed hydrogel was formulated using poloxamer 407 and poloxamer 188 in varying concentrations, which influenced its characteristics. Characterization and in vivo testing demonstrated that the hydrogel exhibited enhanced bioavailability compared to oral tablet formulations [48].

5. Local injection drug delivery:

Thermo-sensitive hydrogels can be utilized for the treatment of various infections through localized injection delivery. Zou MW et al. [51] developed an injectable thermo-sensitive hydrogel incorporating an indomethacin-conjugated polymer. This polymer was synthesized from N-isopropyl acrylamide, methacrylic acid, and 2-hydroxyethyl methacrylate-g-poly (Trimethylene carbonate)-indomethacin. The hydrogel demonstrated good biocompatibility and sustained drug release properties, making it a promising treatment option for uveitis.

6. Buccal drug delivery:

Buccal drug delivery is a promising route for treating pediatric and elderly patients, as well as individuals with deglutition difficulties. It offers several advantages, including high patient compliance, ease of administration, and an effective alternative for drugs with relatively low oral bioavailability. Zeng et al. [52] developed a thermo-sensitive in situ hydrogel incorporating Pluronic F127, Pluronic F68, and xanthan gum for buccal drug delivery. This innovative approach holds significant potential for improving medication administration in pediatric and elderly populations.

7. Temperature sensitive hydrogels for cell culture and tissue engineering:

Hydrogels designed as scaffolds for tissue engineering applications can mimic key characteristics of the extracellular matrix, including surface properties, mechanical strength, and biodegradability. Mechanical strength is particularly crucial when hydrogels are used as implants to replace diseased or damaged tissues, while temperature sensitivity enables them to form different shapes to accommodate various tissue defects.

Niranjan et al. (2013) [53] developed a thermo-sensitive hydrogel containing zinc, chitosan, and glycerophosphate for bone tissue engineering. This hydrogel exhibited geometrically well-defined pores with a crystalline structure, demonstrated swelling ability, enhanced antibacterial activity, and promoted osteoblast differentiation. Additionally, poly(3-caprolactone) (PCL) and poly(ethylene glycol) (PEG) were utilized as tissue engineering scaffolds, as reported by Xu et al., offering a highly

porous surface for cell attachment (Niu et al., 2014) [54].

8. Intravaginal drug delivery:

Locally acting drugs can be effectively absorbed through the vaginal mucosa, which has a large surface area and abundant blood vessels. Additionally, vaginal delivery enables both systemic drug absorption and targeted uterine delivery [55]. This route is widely utilized in various formulations for the treatment of HIV and gynecological diseases [56-58].

9. Ophthalmic drug delivery:

Ophthalmic drug delivery presents challenges due to the eye's complex physiological barriers, which prevent conventional eye drops from effectively reaching lesion sites. Additionally, eye drops lack sustained release properties, often requiring frequent administration, which can reduce patient compliance in the treatment of chronic ophthalmic diseases [59].

Yu YB et al. [60] developed a dual pH- and thermo-responsive hydrogel incorporating nanostructured lipid carriers loaded with baicalin. This hydrogel exhibited a higher apparent permeability coefficient and an extended precorneal residence time compared to conventional baicalin eye drops, offering a more effective drug delivery approach.

IV. CONCLUSION

Thermo-sensitive hydrogels have been extensively studied for over four decades and are widely used in pharmaceuticals and cell culture due to their temperature sensitivity, biocompatibility, and low toxicity. They offer a promising drug delivery system for various diseases, including ophthalmic disorders and cancer.

This review highlights recent advancements in thermosensitive polymeric materials, focusing on their physiochemical properties such as swelling, mechanical stability, release behavior, sensitivity, and adhesion. Their potential applications span various drug delivery routes, including transdermal, oral, ophthalmic, intravaginal, nasal, rectal, and tumor-targeted therapies. Thermosensitive hydrogels are considered green materials with minimal side effects and excellent drug delivery properties, enabling controlled and sustained release of bioactive compounds. Despite their promise, challenges such as delayed temperature response, weak mechanical strength, and limited biocompatibility hinder their broader application. Future research should focus on developing cost-effective, biodegradable, and non-toxic hydrogels using advanced methodologies to enhance their practicality in healthcare.

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