RESEARCH PAPER

Recent advances in $BaTiO_3$-based electrocaloric materials for solid-state thermal modulation: Emerging prospects in targeted drug delivery and biomedical cooling applications

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Abstract
The temperature dependence of drug stability, tissue response and stimulus-responsiveness of drug release is a significant consideration for pharmaceutical and biomedical systems that require on-demand thermal modulation. In this context, $BaTiO_3$ is an important lead-free ceramic oxide because it exhibits dielectric, piezoelectric, pyroelectric and electrocaloric responses near technologically relevant temperature ranges. This review summarizes recent advances in $BaTiO_3$-related electrocaloric materials and critically connects this literature with opportunities in targeted drug delivery, nanocarriers, wearable and implantable therapeutic devices and biomedical cooling. Recent literature was screened using keywords related to $BaTiO_3$, electrocaloric effect, ferroelectric cooling, nanoparticles, targeted drug delivery, nanomedicine and thermally triggered release across PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, Springer, ACS, Wiley and MDPI. Recent research demonstrates that doping, phase-boundary engineering, multilayer structures, thick films and $BaTiO_3$-polymer composites can enhance electrocaloric response, operating range, fatigue resistance and device compatibility (1). $BaTiO_3$ nanoparticles have also been investigated for ultrasound-activated therapy, targeted delivery, piezocatalysis, tissue engineering and bioelectronics. However, direct integration of electrocaloric $BaTiO_3$ systems with drug delivery remains at a conceptual and pre-translational stage. Further progress requires materials optimization, biocompatibility assurance, pharmacokinetic definition, device miniaturization and validation under regulatory standards.

Keywords: $BaTiO_3$; barium titanate; electrocaloric effect; solid-state cooling; targeted drug delivery; biomedical cooling; nanomedicine; thermal modulation (2).
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1. Introduction

Temperature is a subtle but influential factor in drug-delivery science. It affects drug solubility, polymer swelling, membrane permeability, protein stability, immune-cell activation, inflammatory signalling, enzyme-reaction rates and the tolerance of implanted or wearable devices. While traditional pharmaceutical cooling has mainly focused on small-scale storage and cold-chain management, emerging therapeutic systems increasingly require small, local, reversible and electronically controlled thermal cues at the tissue-device interface. This requirement is especially relevant for thermosensitive hydrogels, liposomes, microneedles, implantable depots, bioelectronic patches and nanocarrier systems that release payloads in response to microenvironmental stimuli (3).

The traditional biomedical cooling technologies such as ice-packs, circulating coolants, vapor-compression cooling, Peltier cooling and large temperature controlled cooled boxes are suited well for the macroscale drug delivery systems but are not well suited for the miniaturized scaled ones. Their needs often include moving components, liquid coolants, big heat sinks, or a lot of electrical power and frequently do not

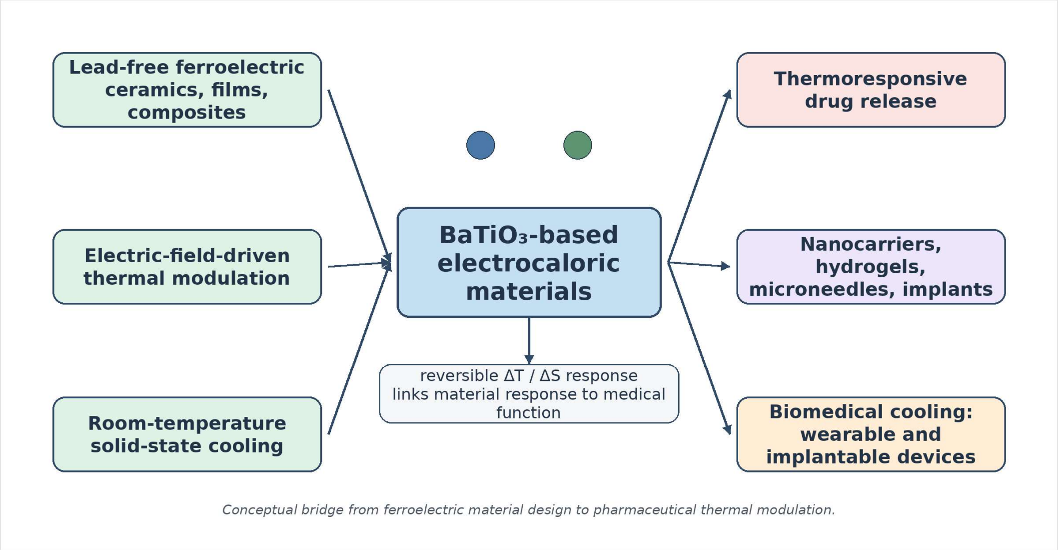
*Author for Correspondence: sethi.arpan10@gmail.com offer exact thermal modulation at an exact level at the tumor margin, diseased tissue site, microneedle array, ocular insert, neural interface, or implant capsule. Another constraint for externally-controlled drug-release systems is hyperthermia which can be very diffuse throughout the tumor; light penetration is limited for penetration into deeper tissues; tailored particles and field systems are required for magnetic heating; and ultrasound-triggered systems require careful dosing. Thus, problem of cool/heat involves creation of safe, local, reproducible and biologically meaningful thermal pulse (4).

$BaTiO_3$ is a well-established lead-free perovskite ferroelectric oxide that has been widely used in capacitors, sensors, actuators and piezoelectric devices. Its crystal structure, domain configuration and polarization behaviour can be modified through particle-size control, strain engineering, dopant substitution, phase-boundary engineering, microstructural regulation and composite design. These properties also make $BaTiO_3$ attractive for nanoscience applications beyond conventional electronics, including piezoelectric and pyroelectric platforms for ultrasound-activated cancer treatment, targeted cell binding, tissue stimulation, bioimaging and smart delivery systems (5).

The electrocaloric effect (ECE) adds another biomedical dimension to $BaTiO_3$-based materials. In an electrocaloric material, electric-field-induced changes in dipolar order and polarization entropy produce a reversible temperature change under adiabatic conditions and an entropy change under isothermal conditions. In principle, this effect can be used for compact, refrigerant-free, solid-state heating and cooling. Recent $BaTiO_3$-based ceramics, doped systems, solid solutions, thick films, multilayers and polymer composites have shown improved electrocaloric response, wider operating windows and better room-temperature performance (6); however, high electric-field requirements and dielectric breakdown remain major engineering challenges.

This review focuses on linking the electrocaloric properties of $BaTiO_3$ materials with pharmaceutical and biomedical translation rather than discussing materials science in isolation. Figure 1 summarizes the conceptual link: electrocaloric systems can be considered solid-state thermal modulators that may be integrated with nanocarriers, thermoactive polymer matrices, microneedles, implants and wearable therapeutic devices. At present, this bridge remains largely conceptual. No convincing clinical studies have demonstrated electrocaloric drug delivery in humans and only limited preclinical evidence is available. Therefore, experimentally demonstrated biomedical functions of $BaTiO_3$ should be clearly distinguished from proposed electrocaloric drug-delivery concepts (7).

This review aims to analyse recent developments in $BaTiO_3$-based electrocaloric materials, clarify material performance and limitations, highlight biomedical research involving $BaTiO_3$ nanoparticles and composites and identify practical future prospects for drug delivery, biomedical cooling and local thermal regulation. The manuscript is intentionally framed for a pharmaceutical audience by connecting material performance with dosage-form design, biological safety, drug-release control and translational feasibility (8).



Conceptual bridge from ferroelectric material design to pharmaceutical thermal modulation.

Figure 1. Graphical overview of $BaTiO_3$-based electrocaloric materials connecting solid-state cooling with biomedical drug-delivery applications. The schematic highlights the transition from ferroelectric material design to pharmaceutical concepts such as thermoresponsive release, implantable patches, wearable biomedical cooling and local thermal regulation (9).

2. Review Methodology

A structured narrative-review approach was followed. Database searches were conducted in PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, SpringerLink, ACS Publications, Wiley Online Library and MDPI. Older background sources were used only where necessary to define the basic terminology of $BaTiO_3$ electrocaloric and ferroelectric behaviour. The search terms included "$BaTiO_3$," "barium titanate," "electrocaloric effect," "$BaTiO_3$ electrocaloric," "solid-state cooling," "ferroelectric cooling," "$BaTiO_3$ nanoparticles," "targeted drug delivery," "biomedical cooling," "nanomedicine," "thermally triggered drug release," "piezoelectric nanocarriers," "ultrasound activated $BaTiO_3$," and "ferroelectric nanoparticles therapy".

English-language peer-reviewed research articles, review articles, experimental studies, computational studies and biomedical application studies relevant to $BaTiO_3$-based electrocaloric and biomedical applications were included. Articles were selected when they reported composition, phase design, structure, electrocaloric performance, dielectric or ferroelectric properties, or thermal response of advanced $BaTiO_3$-based materials and devices. Biomedical studies were included when they discussed $BaTiO_3$ nanoparticles, surface modification, targeting, drug loading, ultrasound or electric-field stimulation, tissue interactions, biosensing, bioelectronics, imaging, cancer therapy, antimicrobial therapy, or safety (13).

The exclusion criteria involved non-peer-reviewed sources, duplicated articles, purely electronics-focused papers that did not contain any meaningful details of compositions or performance, papers that did not provide enough composition or performance data and claims that were speculative and lacked proof with either experiments or computation. Due to their unconfirmed DOI information, no records remain in the final "September 1989" record, therefore the update bibliography comprised of records with DOI bearers only (14).

Advanced Analysis and Development of $BaTiO_3$-Based Materials

$BaTiO_3$ is a perovskite oxide with the general formula ABO_3, in which Ba^{2+} occupies the A-site, Ti^{4+} occupies the B-site and oxygen forms the octahedral framework. Displacement of Ti^{4+} within the oxygen octahedron and the formation of polar domains are the major contributors to ferroelectric behaviour. $BaTiO_3$ exhibits temperature-dependent phase transitions, commonly described as rhombohedral, orthorhombic, tetragonal and cubic phases. The tetragonal phase near room temperature is central to many actuator, capacitor and piezoelectric applications, while compositions that shift phase transitions into room-temperature or physiological windows are particularly important for electrocaloric applications (15).

Ferroelectricity has to do with switchable spontaneous polarization, dielectric has to do with polarization changes due to electric field, piezoelectric has to do with electromechanical coupling, pyroelectric with temperature-induced polarization change and the electrocaloric effect is related to changes in polarization entropy induced by the electric field. These properties are not unique; they are found in various other compounds as well. They originate in the polar lattice instability in $BaTiO_3$ and from the same domain dynamics, thus material engineering strategies can impact on multiple responses. This multifunctionality is appealing for biomedical systems as a single platform can be used for biochemical modification, mechanical strain, temperature control, electric field application and ultrasound.

The effects of size, especially for the transition from bulk ceramics to nanoparticles, thin films or polymer composites, play an important role in the conversion of $BaTiO_3$ to a nano crystal. The nano-$BaTiO_3$ can exhibit different properties such as crystallinity, surface charge, domain stability and dielectric characteristics of the bulk material. The possibility of the suppression or strong influence of the ferroelectric domain structure by surface chemistry and defects arises at very small sizes. From a biomedical point of view, particle size is also critical for biodistribution, cellular uptake, immune recognition, renal clearance and hepatobiliary clearance as well as aggregation risk. Therefore, it is not guaranteed that a nanocarrier designed to be optimized for polarization will have an optimized pharmacokinetic profile (17).

Grain-boundary architecture critically governs dielectric loss, leakage current, breakdown strength, domain-wall mobility, thermal conductivity and fatigue resistance in $BaTiO_3$ ceramics and thick films. Fine, dense and chemically stable grain boundaries can increase breakdown strength and suppress Joule heating, whereas oxygen-vacancy accumulation, secondary phases and incomplete densification may increase leakage and generate artefactual electrocaloric signals. For biomedical devices, these microstructural variables also determine sterilization tolerance, encapsulation reliability and long-term operation in humid physiological environments (18).

Doping and phase-boundary engineering are important strategies for improving $BaTiO_3$ performance. Ca, Sr, Sn, Zr, La, Mn and Bi substitutions can alter Curie temperature, broaden phase transitions, stabilize relaxor behaviour, reduce hysteresis and enhance breakdown strength. Solid solutions such as $Ba(Zr,Ti)O_3$, $Ba(Sr,Ti)O_3$ and $Ba(Ca)(Zr,Ti)O_3$ are used to shift polarization instabilities close to the desired operating range. For biomedical translation, the key objective is not merely the largest laboratory ΔT, but a useful electrocaloric response near 25–45 °C that can operate safely, repeatedly and within a miniaturized device format (19).

The biocompatibility of $BaTiO_3$ is expected but may vary depending on the use. Various research groups have investigated the use of $BaTiO_3$ nanoparticles in cell-based studies, tumor models, as substrates in neural compatibility studies, surface functionalization applications and ultrasound-assisted therapeutic

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applications. These observations, however, need to be translated to drug delivery practice and into focus are concerns around the clearance, immune activation, genotoxicity, reproductive toxicity, barium ion release, protein corona formation, particle aggregation and endotoxin contamination. However, surface coatings (PEG, polydopamine, silica, chitosan, antibodies, peptides or hydrogel matrices) could enhance dispersion and targeting, but also affect the pharmacology and regulator classification (20).

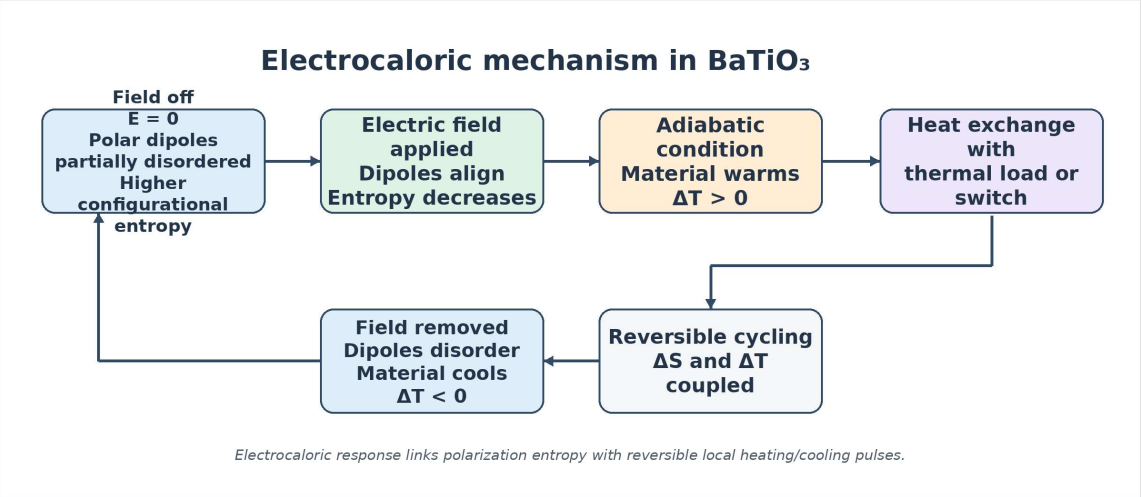
4. Electrocaloric Effect in $BaTiO_3$-Based Materials

The electrocaloric effect is a thermally reversible process that results from variation of polarization order in a dielectric/ferroelectric resulting from an electric field change. For polar dipoles, the applied electric field causes ordering of their dipoles and so reduces the polarization entropy. If this ordering is under adiabatic conditions, then the admixing of gas goes up to preserve total entropy. If the field is turned off, the dipolar disorder increases and the material can be cooled. For any of these cycles, the same cycle can be used in conjunction with, or in lieu of, heat exchangers or thermal switches to introduce heat to or remove heat from any target location, creating a solid-state cooling concept (21).

From a thermodynamic point of view the two most mentioned performance values are the differences in adiabatic temperature and in isothermal entropy, ΔT and ΔS. Indirect estimation is typically performed based on the Maxwell relations deduced from the polarization-electric field relationships measured at different temperatures while direct measurement involves measuring a temperature change under specifically designed electric field cycling. Indirect methods are convenient, but may overestimate performance if there are process leakage, hysteresis, non-equilibrium behavior, or artifacts in the measurements. More device-relevant and technically demanding, the methods of direct calorimetry and infrared thermography examine the film or multilayers (22).

Some parameters are important such as peak ΔT, ΔS, electrocaloric responsivity, operating temperature range, electric-field strength, energy efficiency, dielectric loss, leakage current, thermal conductivity, heat capacity, reversibility, cycling fatigue, response time and breakdown resistance. If the intended application is biomedical, there are additional requirements: the field has to be safely held in a body-sized confine, the field must be able to be safely contained inside the device and the device's architecture must be able to withstand sterilization, enclosure, wet environments and mechanical deformation when used in wearable or implantable form (23).

Room-temperature and physiological-temperature operation is critical in biomedical use. A $BaTiO_3$-based material may be useful for electronics but unsuitable for drug delivery, tissue cooling, or implant management if it functions only outside relevant temperature windows. The attractive biomedical ranges include cold-chain conditions near 2–8 °C, mild tissue modulation around 20–42 °C and physiological or pathological temperature windows suitable for thermo-responsive drug carriers. The electrocaloric mechanism summarized in Figure 2 is therefore relevant only when its thermal output can be produced safely within these biologically meaningful ranges (24).



Electrocaloric mechanism in $BaTiO_3$

Electrocaloric response links polarization entropy with reversible local heating/cooling pulses.

Figure 2. Schematic mechanism of the electrocaloric effect in $BaTiO_3$ under electric-field application and removal. Electric-field application aligns polar domains and decreases polarization entropy, causing adiabatic warming; field removal increases disorder and can produce cooling (25).

5. Recent Advances

Recent $BaTiO_3$ electrocaloric research has moved from simple bulk ceramics toward chemically modified compositions, thick films, multilayers, relaxor-like systems and flexible composites. The field is trying to solve a persistent engineering triangle: achieving large ΔT, maintaining a broad temperature span and reducing the electric-field requirement. Figure 3 classifies the major $BaTiO_3$-based electrocaloric families discussed in this review and Table 1 summarizes representative recent studies (28).

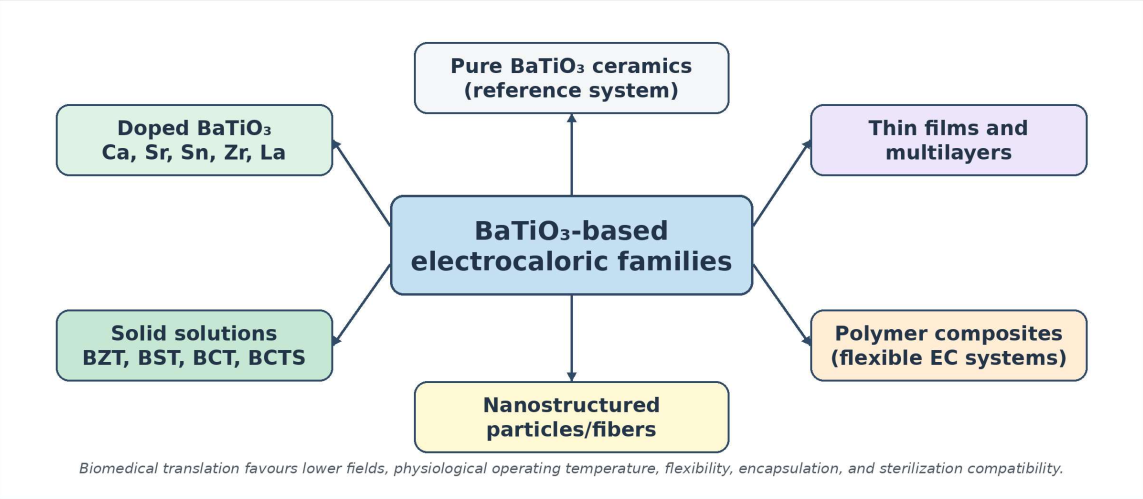


Figure 3. Classification of $BaTiO_3$-based electrocaloric materials: pure $BaTiO_3$, doped $BaTiO_3$, solid solutions, thin films, multilayers, polymer composites and nanostructured materials (29).

5.1 Pure $BaTiO_3$ ceramics and thin films

Pure $BaTiO_3$ is a reference material for electrocaloric research for two reasons: first, its ferroelectric phase transition is well understood; second, lead-free ceramics are more acceptable than lead-based perovskites for environmentally sensitive and biomedical applications. However, the electrocaloric response of bulk $BaTiO_3$ ceramics near room temperature is often modest unless the operating temperature is close to a phase transition or the applied electric field is increased. Its advantages include chemical familiarity, scalable ceramic processing and an extensive historical database; its drawbacks include brittleness, high field requirements, narrow operating range and limited compatibility with soft biomedical interfaces (32).

Although thin films cannot withstand as high an electric field as ceramics do, they could be made to fit in with microfabricated devices. Nevertheless, thermal resistance of the electrodes, strain of the substrate, defects and interfaces can have significant effect on the measured response. Pure $BaTiO_3$ thin film is more feasible for Biomedical applications as it can be used in implants processing in chips, as Micro-Thermal coolers or as a strips for sensor integration, than implantable systems. The problem is to render the heat output useful for biology without creating biohazardous electric fields or unwanted heat (33).

5.2 Doped $BaTiO_3$ systems

Doped $BaTiO_3$ systems have received substantial attention because dopants can shift phase transitions, widen the thermal response, suppress hysteresis and increase breakdown strength. Electrocaloric temperature shifts from the sub-kelvin to kelvin range have been reported in ceramic systems with broad working spans under electric fields in the tens of kV cm^{-1}. Elements such as Sn, Ca, Sr, Zr and La are commonly introduced to tune the ferroelectric-relaxor balance and domain dynamics (34).

A doped $BaTiO_3$ from a pharmaceutical aspect is a double edged sword. There are toxicological and regulatory issues that need to be addressed for every dopant that can improve electrocaloric performance. The elements or processing residues of a composition which is optimized according to electrical response can make biomedical approval difficult. Thus, for drug delivery or implantable cooling applications, $BaTiO_3$ should be tested not only for ΔT and ΔS, but also for the presence of extractables, extractables leached into the pharmaceutical solution, ion release, inflammatory response and chemical stability during sterilization (35).

5.3 $BaTiO_3$-based solid solutions

Solid solutions composed of $BaTiO_3$, e.g., $Ba(Zr,Ti)O_3$, $Ba(Sr,Ti)O_3$ and $Ba(Ca)(Zr,Ti)O_3$, are created by exploiting compositional disorder and phase-boundary engineering, which play a role in their response to polarization. For instance, lattice stress engineering in the case of $Ba(Zr,Ti)O_3$ has been shown to improve electrocaloric effect by controlling phase instability and lattice stress. The other solid-solution solutions aim to cover an extensive range of working temperatures, instead of a distinct peak (36).

For biomedical thermal modulation, a large and flat operating temperature difference may be more useful than a small value of ΔT, max. There is no single ideal laboratory temperature for a drug delivery patch or implant as temperature of the skin, perfusion of tissue, inflammatory processes, fever, heating of the patch or implant by the device itself, or variation in the temperature from patient to patient will change the thermal environment. The intermediate-response materials are more appealing than sharp-transition materials which require carefully adjusted media conditions (37).

5.4 $BaTiO_3$/polymer composites

The properties of $BaTiO_3$/polymer composites are a combination of high dielectric and ferroelectric response of particles and flexibility, toughness and processing characteristics of polymers and also low acoustic/mechanical mismatch. While numerous high-performance electrocaloric polymer systems exist that are not actually made of $BaTiO_3$, they can be fabricated using $BaTiO_3$ fillers which (when properly dispersed and surface treated) serve to enhance the dielectric permittivity, field distribution and multifunctional coupling. Polymer composites are particularly important for use in wearable patches, conformal cooling films, wound dressing and microneedle associated thermal control (38).

Defects at the interfaces; particle agglomeration; failure in the interfaces between ceramic and the polymer; limited effective field in the ceramic phase of heterogenous films; accurate local electrocaloric response measurement in heterogenous films. Surface modification is therefore an essential step and not a cosmetic one since it affects dispersion, dielectric loss and moisture stability, etc., which in turn affects biological contact. In the pharmaceutical field, the polymer matrix can also be used as a drug reservoir, as a hydrogel or as an adhesive material, or be used as diffusion barrier, which render the possible use of $BaTiO_3$ composites as bridges between materials science and dosage-form design (39).

$BaTiO_3$ multilayer and thick-film designs are important because they can reduce driving voltage while retaining high internal electric fields and increasing the active heat-exchange area.

The advantages of the multilayer ceramic capacitors, thick-film design are: low driving voltage, high internal electric field, large heat exchange area and convenient for packaging. Relying upon recent investigations of $BaTiO_3$ thick film and multilayered devices, it seems that internal stress, thickness of layers, design of the electrodes and thermal contacts represent potential factors that can significantly change the electrocaloric behavior. These are similar to (or more like) the architecture of devices, rather than free ceramic pellets and are important for possible biomedical cooling modules (40).

Structural properties such as durability and hermetic or biocompatibly encapsulated structures, compatible with tissue interfaces by temperature-controlled thermal bonding, are essential for implantable or wearable biomedical systems involving multilayers. It must be assessed in terms of the cooling power delivered to tissue, field confinement, heat sink, duty cycle and maximum available surface temperature for the device (41).

5.6 Nanostructured $BaTiO_3$ materials

Examples of nanostructured $BaTiO_3$ are nanoparticles, nanofibers, nanocubes, core-shell particles and hybrid nanocomposites. Nanoscale architecture can affect the phase stability, surface stress, dielectric breakdown and thermal exchange rate in electrocaloric studies. On the biomedical front, the same nanoscopic geometry allows for cellular interaction, surface functionalization, tumor accumulation strategies, ultrasound activation of the nanowire, as well as hydrogels or polymeric carriers to incorporate the nanowire (42).

Currently, nanostructured $BaTiO_3$ is more experimentally advanced in piezoelectric and piezocatalytic therapy than in electrocaloric drug delivery. The opportunity is to couple electrocaloric thermal modulation with nanoparticle or composite platforms already investigated for ultrasound-sensitive therapy. The risk is overextension: ultrasound-induced piezoelectric ROS generation does not automatically demonstrate electrocaloric drug release and tumour toxicity in an animal model does not by itself establish a clinically viable drug-delivery system (43).

Table 1. Summary of recent $BaTiO_3$-based electrocaloric materials, including composition, form, synthesis route, electric field, ΔT, ΔS, operating temperature and key findings (44).

Composition / system	Form	Synthesis or fabrication route	Electric field	ΔT	ΔS	Operating temperature	Key findings and biomedical relevance
Chemically modified $BaTiO_3$, BTS-BMT	Ceramic	Solid-state ceramic processing	50 kV cm⁻¹	Up to 0.41 K; RT value about 0.33 K for selected composition	Not consistently reported in accessible abstract	Broad response reported around 30-130 °C for selected composition	Doping broadened operating span; useful direction for physiological thermal modulation, but exact biocompatibility of doped chemistry

Composition / system	Form	Synthesis or fabrication route	Electric field	ΔT	ΔS	Operating temperature	Key findings and biomedical relevance
							needs testing. (11)
$Ba(Zr_{0.2}Ti_{0.8})O_3$	Lead-free ceramic	Lattice stress engineering	High field; verify exact value	Enhanced ECE reported	Verify	Near phase-instability region	Internal stress improved EC response; relevant to miniaturized device layers, not direct drug delivery. (10)
$BaTiO_3$-based thick films	Thick film / multilayer	Tape casting or film deposition; internal stress regulation	Verify exact value	Enhanced relative to monolithic forms	Verify	Near room-temperature design window	Layer design can improve field tolerance and device integration. (2,54)
Ba-Ca-Ti-Sn based system	Ceramic	Solid-state sintering	Verify	Sub-kelvin to about 1 K range reported	Verify	Wide working area reported	Ferroelectric-to-nanodomain transition can broaden usable response. (16,22)
$BaTiO_3$-based co-doped ceramics	Ceramic	Compensatory ion co-doping	Verify	Large ECE claimed; verify numerical value	Verify	Wide temperature range	Phase-boundary regulation targets broad biomedical operating ranges. (23)
$BaTiO_3$-based domain-engineered ceramics	Ceramic	Compositional/domain engineering	Verify	Enhanced ECE reported	Verify	Wide working range	Highlights domain engineering; biomedical use remains prospective. (13,20)
$(Ba,Ca,La)(Ti,Sn)O_3$	Ceramic	Composition engineering	Verify	Reported ΔT around 1.6 K in accessible summary	Verify	Broad range near 92 K span reported	Broad operating span could help device robustness; exact values must be verified. (21)
$BaZrO_3$-$BaTiO_3$ solid solution	Ceramic	Solid-state reaction	Verify	EC properties characterized	Reported in source; verify	Composition-dependent phase region	Useful for understanding BZT phase-fraction design. (39)

Composition / system	**Form**	**Synthesis or fabrication route**	**Electric field**	**ΔT**	**ΔS**	**Operating temperature**	**Key findings and biomedical relevance**
$Ba_{0.9}Sr_{0.1}Ti_{1-x}Sn_xO_3$	Ceramic	Solid-state synthesis	Verify	Enhanced ECE and energy storage	Verify	Near room temperature	Combines EC and energy storage; potential for integrated device modules. (31)
$Ba_{0.9}Sr_{0.1}Ti_{0.9}Sn_{0.1}O_3$	Ceramic	Solid-state ceramic route	Verify	Improved near room temperature	Verify	Near room temperature	Lead-free room-temperature strategy; biomedical testing not reported. (36)
(1-x)BZT-x$NaNbO_3$	Ceramic	Solid-state synthesis	High breakdown field	Improved ECE	Verify	Room-temperature-related	High breakdown strength and energy density support device concepts. (18)
$BaTiO_3$-based phase-fraction systems	Ceramic	Phase-fraction tailoring	Verify	Tunably enhanced	Verify	Composition-dependent	Phase fraction is a design lever for balancing ΔT and operating span. (15)

Interpretation of Table 1 should be conservative: many electrocaloric values are method-dependent and direct comparison across bulk ceramics, films and multilayers can be misleading unless field strength, heat capacity, measurement protocol, leakage current and thermal boundary conditions are normalized (45).

Table 2. Comparison of $BaTiO_3$-based material types for biomedical translation: ceramics, thin films, multilayers, nanoparticles and polymer composites.

Material type	**Biomedical strengths**	**Biomedical limitations**	**Most plausible translation path**	**Critical tests before translation**
Bulk ceramics	Chemically robust; scalable; strong ferroelectric response	Brittle; high voltage; poor conformability; not injectable	Implantable encapsulated microcooler or benchtop drug-storage module	Dielectric fatigue, sterilization, encapsulation leakage, tissue thermal output
Thin films	High field tolerance; microfabrication compatible	Small thermal mass; substrate constraints; electrode interfaces	On-chip thermal control for biosensors, implants, microfluidic drug devices	Direct EC measurement, interface durability, biocompatible packaging
Multilayers	Lower operating voltage; larger area; device-like architecture	Complex fabrication; heat rejection needed; dielectric breakdown	Wearable or implantable cooling element	Thermal cycling, humidity, encapsulation, ISO biocompatibility
Nanoparticles	Surface functionalization;	Aggregation; biodistribution;	Active nanocarrier or hydrogel filler	PK, biodistribution, chronic toxicity,

Material type	Biomedical strengths	Biomedical limitations	Most plausible translation path	Critical tests before translation
	cellular interaction; ultrasound response	clearance; toxicity uncertainty		immune response, drug loading
Polymer composites	Flexible; wearable; soft-tissue compatible; can store drug	Interfacial breakdown; lower EC response; dispersion problems	Thermoresponsive patch, microneedle backing, wound dressing	Mechanical fatigue, release reproducibility, cytotoxicity, sterilization

6. $BaTiO_3$-Based Materials in Biomedical and Drug-Delivery Research

It is the mechanotranslation of mechanical, acoustic or thermal stimuli, through to electrical polarization-related effects, which explains why $BaTiO_3$ nanoparticles are interesting to be used in biomedicine. Their active functionality, interaction with external fields and biological interfaces makes them relative drug-delivery excipients, not passive. In recent reviews, $BaTiO_3$ nanocarriers have been mentioned as candidates for various purposes of smart release, targeted surface therapy, activation with application of ultrasound and for multifunctional nanomedicines and also demonstrated the lack of resolved toxicity and translation barriers (46).

The functionalization of the surface is key for $BaTiO_3$ biomedical applications. Native nanoparticles may form oligomers in physiological solutions and demonstrate an unpredictable protein corona, which limits their clinical applications.The in vivo aggregation of oxide nanoparticles in physiological media may result in unpredictable protein corona, often limiting the application of nanoparticles in clinical situations. Aqueous dispersibility, nonspecific interaction reduction and capability of drug loading and targeting can be achieved by applying coatings like carboxylated ligands, phosphonic acids, PEG-like shells, polydopamine, silica, chitosan, antibodies, peptides and hydrogels. Comparative studies on surface-modified $BaTiO_3$ have demonstrated the significance of ligand chemistry on the surface with respect to stability in aqueous systems and its use for biomedical applications (47).

Ferroelectric nanoparticles can be combined with biomolecular recognition strategies with the use of antibody-conjugated nanoparticles for cell-specific targeting. This is critical for targeted drug delivery as without the ability of the electroactive particles to get to selected tissue/cells/any external trigger is not worth much. However, targeting ligand attachment brings a number of steric, immunogenic, stability and manufacturing issues that must be addressed in compliance with pharmaceutical quality requirements (48).

One of the best experimental coupling of $BaTiO_3$ with therapy is the ultrasound-activated $BaTiO_3$. The generation of piezocatalytic ROS, splitting of water, controlled release of nitric oxide or chemotherapeutics, assembly of nanoplatforms triggered by a source in the tumor microenvironment and combination therapies with $BaTiO_3$-based nanoplatforms or hybrid nanoplatforms that include other types of ceramics are reported in several preclinical models. These studies demonstrate that $BaTiO_3$ is a biomedical material which can be remotely activated under noninvasive stimulation, but they are not "drug delivery" demonstrations.

The controlled release mechanisms of $BaTiO_3$ can be categorized as one of the surface desorption, polymer-shell diffusion, hydrogel matrix release, peptide, or piezoelectric charge release, ultrasound induced catalytic chemistry, thermal/pyroelectric effect and hybrid photothermal/chemodynamic pathway. Some drug-delivery oriented systems using a microemulsion containing lidocaine and $BaTiO_3$ (51) or radiolabeled hydrogel-coated $BaTiO_3$ (50) were described recently, but it is desirable to independently verify full bibliographic and functional details before submission.

In addition to cancer therapy, the use or application of $BaTiO_3$ materials has been explored or proposed in applications related to tissue engineering, neural stimulation, antimicrobial treatment and treatment of osteomyelitis, bioimaging, biosensing and wearable bioelectronics. Some examples are piezoelectric stimulation of cancer cells, $BaTiO_3$-Au@polydopamine nanoplatforms for imaging-guided synergistic therapy, the exciting prospect of the use of pyro-piezoelectric bio-nanocarriers for treatment of osteomyelitis and the use of piezoelectric hydrogel conduits for peripheral nerve regeneration (51).

Safety is the all crucial point. Acute cytocompatibility is not a good indicator of clinical safety. For in vivo injectable $BaTiO_3$ systems, the following size distribution, surface charge, endotoxin, hemocompatibility, complement activation, protein corona, RES uptake, organ accumulation, renal clearance and/or hepatic clearance, degradation, barium release, repeated dose toxicity and genotoxicity must be assessed. There are other safety packages required for implantable or wearable devices: encapsulation integrity, dielectric insulation, electrical safety, thermal dose limits, sterilization and extractables/leachables (52).

Table 3. Biomedical applications of $BaTiO_3$-based materials, including drug delivery, tissue engineering, cancer therapy, bioimaging, biosensing and wearable devices (53).

Application area	$BaTiO_3$ role	Evidence level from reviewed literature	Representative material/platform	Translation caution
Targeted cell binding	Functional nanoparticle core with antibody or ligand	In vitro targeting demonstrated	Antibody-conjugated $BaTiO_3$ nanoparticles	Targeting does not prove therapeutic delivery or in vivo selectivity
Cancer therapy	Ultrasound-activated piezo/piezocatalytic nanoplatform	Preclinical cell and animal studies	$BaTiO_3$ nanoparticles, ultrasmall $BaTiO_3$, $BaTiO_3$ hybrids	ROS therapy, drug release and immune effects need reproducibility and safety validation
Drug release	Carrier filler or active stimulus-responsive component	Early experimental and conceptual studies	$BaTiO_3$-polymer/hydrogel/microemulsion systems	Drug loading, release kinetics and batch consistency remain underdeveloped
Bioimaging	High-Z or hybrid nanoplatform component	Preclinical imaging-guided therapy concepts	$BaTiO_3$-Au@polydopamine	Imaging dose, clearance and long-term retention require study
Tissue engineering	Piezoelectric stimulation filler	Preclinical scaffold and conduit concepts	Piezoelectric nanofibers or $BaTiO_3$ composites	Mechanical and electrical cues must match tissue-specific regeneration biology
Biosensing/wearables	Piezoelectric/dielectric component	Prototype-level device research	Flexible composites and bioelectronic patches	Skin contact, sweat, fatigue and electrical insulation must be validated

7. Linking Electrocaloric Thermal Modulation with Targeted Drug Delivery

The correlation between electrocaloric $BaTiO_3$ and drug targeting should be clearly speculated. There are already two, although presently separate and not fully integrated, experimental areas with strong evidence: i) electrocaloric materials based on $BaTiO_3$ for solid-state thermal modulation and ii) biomedical nanoparticles and/or composites with piezoelectric, ultrasound-responsive and targeted therapeutic functionalities based on $BaTiO_3$. In the accessible literature from recent literature, direct evidence of the electrocaloric cycling of BT, as a means to trigger the in vivo release of drugs from capsules/bulbs, is still a rare and/or elusive occurrence. So, in this section it is important to distinguish between existing data and potential designs that are likely scientifically (54).

The localized modulation of temperature is a rational drug delivery target where many drug carriers can be designed to act when the temperature is at a certain level. Based on these general properties, thermosensitive liposomes, hydrogels, microneedle systems and polymeric nanoparticles have been developed to trigger the permeability of a cell membrane, swelling or shrinkage, spherical or gelation or destabilization at temperature changes and alteration of the diffusion and/or degradation rate with temperature, respectively. In principle, such electrocaloric elements of $BaTiO_3$ should be able to supply the local thermal cue for such carriers (55).

A thermal switch based on $BaTiO_3$ (barium titanate) as the switching material has been proposed for the proposed design of a micro/nano thermal switch that is intended for on-demand drug release. For a patch (or implant), an electric switching of a multilayer or a composite structure of $BaTiO_3$ could produce a short cooling or warming pulse. This pulse may be capable of changing the state of a neighbouring thermoresponsive hydrogel, or speed up or slow diffusion through a membranar, or even shield a temperature sensitive biologic from local storage. This type of device would be more active than a conventional patch containing a material actuator, thermal feedback, drug reservoir and electronic control loop (56).

The second idea is based on hybrid nanoparticle-thermoresponsive carrier for $BaTiO_3$ composite. The nanoparticles of $BaTiO_3$ may be incorporated in the structure of a hydrogel, liposome coating, polymer nanocarrier or microneedle matrix. The electrocaloric effect on the scale of a single nanoparticle is likely to be an atomistic phenomenon that is hard to use in practice since the nanoscale heat exchange from the nanoparticle is quickly diffused in the water-rich tissue. A high value of the volume fraction for the composite or structured film could, however, create measurable local thermal modulation when combined with electrodes and thermal insulation. This allows the conception and construction of patch, implant and microfluidic configurations more realistic, than the freely circulating electrocaloric nanoparticles (57).

In the future, cancer therapy is a potential area for application; tumor therapy may need spatially localized therapy and multiple modalities can be used. There are already pre-clinical proofs in ultrasound triggered piezocatalysis, NO release, chemodynamic therapy and immune modulation of the $BaTiO_3$ systems. Electrocaloric thermal control may be beneficial in the following ways: for mild cooling, reducing the inflammation after treatment; for mild heating to promote thermosensitive release and/or for thermal cycling to increase or decrease perfusion. These are only suggested ideas and there is currently no validated evidence supporting the use of these as active nanomaterials which releases tumour drugs for clinical use, but rather, as electrocaloric $BaTiO_3$ (58).

Also, inflammation control and wound healing are interesting, but must be managed clinically without the flair of clinical promises. In some circumstances, local cooling is useful to diminish pain, tissue swelling and inflammatory signals and/or controlled warming can improve perfusion and polymer delivery in other cases. The electrocaloric $BaTiO_3$ wound patch would have the potential to integrate a drug containing hydrogel with electronically-controlled thermal pulses and sensor feedback. Studies must be able to show a repeatable thermal output and maintenance of the drug activity as well as no leakage of electricity to the skin and the biocompatibility of each of the contact materials (59) before this can be believable.

Pharmaceutical: Temperature-sensitive biologics (peptides, proteins, vaccines, enzymes, growth factors, cell derived products) raise the additional motivation. In point-of-care storage cartridges, wearable infusion devices, or implantable reservoirs, electrocaloric microdevices (ECDs) might come into play when cooling is needed in a specific location. This is closer to actual than the systemic electrocaloric nanocarriers as the material stays in the device and does not circulate. The regulated product would be complex: It would be a combination of drug, device, electronics or even software-controlled thermal feedback (60).

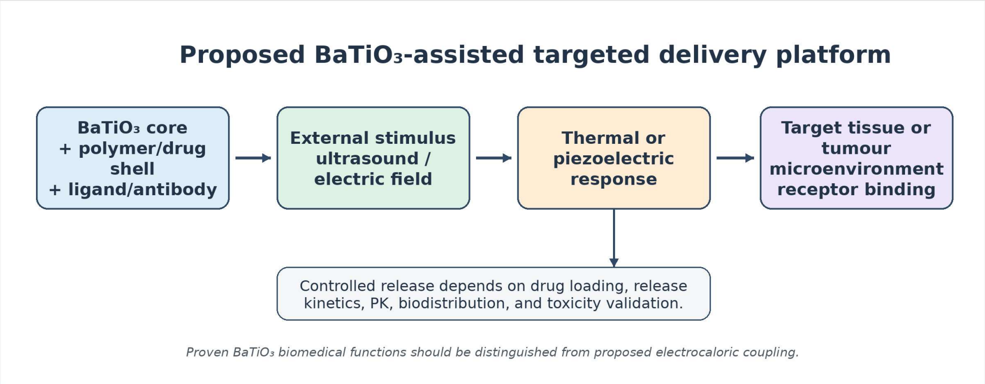


Figure 4. Proposed $BaTiO_3$-assisted targeted drug-delivery platform showing drug loading, surface functionalization, targeting ligand, external stimulus and controlled release. The figure distinguishes the functional $BaTiO_3$ core from the drug reservoir and biological targeting interface (61).

Table 4. Possible mechanisms connecting $BaTiO_3$ electrocaloric/piezoelectric behavior with targeted drug delivery and biomedical cooling.

Mechanism	**$BaTiO_3$ property involved**	**Drug-delivery/cooling function**	**Evidence status**	**Key design requirement**
Electrocaloric local thermal pulse	Field-induced polarization entropy change	Trigger or modulate thermoresponsive release; local cooling/heating	Proposed for drug delivery; EC demonstrated in materials	High ΔT near 25-45 °C at safe voltage and low leakage
Piezoelectric ultrasound activation	Mechanical-to-electrical conversion	ROS generation, NO release, chemodrug penetration, tissue stimulation	Preclinical biomedical evidence	Controlled acoustic dose and particle targeting
Pyroelectric/piezoelectric catalytic effect	Thermal/mechanical polarization changes	Antimicrobial or tumor therapy;	Preclinical evidence in selected systems	Distinguish catalytic toxicity

Mechanism	$BaTiO_3$ property involved	Drug-delivery/cooling function	Evidence status	Key design requirement
		possible release coupling		from therapeutic effect
Surface functionalized targeting	Ferroelectric nanoparticle surface + coating chemistry	Cell-specific binding and drug localization	In vitro demonstrated	Stable ligand orientation and low nonspecific uptake
Composite hydrogel or microneedle coupling	Dielectric/thermal filler in polymer matrix	Reservoir, diffusion barrier, or tissue-contact patch	Thermoresponsive carriers established; $BaTiO_3$ EC coupling proposed	Reproducible loading, release kinetics and sterilization
Encapsulated device cooling	EC layer in multilayer or film device	Implant/wearable thermal management and drug protection	Device-level EC cooling demonstrated outside drug delivery	Thermal switch, heat sink, insulation and feedback control

8. Biomedical Cooling Applications

Biomedical cooling is a family of temperature-control problems rather than a single application. It includes local anti-inflammatory modulation, thermal protection around implants, thermal-drift protection for sensors, temperature control of sensitive drugs and tissue-specific hypothermia concepts. For any electrocaloric $BaTiO_3$ system, the essential requirement is useful, reproducible and safe cooling or heating at the tissue-device interface under realistic heat-transfer conditions (64).

Local cooling of inflamed tissue may be beneficial for peri-wound care, recovery following surgical procedures, arthritis patches, dermatologic applications and intra-mucosal drug delivery. It would be theoretically possible to use a flexible, $BaTiO_3$-polymer electrocaloric patch to produce short cooling pulses and deliver anti-inflammatory drugs from a hydrogel layer. There may not be a clinical claim until controlled preclinical studies of familial hypercholesterolemia and other disease contexts are available: the pharmacological benefit will depend on the dose, kinetics for drug release, skin tolerance and disease context (65).

Another future path is to control the temperature around implants. For example, implants can cause inflammation, infection, fibrotic encapsulation or drug elution at temperatures in the human body. An encapsulated $BaTiO_3$ electrocaloric element might be used to control the microenvironment surrounding an implant, or to guard the drug reservoir from over heating. However, the field insulating material is a huge challenge, along with fatigue, heat rejection and power supply, hermetic sealing and long-term reliability in saline biological media (66).

A major challenge for wearable biomedical sensors is thermal drift, sweat, temperature variations and curvature of the skin. There is a need to consider cooling solutions in wearables, particularly solid-state ones, highlighted by thermal management reviews. However, if electrocaloric or electrocaloric based electrocaloric composites are capable of being made flexible and low voltage, they may lend a hand in localizing sensor stabilizations and/or improving skin interface comfort. In this case, the device is kept outside the body, to reduce the toxicity risk compared to injectable nanocarriers (67).

Thermal protection of temperature sensitive drugs or biologics is one such pharmaceutical use. Controlled storage, delivery conditions for vaccines/peptides/proteins/RNA-based products and enzymes. It is suggested that the electrocaloric microdevices, capable of holding temperature excursions, can be used with point-of-care cartridges, implantable pumps or in wearable infusion systems. A near-term opportunity is likely to be device-level thermal management, as opposed to direct tissue cooling and encapsulated materials are easier to control than dispersed particles (68).

There should be caution in discussing the concepts of cooling the brain, nerves and local tissues. The introduction of a $BaTiO_3$ electrocaloric implant in neural or cerebral applications would necessitate high safety validation compared with different medical applications investigated. Studies of nerve regeneration using piezoelectric materials and the local stimulation are promising but electrocaloric cooling of neural tissue is still a future concept, rather than a proven treatment (69).

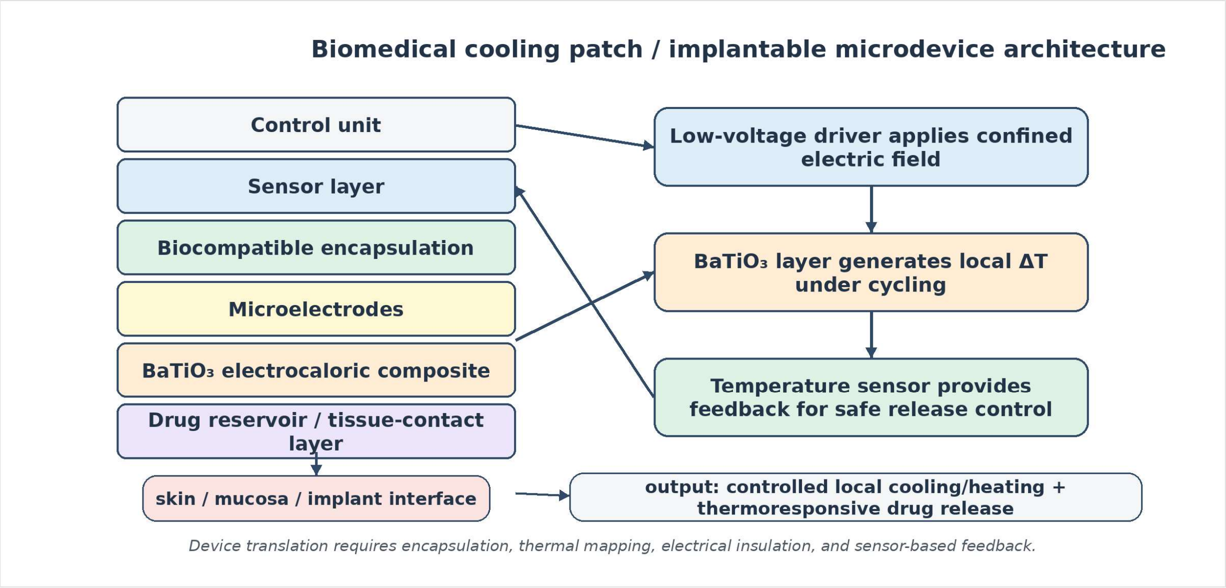


Figure 5. Conceptual biomedical cooling patch or implantable microdevice using $BaTiO_3$-based electrocaloric thermal modulation. The device contains a flexible encapsulation layer, microelectrodes, $BaTiO_3$ electrocaloric composite layer, adhesive or tissue-contact layer, sensor feedback and thermal control circuit (70).

9. Challenges and Limitations

The first major drawback is that of the high electric field requirement. To achieve a useful ΔT, many of the electrocaloric systems based on $BaTiO_3$ have to achieve tens to hundreds of kV cm^{-1} applied field. The high internal fields may be acceptable in well-insulated – i.e., multilayered – devices, but are intolerable if there is leakage into tissue or if high external voltages are necessary. For biomedical translations, multilayers, thin films, high breakdown composites and designs that decrease field intensity and prevent leakage that is large enough compared to the voltage differ of the potential barrier, are essential for the device (73).

The second drawback is the variability of the electrocaloric response very close to the physiological temperature. Others give peaks that are strong at particular phase transitions, but not at 25-45 °C.Others have a wider operating range but lower peak ΔT. The critical value for pharmaceutical application is not such a large change at a non- physiological temperature, but rather a moderate change in response when exposed to the desired therapeutic temperature (74).

Problems of material fatigue, dielectric breakdown, leakage current and joule heating may affect prolonged use. A drug-delivery device may be expected to handle thousands to millions of cycles, have to be stable during storage, be able to be sterilized and function in humid environments. When a material fails these lab trials in short cycles, it can't back implantable and wearable therapy. Cyclic field exposure to testing, thermal cycling, simulated body fluid and relevant sterilizing should thus be included in the fatigue testing (75).

Miniaturization and integration are not an option. The biomedical cooling module must include the electrodes, insulation, thermal switch/heat sink, temperature sensor, power source, control algorithm, drug reservoir, biocompatible packaging and failure mode protection. The more the components added, the thicker, harder, more costly and more complicated it becomes (76).

In the case of nanoparticle concepts, biocompatibility and long-term toxicity are still undecided. Systemic administration requires comprehensive toxicological characterization of $BaTiO_3$, although for selected cell experiments the material seems relatively innocuous. Several factors might influence biological fate of particles including particle size, shape, crystallinity, surface charge, stability of coatings, residual solvents, endotoxin levels, aggregation and corona of particles. Safety in a single cell-viability assay alone is therefore not accepted as adequate to substantiate safety for biomedical use systemically and/or as implants and/or repeated doses (77).

Also, the drug-loading efficiency and reproducibility of drug release are not well developed. Most papers on materials emphasize the electrical performance aspects but regard drug loading as a “bonus” demonstration. A pharmaceutical review has to be based on the loading capacity, encapsulation efficiency, release time, burst release, sink conditions, stability of the active ingredient, batch-to-batch variation and the pharmacodynamic relevance. When these data are not available, claims for the use of drugs are not sufficiently substantiated (78).

There are significant regulatory obstacles. $BaTiO_3$ electrocaloric drug-delivery systems would almost certainly be considered as combination products (drug/device and perhaps software-controlled electronics). Testing includes ISO 10993 biocompatibility testing, IEC electrical safety testing, sterilization validation testing, extractables/leachables testing, thermal safety testing, electromagnetic compatibility testing, pharmacokinetics testing, toxicology testing and human factor testings. It is very important that these requirements be considered at the very start of designing the system (79).

Table 5. Challenges, limitations and proposed solutions for medical translation of $BaTiO_3$-based electrocaloric systems.

Challenge	Why it matters medically	Likely consequence	Proposed solution
High electric field	Tissue and user safety require electrical insulation	Unsafe voltage or bulky driver	Multilayers, high-breakdown composites, encapsulation, low-voltage driving
Weak EC response near body temperature	Thermal modulation must occur at physiological conditions	Insufficient release/cooling effect	Phase-boundary engineering and broad-response compositions
Dielectric breakdown and fatigue	Wearables and implants need repeated cycling	Device failure or heating	Accelerated fatigue tests in humid and sterilized conditions
Poor nanoparticle dispersion	Aggregation alters dose and biodistribution	Toxicity, embolic risk, inconsistent targeting	Surface functionalization, colloidal stability testing, protein corona control
Unknown long-term toxicity	Chronic retention and immune response may occur	Regulatory rejection	Full in vivo biodistribution, clearance, repeated-dose toxicology
Drug-loading/release variability	Dose reproducibility is central to pharmaceutical quality	Unreliable therapeutic effect	Validated loading protocols, release models, quality-by-design
Sterilization incompatibility	Clinical products must be sterile	Loss of material/drug performance	Compare gamma, ethylene oxide, filtration, aseptic processing
Regulatory complexity	Combination products face multiple standards	Long development timelines	Early regulatory strategy and risk management

10. Future Scope in Medicine and Pharmaceutical Technology

For further pharmaceutical studies, the shift from loosely conceptual connections to experimentable smart nanocarriers and devices for pharmaceutical applications, based on barium titanate ($BaTiO_3$), should be implemented. The next key step will be to create systems in which the thermal output from the $BaTiO_3$ will be directly related to a measurable drug change in release. The simultaneous testing side by side of identical carriers, both with and without $BaTiO_3$, electric-field-on and electric-field-off controls, direct mapping to maps of temperatures and drug stability assessment and the release kinetics in the physiologically relevant media (80), is achieved thereby.

While injectable electrocaloric nanomedicine is expected to take longer to develop, electrocaloric microdevices which would provide relief for localized biomedical cooling are expected to become more mature. Embedded multilayers or composites of $BaTiO_3$ may be used to construct wearable and implantable patches, drug reservoirs and biosensor housings and microfluidic cartridges without risk of releasing free nanoparticles into the tissues. They might be used for local heating and cooling of inflamed tissue, thermal protection of biologic products, active transdermal drug delivery and for temperature stabilization around sensors (81).

Special mention here should be made of systems of hybrid form, composed of the matrix $BaTiO_3$ and polymers. There are several functions that a flexible polymer can offer, such as mechanical comfort, adhesion, drug storage and tissue compatibility and $BaTiO_3$ can offer dielectric, piezoelectric, pyroelectric/electrocaloric functions. Thermoreponsive hydrogels, polyurethane elastomers, silicone encapsulants, poly(vinylidene fluoride)-based ferroelectric polymers, chitosan, gelatin, alginate, PEG-based systems and microneedle-forming polymers are all candidates for the matrices. There is a need to find a balance between maximizing ceramic loading and the field response, flexibility, release control and cytocompatibility of the research goal and not maximum ceramic loading, at any cost (82).

Drug delivery could go in a strong direction with integration with microneedles. Microneedles can be used to direct drug delivery to the skins and mucosae and an electrocaloric backing material may be used to regulate the temperature of a drug-loaded hydrogel/polymeric needle matrix. The effects of small temperature pulses in a field to release payloads such as insulin, analgesics, vaccines, anti-inflammatory agents, peptides, or dermatologic cosmetics should be tested in further studies to see if the skin is damaged or the payload denatured (83).

The opportunity to integrate with liposomes and thermoresponsive nanoparticles exists, too. If the electrocaloric component is applied on the surface of the carrier as a patch, it can be used as a trigger, or applied as a part of a composite reservoir, as local heat element. The issue that remains is whether the thermal changes due to electrocaloric activity in $BaTiO_3$ electrocaloric modules can be localized and repeatable enough, that the transition can be controlled in vivo (84).

For the systems based on ultrasound/electric field, remote controlled therapy might be possible. The piezoelectric literature has proven ultrasound activation in animal models for cancer research and the electrocaloric literature, electric-field thermal modulation in biomaterials. An upgraded platform might incorporate the features of targeting with ultrasound, electric-field heat and a polymer reservoir for drug delivery. But when combined stimuli add to regulatory and safety complexity, the mechanism of each stimulus needs to be separated out before it could be established that these stimuli are synergistic (85).

Personalized medicine applications might appear for thermal dose/drug release that can be patient-specific that could be associated with tissue inflammation measurement or sensor feedback or location and temperature of tumors. Closed-loop systems may allow for the temperature of surface or implant to be measured and thus release the drug only if a specified temperature profile has been attained. These would need to be validated using software, designed to be fail safe and require pharmacokinetic modelling and conform with the trend towards smart wearable/implantable therapeutics (86).

High-priority prospects involve the treatment of cancer and alteration of the tumor microenvironment. Previous studies have already demonstrated Piezocatalytic activities in ROS generation, enhancing penetration and combined with other modalities in pre-clinical settings using $BaTiO_3$-based piezocatalytic therapy. Potential micro cycles of thermal modulation by an electric field may be implemented in the area of tumor.concurrent management, but should be verified with direct thermal mapping and pharmacodynamic endpoints in concurrent animal models and spheroids/organoids (87).

Thermal protection of vaccines, peptides, proteins and biologics may be one even more of the most practical pharmaceutical uses. A point-of-cre storage device or a portable (wearable) infusion cartridge, in which the transport domain sent an electrocaloric nanocarrier with a biologic would protect the biologic during transport or short-term non-refrigerated storage, would make use of the nanocarriers' solid-state cooling capability based on the property of $BaTiO_3$. Yet, this application needs further energy efficiency analysis, device level heat-transfer design and assessment of thermodynamic stability of the applied biologic in the cycling conditions (88).

In vivo studies, pharmacokinetic study, toxicological profile and regulatory standard testing are needed in the field. For nanoparticle systems, bio-distribution, clearance, bio-transformation, immune response, repeated dosage and histopathology is what it means. For device systems, these include the software-controlled operation, extractables/leachables, thermal dose, electrical safety, mechanical reliability and sterilization. This collaborative strategy involves cooperation among pharmaceutical scientists, materials engineers, clinicians, biomedical device developers, toxicologists (89) and particularly perhaps the genetic engineering of pharmaceuticals, will be most productive in the future.

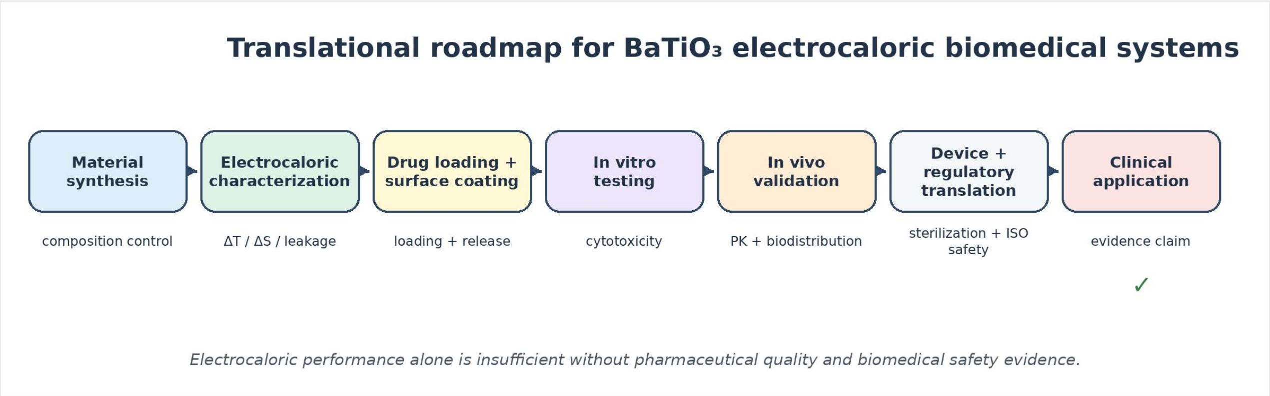


Figure 6. Future translational roadmap from material synthesis to in vitro testing, in vivo validation, device integration, regulatory testing and clinical application. The roadmap emphasizes that electrocaloric performance alone is insufficient without pharmaceutical quality and biomedical safety evidence (90).

Table 6. Future research directions for $BaTiO_3$-based electrocaloric materials in pharmaceutical and biomedical applications.

Future direction	Pharmaceutical rationale	Suggested first experiment	Expected translational value
$BaTiO_3$ smart nanocarriers	Combine targeting with active stimulus response	Compare drug release with/without electric or ultrasound stimulus	On-demand localized therapy
Electrocaloric cooling microdevices	Protect tissue or drug reservoirs from thermal excursions	Measure cooling through skin/tissue phantoms	Wearable or implantable thermal management
$BaTiO_3$-polymer drug patches	Flexible matrix can store drug and contact tissue	Quantify release under EC cycling	Transdermal and wound-care applications
Microneedle integration	Localized minimally invasive delivery	Test thermoresponsive microneedle release with EC backing	Programmable skin delivery
Liposome/hydrogel coupling	Thermal transitions can control release	Thermal mapping plus release kinetics in biological medium	Controlled biologic and anticancer delivery
Remote-controlled therapy	Ultrasound/electric fields permit noninvasive activation	Separate piezoelectric, electrocaloric and thermal effects experimentally	Personalized and image-guided treatment
Biologic protection	Peptides/proteins/vaccines need temperature control	Test stability of biologic in EC-cooled cartridge	Point-of-care storage and wearable infusion
Regulatory-grade safety package	Clinical translation requires standards-based evidence	ISO 10993, PK, biodistribution, extractables/leachables	Reduced translational risk

11. Conclusion

The development of electrocaloric properties in $BaTiO_3$-containing systems has progressed considerably, from conventional ferroelectric ceramics to doped systems, solid solutions, thick films, multilayers and flexible composites. Despite these advances, major limitations remain, including restricted working ranges, high electric-field requirements, dielectric breakdown, fatigue and the need for device-level integration. Composition design, phase-boundary regulation, domain engineering, internal-stress control and multilayer architecture have improved performance, but these strategies must still be translated into stable, safe and reproducible biomedical formats (93).

$BaTiO_3$ is particularly interesting for pharmaceutical and biomedical science because electrocaloric behaviour can coexist with piezoelectric, pyroelectric, dielectric and surface-functionalizable properties. $BaTiO_3$ nanoparticles and hybrids have already been investigated for targeting, ultrasound-activated therapy, piezocatalysis, bioimaging, tissue engineering and smart nanomedicine. However, these biomedical studies provide a foundation rather than definitive proof of electrocaloric drug delivery (94).

Encapsulated electrocaloric microdevices, barium titanate-based compliant patches, in situ thermal protection of sensitive drugs and biologics and flexible $BaTiO_3$-polymer patches represent the most realistic short-term possibilities. The most promising near-term directions are device-contained electrocaloric modules, flexible $BaTiO_3$-polymer patches, thermoresponsive hydrogels, microneedles and protected reservoirs for fragile biologics. In contrast, injectable electrocaloric nanocarriers remain more speculative because nanoscale temperature gradients dissipate rapidly in aqueous tissue environments and systemic safety remains challenging. Direct release experiments, physiological thermal mapping, pharmacokinetic studies, long-term toxicology and device-safety testing are required before clinical readiness can be claimed (95).

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