

Compounding pharmacy in sports medicine: Enabling personalized therapeutics and bridging clinical gaps

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Received 11 March 2026 ♦ Accepted 23 March 2026 ♦ Published 11 May 2026

Citation: Pehlivanov I, Andonova V, Vladeva E, Nedyalkova-Petkova D, Panayotova-Ovcharova L, Petkov P (2026) Compounding pharmacy in sports medicine: Enabling personalized therapeutics and bridging clinical gaps. Pharmacia 73: e191297. <https://doi.org/10.3897/pharmacia.73.e191297>

Abstract

Compounding pharmacy addresses critical therapeutic gaps in sports medicine by enabling personalized formulations for injury management. This review synthesizes evidence on customized topical medications, particularly for advanced delivery systems, including iontophoresis and phonophoresis, which enhance localized drug delivery while minimizing systemic side effects that impair athletic performance. Frequently prescribed combinations incorporate analgesics, nonsteroidal anti-inflammatory agents, corticosteroids, and muscle relaxants at standardized concentrations. Clinical applications span acute injuries, chronic overuse conditions, and neuropathic pain syndromes, though randomized controlled trials demonstrate variable efficacy, necessitating cautious, patient-specific implementation. Regulatory frameworks differ substantially between jurisdictions, with European models integrating compounding within licensed pharmacy practice through centralized formularies and quality systems, while the United States maintains bifurcated oversight distinguishing traditional compounding from outsourcing facilities. These structural variations fundamentally shape the safety, accessibility, and clinical integration of personalized therapeutic solutions for active populations.

Keywords

drug delivery systems, musculoskeletal injuries, pain management, regulatory framework, topical drug delivery

Introduction

According to the WHO (World Health Organization 2022), 81% of adolescents and 27.5% of adults globally are insufficiently physically active. In this context, it is important to promote an increase in recreational and professional sports and overall physical activity. Despite the substantial enjoyment and health benefits of sports, a major draw-

back is the prevalence of sports-related injuries. Accidents, overtraining, and contact sports can be the leading causes.

Recent statistics from Johns Hopkins Medicine indicate that injuries caused by recreational and professional sports activities are a significant issue. It is estimated that approximately 8.6 million injuries occur each year; among them, 3.5 million involve children and adolescents, and over 775,000 individuals under the age of 14 are treated

in emergency departments. Ankle sprains have emerged as the most frequently occurring sports injury across all age groups, and sports such as cycling, basketball, football, and soccer account for the highest number of emergency room visits (Johns Hopkins Medicine (n.d.) 2026).

According to data from the Cleveland Clinic (Cleveland Clinic 2021), sports injuries can be broadly classified as acute and chronic or overuse injuries. The choice of treatment is contingent on the specific injury, its severity, and the patient's goals but generally adheres to a progressive model from acute care to functional rehabilitation. The treatment plan generally comprises rest, application of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroid injections, targeted stretching and strengthening exercises, use of ultrasound or electrical stimulation, manual therapy, functional and sport-specific training, and, in the case of severe injuries such as a complete ligament tear, surgical intervention.

Within the multidisciplinary framework of sports medicine, which is dedicated to the care of athletes and active individuals (McCrory 2006), the customization of therapies is paramount for addressing unique physiological and performance needs. While physical therapy provides essential rehabilitative interventions (New York Education Law 1985) and sports pharmacy ensures medication safety and anti-doping compliance (FIP 2023), compounding pharmacy serves as a critical pillar for personalized therapeutic solutions. Moreover, in present days, due to medicinal product shortages in the EU, such as antimicrobials (76%), followed by painkillers (43%) and anesthetics (37%), compounding pharmacy activities present a frequent measure (64%) to overcome this problem (EMA 2025).

Compounding pharmacy practices are uniquely positioned to address a significant gap in sports medicine: the lack of commercially available, patient-specific medications. These practices enable the tailoring of treatments that are injury-specific with regard to metabolic profile and performance demands, which is crucial for promoting optimal healing and preventing recurrent injury (Allen 2010). This is particularly vital in pain management, where conventional systemic analgesics often produce undesirable side effects, such as drowsiness, that can impede training and recovery.

To overcome this, compounded topical analgesics represent a sophisticated therapeutic strategy. By creating customized topical dosage forms, compounding pharmacists facilitate localized drug delivery, providing targeted analgesia at the site of injury while significantly reducing systemic absorption and its associated performance-limiting effects (Cline and Turrentine 2016). Therefore, the integration of specialized compounding practices is essential for advancing a more precise, effective, and safe pharmaceutical care model in sports medicine.

Aim

This review aims to critically examine the indispensable role of compounding pharmacy in addressing the therapeutic gaps within sports medicine and physical rehabil-

itation. It synthesizes evidence on the formulation and application of customized topical medications, particularly for advanced delivery systems such as iontophoresis and phonophoresis, and evaluates the regulatory frameworks that govern this personalized practice across different jurisdictions.

Materials and methods

Scoping literature review using PubMed, Scopus, and Web of Science (up to March 2026). Keywords: compounding, rehabilitation, sports injury, topical NSAIDs.

Sports-related injuries

The nature of sports-related injuries varies significantly across athletic populations, differing in primary etiology, psychological impact, and typical injury patterns. For elite athletes, injuries are often the result of high-intensity training and competition, with a high prevalence of overuse and acute traumatic injuries, such as hamstring strains and knee derangements; the meaning of injury is complex, frequently perceived as a major career disruption or existential threat, which profoundly influences recovery psychology (Hootman et al. 2007; Reussner et al. 2024; Zupancic and Marušić 2024). In adolescents, injuries are highly prevalent and are closely tied to growth-related factors, biomechanical immaturity, and sport specialization; risk is amplified by higher BMI, excessive practice volumes, and gender (females at higher risk for certain injuries), with the experience often marked by fear of re-injury and significant social and emotional distress (Prieto-González et al. 2021; Al-Qahtani et al. 2023). Conversely, recreational adult athletes typically face injuries stemming from deconditioning, improper technique, or sporadic participation, with common issues including sprains, strains, and tendinopathies, often related to the specific physical demands of their chosen activities (Garrick and Requa 1993). Different surveys highlight the substantial public health burden, estimating 8.6 million such injuries annually, with sprains and strains and lower extremity injuries being most prevalent (American Physical Therapy Association 2017; Herzog et al. 2019; Gurau et al. 2023). These injuries are frequently complicated by longer recovery times due to age and lower baseline fitness.

A significant therapeutic challenge is the management of pain and inflammation. Systemically administered analgesics and anti-inflammatory drugs frequently produce adverse effects, such as drowsiness, which can be detrimental to athletic performance and recovery regimens regardless of age. To mitigate these issues, compounded topical dosage forms present a viable alternative. These formulations allow for localized drug delivery through the dermis, providing targeted relief at the site of application while minimizing systemic absorption and the associated undesirable effects that can impede an athlete's performance (Cline and Turrentine 2016).

Types of sports injuries

Sports injuries represent a multifactorial spectrum of pathology, systematically classified through an integrated framework that combines etiological mechanisms, anatomical specificity, tissue pathology, and clinical severity. The foundational etiological dichotomy distinguishes acute traumatic injuries, such as sprains, fractures, and dislocations (Micheli and Purcell 2018), from chronic overuse injuries, which result from repetitive microtrauma and insufficient recovery, exemplified by tendinopathies and stress reactions (Malliaras et al. 2015). This mechanistic classification is critical for prevention and initial management.

The model is refined by anatomical specificity, with predictable injury patterns occurring in high-stress joints. Table 1 synthesizes common injuries by site and mechanism.

Table 1. Main types of injuries.

Injury mechanism	Shoulder and upper arm examples	Knee examples	Back examples
Acute/traumatic	Clavicle fracture, shoulder dislocation, and torn rotator cuff (Bakhsh and Nicandri 2018)	*MCL/ACL sprain and meniscus injury (Logerstedt et al. 2022)	Muscle strain and ligament sprain
Chronic/overuse	Impingement syndrome, rotator cuff tendinitis, and adhesive capsulitis (Lewis 2016)	Patellofemoral pain syndrome and iliotibial band syndrome (Witvrouw et al. 2014)	Lumbar disc disease and spondylolysis (Micheli and Wood 1995)

*MCL: medial collateral ligament; ACL: anterior cruciate ligament.

A critical advancement is the stratification of injuries by clinical severity, which directly informs management. Injuries are categorized as mild (pain only post-activity), moderate (pain affecting performance), or severe (constant pain disrupting daily function) (Brukner and Khan 2017). This grading guides rehabilitation and return-to-play decisions. Furthermore, the framework explicitly identifies emergency conditions, such as obvious deformity, altered consciousness, or neurological deficits, which necessitate immediate intervention to prevent catastrophic outcomes (American College of Sports Medicine 2021).

Finally, the model encompasses integumentary (skin) injuries, which are often overlooked. These range from mechanical insults, such as abrasions and blisters, to environmental and infectious conditions, such as swimmer's ear and fungal infections, which are common in athletic populations (Adams 2006).

Therapeutic approaches

The initial management of acute soft-tissue injuries, such as sprains and contusions, has long been guided by the RICE principle (Rest, Ice, Compression, Elevation), a foundational protocol aimed at minimizing hemorrhage, swelling, and pain in the immediate post-injury phase (Brukner and Khan 2017). It is important to note that contemporary practice has evolved this concept, with recent evidence emphasizing gentle movement over strict rest and cautioning against the potential anti-inflammatory effects of ice that may impair long-term tissue regeneration; the updated PEACE & LOVE (Protect, Elevate, Avoid anti-inflammatories, Compress, Educate & Load, Optimism,

Vascularization, Exercise) protocol reflects this more nuanced understanding (Dubois and Esculier 2020).

Beyond first aid, treatment expands into a wide array of physical and pharmacological modalities, each targeting specific phases of the healing process or symptoms (Brukner and Khan 2017; Prentice 2023). Table 2 categorizes common therapeutic interventions used in sports medicine practice.

Recovery timelines are highly contingent on the injury type and patient demographics. In general, high-level athletes often experience shorter, more predictable healing times. This is due to a confluence of favorable factors: their injuries receive immediate expert care, they follow structured rehabilitation protocols meticulously, and they typically possess superior baseline physical conditioning and the enhanced healing capacity associated with younger age (Micheli and Purcell 2018). In contrast, recreational

athletes present a more variable prognosis. Their recovery is influenced by a wider range of intrinsic factors (e.g., age and underlying health) and extrinsic factors (e.g., consistency of self-treatment and access to therapy), as outlined in models of overuse injury risk (Physiopedia 2020). Crucially, the injury mechanism (acute trauma vs. chronic overuse) and the tissue type involved directly dictate the physiological healing timeline, which these treatments aim to support optimally.

Combined modality therapies: phonophoresis and iontophoresis

For persistent, localized musculoskeletal conditions that prove refractory to first-line rehabilitative care, advanced combined modality therapies, such as phonophoresis and iontophoresis, offer a targeted, non-invasive therapeutic bridge between conservative management and more invasive interventions (Brukner and Khan 2017). These techniques synergistically integrate physical energy with pharmacological agents to enhance transdermal drug delivery, thereby maximizing local tissue concentration while minimizing systemic exposure and side effects (Cagnie et al. 2003; Prentice 2023).

Phonophoresis employs therapeutic ultrasound waves to facilitate skin permeation and deeper tissue penetration of topically applied anti-inflammatory medications (such as 10% hydrocortisone ointment, lidocaine, or salicylate gels), making it particularly suitable for treating structures like chronic tendinopathies located 2–5 cm beneath the skin (Prentice 2023). This technique is used in the post-acute stage in conditions such as tendinitis, bur-

Table 2. Common therapeutic interventions.

Phase of treatment	Treatment modality	Description/primary mechanism	Common examples of use
Immediate/first-line care	RICE protocol	A first-aid staple: Rest, Ice, Compression, Elevation . Aims to reduce initial swelling, pain, and hemorrhage (Brukner and Khan 2017).	Acute ankle sprains, muscle strains, and contusions.
	POLICE/PEACE & LOVE Principle	An evolution of RICE. POLICE : Protection, Optimal Loading , Ice, Compression, Elevation. PEACE & LOVE further emphasizes avoiding anti-inflammatories and adding education, vascularization, and optimism (Dubois and Esculier 2020).	Minor to moderate ligament sprains and muscle strains.
Pharmacological	NSAIDs	Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen). Used for short-term pain and inflammation control (Agroff 2013; Derry et al. 2015).	Acute inflammatory phase of tendinitis, bursitis, and strains.
Rehabilitative/core management	Physical therapy	The cornerstone of recovery. Includes therapeutic exercises , manual therapy, and adjunct modalities (Prentice 2023) to restore strength, range of motion, and proprioception.	Post-surgical rehab (e.g., ACL reconstruction), rotator cuff injuries, chronic back pain.
	Therapeutic exercises	Targeted stretching, strengthening (e.g., eccentric loading), and neuromuscular re-education drills to address deficits and prevent re-injury.	Muscle strengthening after a strain and balance training post-ankle sprain.
	Adjunct modalities	Includes electrotherapies (TENS, stimulation) , acoustic therapies (ultrasound) , and thermal therapies . Used to manage pain, reduce swelling, and facilitate exercise participation (Watson 2008; Prentice 2023).	Pain modulation during rehab, soft tissue healing, and managing chronic stiffness.
Interventional/advanced	Corticosteroid injections	Powerful anti-inflammatory injections for localized, stubborn pain. Use is often limited due to potential tissue weakening with repeated doses.	Severe bursitis, tendinitis (e.g., tennis elbow) not responding to oral medication.
	Orthobiologics (e.g., PRP)	Injections using concentrated growth factors from the patient's own blood to potentially stimulate healing in damaged tissues.	Chronic tendon injuries (e.g., Achilles tendinopathy) and some ligament sprains.
Surgical	Surgical repair/reconstruction	Reserved for severe structural damage (complete tears and complex fractures) that fails to heal with conservative treatment or when joint instability is present.	Complete ACL tears, recurrent shoulder dislocations, and complex intra-articular fractures.

sitis, or contusions. The standard coupling gel is replaced with a gel or cream containing the medication (Anderson et al. 2005).

In contrast, iontophoresis utilizes a low-voltage electrical current to actively drive ionized drug molecules (such as dexamethasone or ketoprofen) across the skin barrier, rendering it highly effective for superficial pathologies such as plantar fasciitis or insertional Achilles tendinopathy (Clijsen et al. 2012; Castro-Méndez et al. 2025). The polarity of the medication determines which electrode is used to drive it into the skin. The medication is placed under the electrode of the same polarity, and when current is applied, the molecules are pushed away and driven toward the injured site. This localized treatment is often preferred over more disruptive systemic treatments (Anderson et al. 2005).

Clinically, these modalities are strategically deployed in the treatment continuum for overuse injuries such as lateral epicondylitis or patellar tendinosis when therapeutic exercise and manual therapy yield suboptimal results but before progressing to corticosteroid injections or surgical consultation (Brukner and Khan 2017). Their primary rationale lies in providing a potent, localized anti-inflammatory and analgesic effect that can resolve persistent inflammation and pain, thereby facilitating more effective participation in the essential loading and strengthening exercises required for full functional recovery.

Medications

The application of combined modality therapies is grounded in the broader field of sports pharmacy, which utilizes a specific armamentarium of drugs to manage injury (Anderson et al. 2005). These include analgesics, nonsteroidal anti-inflammatory agents (NSAIDs), corticosteroids, anesthetics, and muscle relaxants, formulated into various topical dosage forms. As noted in sports pharmacology literature, phonophoresis and iontophoresis represent two specialized delivery systems that are employed more frequently in athletic populations than in the general patient care setting (Anderson et al. 2005). These modalities are not standalone treatments but are defined by the active pharmaceutical ingredients they transport. Phonophoresis is optimally performed by incorporating the chosen drug (e.g., a corticosteroid or NSAID) into a coupling gel, while iontophoresis typically utilizes simple aqueous solutions of ionized medications (e.g., dexamethasone or ketoprofen) (Castro-Méndez et al. 2025; Gross et al. 2025). This direct link between drug category and delivery mechanism underscores the purpose of these techniques: to achieve targeted, localized pharmacological effects such as potent anti-inflammatory and analgesic action for conditions such as chronic tendinopathies and plantar fasciitis, thereby facilitating the rehabilitative process (Clijsen et al. 2012).

The specialty of sports pharmacy is a globally recognized field in which pharmacists, designated as Athlete Support Personnel (ASP), play a critical and expanding role in sports medicine. Their primary responsibilities include managing athlete medications, ensuring pharmacy safety at events, and preventing inadvertent doping through expert consultation (FIP 2023). This specialized domain, dedicated to optimizing pharmacotherapy for athletic populations, has been a formal component of clinical practice and professional education for decades (Price et al. 1995; Sato et al. 1993). A central application of this expertise is found in patient-specific compounding, which enables the customization of therapies for conditions often refractory to conventional treatments, thereby promoting prompt healing tailored to an athlete's age and lifestyle (Allen 2010). This practice is governed by a complex, tiered global regulatory framework designed to ensure quality and safety. Practitioners must adhere to enforceable regional standards such as the United States Pharmacopeia (USP) chapters or the European Pharmacopoeia (Ph. Eur.) monographs, while also integrating principles from international harmonization bodies. For athlete patients, this pharmaceutical regulation is further overlaid by mandatory global compliance with the World Anti-Doping Agency (WADA) Prohibited List, requiring rigorous ingredient verification (USPC 2024a, b; European Directorate for the Quality of Medicines 2024; World Anti-Doping Agency 2024). A significant therapeutic challenge in this regulated context is managing pain and inflammation without the performance-impairing adverse effects, such as drowsiness, commonly associated with systemic drug administration. Compounded topical dosage forms, prepared in compliance with these standards, present a viable alternative by facilitating localized drug delivery through the dermis. This approach provides targeted relief while minimizing systemic absorption and its detrimental effects on performance and recovery (Cline and Turrentine 2016).

This compounding expertise is directly applied to the preparation of agents for advanced combined modality therapies, where treatment efficacy is critically contingent upon the specific pharmacological agent and its precise

formulation. For example, iontophoresis protocols routinely employ aqueous solutions of dexamethasone at a concentration of 0.4%, while phonophoresis commonly utilizes gel-based formulations containing ketoprofen within a 2–10% range – concentrations standardized within sports pharmacy compendia (Table 3). The value of this sports pharmacy expertise extends beyond elite competitors to the vast population of recreational athletes, for whom customized compounded preparations and precise topical delivery can similarly optimize recovery from common injuries while accommodating individual physiologic and lifestyle factors. The drugs utilized in these therapies originate as either prescription or over-the-counter agents; pharmacy compounding practices transform these standard medications into customized topical and transdermal preparations that meet the unique dosage, combination, and delivery system requirements of individual athletes. The major drug categories utilized in these therapies include local anesthetics, analgesics and NSAIDs, adrenocorticoids, and skeletal muscle relaxants. Local anesthetics, such as lidocaine, eliminate short-term pain by blocking sensory neural transmissions and can be topically applied or introduced via phonophoresis or iontophoresis for conditions such as tendinitis (Houglum 1992; Ciccone 2007). Analgesics and NSAIDs (e.g., ibuprofen) work primarily by inhibiting prostaglandin production to decrease inflammation and relieve pain, with their most critical administration period being the early stages of healing (Ciccone 2007). Adrenocorticoids (e.g., hydrocortisone) are used to potently decrease edema and inflammation and may be topically applied or injected, though long-term use is contraindicated due to risks such as tissue breakdown (Ciccone 2007). Finally, skeletal muscle relaxants (e.g., cyclobenzaprine) are used to break the pain–spasm cycle associated with musculoskeletal injuries by depressing somatic motor activity at the brain stem to reduce muscle excitability and pain (Ciccone 2007). For conditions involving significant muscle spasm, topical formulations of agents such as baclofen (2–5%) may be compounded as an adjunctive therapy. Together, these pharmacological strategies, prepared and guided by the specialized knowledge of the sports pharmacist, form a comprehensive approach

Table 3. Active ingredients commonly used in topical sports medicine preparations.

Therapeutic category	Specific drug and common concentration	Example clinical application and relevance to compounding
Analgesics, topical	Camphor (3–11%), capsaicin (0.025–0.25%), menthol (1.25–16%), and methyl salicylate (up to 60%)	Formulated in creams, gels, or sprays for symptomatic relief of muscle aches and minor pains; Often available over-the-counter.
Anesthetics	Lidocaine hydrochloride (5–10%) and ketamine hydrochloride (5–10%)	Used in topical preparations or compounded solutions for iontophoresis to provide localized pain control, sometimes combined with corticosteroids.
Anti-inflammatory agents, corticosteroids	Dexamethasone (0.4–1.5%) and triamcinolone (0.025–0.5%)	The primary drugs for iontophoresis . A 0.4% dexamethasone solution is a standard for treating inflammatory conditions like plantar fasciitis or tendonitis.
Anti-inflammatory agents, nonsteroidal (NSAIDs)	Ibuprofen (2–20%), ketoprofen (2–10%), and piroxicam (0.5–1%)	Frequently compounded into coupling gels for phonophoresis to deliver anti-inflammatory effects directly to injured soft tissues.
Muscle relaxants	Baclofen (2–5%) and cyclobenzaprine (0.5–1%)	Compounded into topical gels or creams for adjunctive treatment of muscle spasms and associated pain; requires precise dosing.

to managing sports injuries while supporting the athlete's health and performance goals.

The preparation of these patient-specific compounded medications, from standard 0.4% dexamethasone solutions to customized ketoprofen gels, does not occur in a regulatory vacuum. Instead, it is governed by a complex, multi-tiered global framework designed to ensure quality, safety, and efficacy. Sports pharmacists must synthesize their compounding expertise with a precise understanding of this landscape, adhering to enforceable regional pharmacopeial standards—such as the United States Pharmacopeia (USP) chapters or the European Pharmacopoeia (Ph. Eur.) monographs—while also ensuring rigorous compliance with the World Anti-Doping Agency (WADA) Prohibited List to prevent inadvertent doping violations (USPC 2024a, b; EDQM 2024; WADA 2024). The critical role of these regulations in enabling safe and effective therapy invites a comparative examination of the foundational models that structure compounding practice worldwide.

Comparative analysis of regulatory models

Pharmacy compounding, the practice of preparing personalized medications to meet specific patient needs not addressed by commercially available drugs, occupies a critical but complex space in global healthcare systems. Its regulation balances the imperative for patient access with the paramount need for quality and safety, with approaches varying significantly across jurisdictions. The following analysis synthesizes the regulatory frameworks of the United States, Italy, Germany, and Spain, highlighting their distinct philosophies and mechanisms.

The United States operates under a bifurcated model established by the Drug Quality and Security Act (DQSA) of 2013. This system distinguishes between traditional pharmacy compounding and outsourcing facilities (U.S. Food and Drug Administration 2013). Traditional compounding is conducted pursuant to a valid prescription for an individual patient and is primarily overseen by state boards of pharmacy. In contrast, outsourcing facilities are subject to federal oversight by the FDA, must comply with Current Good Manufacturing Practice (CGMP) (USPC 2024a, b), and can compound larger volumes of medications without patient-specific prescriptions (Vail 2008). This structure aims to accommodate scale while introducing a higher level of federal quality control, though the system remains predominantly reactive, with significant regulatory action often following post-market adverse events.

In the Italian system exemplifies a pharmacy-centric model grounded in EU Directive 2001/83/EC. Italian regulation formalizes a clear distinction between *preparazioni magistrali* (magistral formulations), tailored to an individual patient's prescription, and *preparazioni officinali* (officinal formulations), which are standard preparations listed in official pharmacopoeias (Decreto Ministeriale (D.M. 18 November) 2003). The “galenic exception” is a recognized legal derogation that permits the use of pat-

ented active ingredients within magistral preparations under stringent conditions, provided the preparation is not a mere copy of an existing industrial drug—a principle upheld by the *Corte di Cassazione* and analyzed in academic commentary (Pandolfini 2023). Quality assurance is mandated through the *Norme di Buona Preparazione* (NBP), which provides detailed requirements for facilities, equipment, documentation, and personnel training, placing direct legal responsibility on the supervising pharmacist (EMA 2022).

Germany enshrines compounding as a core professional responsibility for community pharmacists, regulated by the *Arzneimittelgesetz* (AMG) and the *Apothekenbetriebsordnung* (ApBetrO). The law obligates pharmacies to prepare simple, low-risk dosage forms (e.g., creams or capsules) upon prescription, ensuring broad patient access (ApBetrO 2023). A cornerstone of the German system is the *Neues Rezeptur-Formularium* (NRF), a standardized collection of over 200 tested formulations that serves as the primary reference, promoting national consistency (Zueck 2008). Oversight includes official inspections with product sampling, supplemented by a robust culture of self-assessment; many pharmacies voluntarily participate in triannual comparative quality tests organized by the Central Laboratory of German Pharmacists to benchmark and unify preparation standards nationwide.

Similarly, Spain integrates compounding as a key component of pharmaceutical care within community pharmacies. The *Formulario Nacional* and “Real Decreto 175/2001,” which mandates that all pharmacies engaging in compounding implement a formal Quality Assurance System (AEMPS 2024), anchor the regulatory framework. The Spanish Agency of Medicines and Health Products (AEMPS) provides a comprehensive set of standardized operational procedures (SOPs) within the *Formulario*, covering general processes, preparation methods, galenic operations, and product control. These SOPs are designed for uniform application but allow adaptation to a pharmacy's specific operational conditions. This structured approach supports a significant and growing market, valued at \$288.6 million USD in 2023 (Grand View Research 2024).

Compounding for electrophoresis and phonophoresis

Compounding for iontophoresis and phonophoresis represents a specialized frontier in personalized medicine, where formulations are specifically engineered for use with medical devices that enhance transdermal drug delivery. This high degree of specialization exists within a broader pharmaceutical landscape where foundational compounding expertise has diminished. As the core of pharmacy practice has shifted from the art of formulation to the dispensing of commercially manufactured, FDA-approved drugs, corresponding education in pharmacy schools has declined (NASEM 2020). Consequently, contemporary compounding instruction is often inconsistent and minimal, particularly in guiding which formulations are most efficacious for specific conditions or

patient populations (NASEM 2020). This knowledge gap introduces significant risk, as topical medications—including complex pain creams—compounded without adequate expertise in potency, purity, quality, and bioavailability assessment can pose a direct public health concern (NASEM 2020).

These risks are exacerbated in the context of advanced delivery systems. For iontophoresis, the compounder must engineer an electrochemically compatible system, which involves selecting ionizable drug salts, meticulously controlling pH and ionic strength to maximize drug transport, and using nonionic gelling agents that maintain conductivity without interfering with the electric field (Singhal et al. 2017). Any extraneous ions from buffers or preservatives compete with the drug, reducing delivery efficiency. Similarly, phonophoresis formulations must act as efficient acoustic coupling media (Ibrahim and Li 2009). They require high water content for energy transfer, must be meticulously degassed to prevent ultrasound scattering, and often incorporate specific chemical en-

hancers chosen based on structure–activity relationships, such as logP and hydrogen-bonding capacity, to facilitate sonophoretic penetration (Ibrahim and Li 2009).

The inherent variability of compounding further complicates this picture. Unlike standardized manufacturing, the compounding process differs between practitioners and facilities, making formulations susceptible to inconsistencies in critical process variables (NASEM 2020). This issue is particularly acute for multi-ingredient topical formulations, including those for device-enhanced delivery, for which a robust evidence base is urgently needed to clarify the individual contribution of each component to overall effectiveness, appropriate dosage and dosing intervals for each agent, and potential pharmacological interactions among the combined ingredients (NASEM 2020). To mitigate this variability, it is recommended that any pharmacist formulating a preparation for iontophoresis or phonophoresis follow a standardized set of guidelines; such an approach would significantly improve the reproducibility and clinical efficacy of the final product (Table 4).

Table 4. Comparative formulation considerations for iontophoresis and phonophoresis.

Dimension	Iontophoresis	Phonophoresis
Core principle	Electrochemical drug delivery via applied electric current.	Acoustic energy-enhanced delivery via ultrasound.
Key formulation goal	Create an electrochemically compatible system that maximizes drug ion transport.	Create an acoustic coupling medium that optimizes ultrasound energy transfer.
Drug requirements	Must be ionizable (salt form preferred; e.g., dexamethasone sodium phosphate).	Works best with lipophilic, low-MW molecules (log P ~1-3 optimal); hydrophilic drugs also possible.
Critical physical-chemical factors	1. pH/pKa: Must keep drug ionized (typically pH 4–8).	1. Acoustic impedance: Must match skin for efficient energy transfer.
	2. Ionic strength: Must be minimized ; extraneous ions compete for current.	2. Cavitation potential: Formulation should facilitate ultrasound-induced micro-bubble activity.
	3. Conductivity: Formulation must conduct current effectively.	3. Viscosity/rheology: Must allow for efficient coupling without excessive damping.
Vehicle/base design	Gel: Uses nonionic gelling agents (e.g., HEC) to avoid current competition.	Gel: High water content for coupling; shear-stable polymers (e.g., carbomer).
	Solvent: Deionized water is essential.	Solvent: Deionized, degassed water to eliminate air bubbles.
	Key Trait: Low electrolytic content.	Key trait: Homogeneous and bubble-free.
Key excipient considerations	• Buffers: Use minimally; they add competing ions.	• Coupling enhancers: Propylene glycol or glycerol (low %).
	• Preservatives: Choose nonionic or very low concentration ionic types.	• Chemical penetration Enhancers: Terpenes and fatty acids can be integrated (Ibrahim and Li 2009).
	• Chelators/antioxidants: May be needed for electrochemical stability.	• Preservatives: Compatible with gel structure and acoustic properties.
Stability and safety concerns	1. Drug stability: Degradation via electrolysis or oxidation.	1. Drug stability: Degradation from ultrasonic shear or localized heat.
	2. Skin irritation: From pH extremes, current density, or electrode reactions.	2. Skin irritation: From enhancers or thermal effects.
	3. Contamination: Risk from conductive ingredients.	3. Physical stability: Gel breakdown under ultrasonic energy.
Compounding precision required	Extremely high. Minor variations in ionic strength, pH, or drug salt form drastically alter delivery efficiency and safety.	Very high. Inconsistent viscosity, entrapped air, or poor enhancer selection nullify the ultrasound benefit and risk inconsistency.
Evidence-based guidance needed	Standards for: drug concentration limits, safe current density per formulation, pH ranges, and acceptable ionic excipient thresholds.	Standards for: effective enhancer types/concentrations, safe ultrasound parameters per formulation, and validated degassing procedures.
Primary clinical applications	Local inflammation, analgesia (e.g., dexamethasone and lidocaine), systemic delivery (e.g., fentanyl).	Musculoskeletal conditions (e.g., diclofenac for tendinitis), deep tissue analgesia, and anti-inflammatory therapy.

Therefore, ensuring the safety and efficacy of compounded preparations, including those for device-enhanced delivery, requires that the use of individual ingredients, their interactions, and their absorption profiles be guided by standardized, evidence-based thresholds (NASEM 2020). For iontophoresis, evidence must guide the choice of salt form, buffer capacity, and rheology. For phonophoresis, it must inform the selection of coupling enhancers and drug solubility parameters. Such a framework is essential to mitigate risk while preserving the vital capacity of pharmacists to customize therapeutic compounds for specific, unmet clinical needs (NASEM 2020). Mastering these formulations requires moving beyond general compounding principles to a deep understanding of interfacial science, electrochemistry, and acoustics. Closing the current knowledge gap is imperative to ensure that these powerful, device-enhanced delivery systems are both safe and effective, fulfilling their potential in personalized patient care.

Frequently prescribed formulations

In recent years, topical dosage forms containing NSAIDs, analgesics, corticosteroids, and muscle relaxants have emerged as a promising alternative to oral therapy for neuropathic pain (NeP) and musculoskeletal pain (Yang et al. 2019). This growing preference stems from their superior clinical utility, which is characterized by targeted delivery, enhanced safety (by reducing the systemic exposure of drugs such as pregabalin, gabapentin, amitriptyline, and tramadol), and sustained release, offering prolonged pain relief from fewer applications, which can improve patient adherence (Jorge et al. 2010).

The practical realization of this utility is fundamentally dependent on pharmacy compounding, since many are not commercially available. Compounding pharmacies play an indispensable role in translating this therapeutic concept into patient-specific solutions by:

Customizing formulations: Creating gels with specific drug combinations, strengths, and penetration enhancers tailored to individual patient needs and pain localization, thereby addressing adherence challenges associated with mismatched therapies (Jorge et al. 2010).

Enabling innovation: Developing stable and enhanced-efficacy gels, such as advanced systems like transdermal proniosomes for drugs such as tramadol to improve antinociceptive effects (Shah et al. 2019), for agents that often lack commercially manufactured topical versions.

Providing access: Offering a viable and personalized treatment pathway when standard commercial products are unavailable or unsuitable, making the theoretical benefits of topical management clinically accessible (Yang et al. 2019).

Therefore, while the pharmacologic rationale for topicals lies in their localized action and improved risk-benefit profile, it is through the specialized art and science of pharmacy compounding that these evidence-based benefits are effectively delivered, offering a tailored and targeted strategy in pain management. Of course, based on

the controversial effectiveness of the topical application of some of the drugs (Brutcher et al. 2019) presented in Table 5, these cannot be considered a first-line treatment but rather an alternative to a more traditional approach that has failed. Therefore, caution and a patient-specific approach are encouraged, since a sound rationale does not always guarantee clinical effectiveness.

Novel drugs for iontophoresis and phonophoresis

Looking forward, the therapeutic potential of topical pain management is being further expanded by the exploration of novel active pharmaceutical ingredients (APIs) and sophisticated delivery systems designed for use with physical enhancement methods such as iontophoresis and phonophoresis (Table 6). These techniques, which use electrical current or ultrasound to enhance transdermal drug penetration, can unlock the localized delivery of molecules that are otherwise challenging to administer. Recent research points to promising candidates for such enhanced systems. For instance, compounds such as N-acetyl-L-cysteine (NAC), studied for its tenogenic and reparative effects in tendon repair, represent a category of agents whose therapeutic application in musculoskeletal disorders could be optimized via phonophoresis (Lu et al. 2023). Simultaneously, the ongoing discovery of novel pharmacotherapies for neuropathic pain—including agents targeting specific voltage-gated sodium channels or other modulatory pathways—creates a pipeline of substances that may be ideal for iontophoretic delivery to achieve site-specific effects with minimal systemic burden (Bernatoniene et al. 2023; Kaye et al. 2025). Beyond these drugs, innovations also lie in the formulation vehicles themselves. Research into advanced bases, such as thermosensitive gels designed for use with microneedle arrays to control the release of drugs such as naltrexone, exemplifies the next generation of customizable delivery platforms (Tobin et al. 2021). As with conventional topicals, the clinical translation of these innovative pairings—novel drugs, smart vehicles, and advanced physical modalities—will heavily rely on the adaptive capabilities of pharmacy compounding. Compounding pharmacists are essential in formulating stable, biocompatible, and technically suitable gels with the precise drug concentration, pH, and rheological properties required for these devices, thereby bridging the gap between promising pre-clinical research and personalized, targeted patient care for complex pain conditions.

Building upon the pipeline of novel synthetic agents, naturally derived proteolytic enzymes—particularly bromelain, ficin, and papain—emerge as compelling candidates for advanced transdermal delivery, supported by a distinct therapeutic rationale and existing clinical precedent. The medicinal value of papaya-derived papain, long recognized in clinical practice for its enzymatic activity, provides a foundational rationale for its therapeutic exploration (Abdullaevich and Myradovich 2016). These enzymes, primarily recognized for their exfoliating and anti-inflammatory properties in functional skincare and cosmeuticals, offer a multi-targeted approach to pain management by promoting tissue debridement, reduc-

Table 5. Sample of some frequently prescribed compounded formulations.

Formulation and concentration	Proposed rationale	Primary clinical application	Key reference citations and notes	Additional contextual references and notes
Diclofenac 3% / baclofen 2% / lidocaine 5% / ketamine 10% / gabapentin 6% (compounded cream)	Multi-mechanistic: NSAID (diclofenac), GABA-B agonist (baclofen), local anesthetic (lidocaine), NMDA antagonist (ketamine), and neuropathic agent (gabapentin) for comprehensive pain relief.	Complex nociceptive and neuropathic pain conditions.	(Swarm et al. 2010): Recommend specific concentrations.	Brutcher et al. 2019 (RCT) : A high-quality trial found no significant benefit over placebo for customized compounded creams for localized chronic pain, directly challenging the efficacy of this approach.
			(Kopsky 2015): Supports ketamine 10% efficacy.	(Gewandter et al. 2014): concluded that ketamine/ amitriptyline cream does not reduce chemotherapy-induced peripheral neuropathy.
			(Bryson 2014): Discusses gabapentin 6% penetration dependent on base (e.g., PLO).	Dworkin et al. 2010 (guideline) : Provides foundational neuropathic pain management context; notes limited evidence for compounded topicals at that time.
Diclofenac sodium 3% / lidocaine 5% / gabapentin 6% gel (lipoderm or PLO base)	Combines NSAID (anti-inflammatory), local anesthetic (nerve block), and neuropathic agent for multi-mechanistic relief. The base is critical for enhancing skin permeation.	Chronic tendonitis or complex sprains with a neuropathic pain component (e.g., tennis elbow).	(Praxis Medical Insights 2025): Support use of these concentrations.	Brutcher et al. 2019 (RCT) : Applies caution to this triple-combination rationale for localized pain.
			(Scheinfeld 2014): Highlights the importance of vehicle (PLO) for gabapentin efficacy.	Scheinfeld 2014 (review) : Supports the general use of topical agents (like lidocaine, NSAIDs) for localized skin and soft tissue pain.
Ketamine 10% / amitriptyline 5% / lidocaine 5% (lipoderm cream)	Ketamine (NMDA antagonist) and amitriptyline (TCA) synergistically dampen peripheral and central sensitization. Lidocaine provides immediate local anesthesia.	Neuropathic pain; chronic pruritus (neuropathic and prurigo nodularis).	Lynch et al. 2005 (J Pain). Poterucha et al. 2013 (J Am Acad Dermatol). Lee et al. 2017 (J Am Acad Dermatol) Puşcaşu et al. 2023.	Dworkin et al. 2010 (guideline) : Recommends tricyclic antidepressants (e.g., amitriptyline) as first-line oral therapy for neuropathic pain, providing a benchmark for topical formulation goals.
Dexamethasone 0.4% / lidocaine HCl 4% solution for iontophoresis	Dexamethasone provides targeted anti-inflammatory; lidocaine provides immediate analgesia. Combined non-invasive delivery.	Localized inflammatory musculoskeletal conditions (e.g., plantar fasciitis and lateral epicondylitis).	Gökoglu et al. 2005; Nirschl et al. 2003; Gudeman et al. 1997; Osborne et al. 2006; Brown and Lauber (1992) guidelines. Allen 2010	Scheinfeld 2014 (review) : Discusses iontophoresis as a drug delivery method for localized pain, providing context for this administration route.
Ketoprofen 5% / capsaicin 0.075% gel for phonophoresis	Ketoprofen (NSAID) reduces inflammation. Capsaicin modulates neurogenic pain. Ultrasound enhances percutaneous absorption.	Chronic musculoskeletal pain with inflammatory and neurogenic components.	Cagnie et al. 2003 (Phys Ther).	Dworkin et al. 2010 (guideline) : Recommends topical capsaicin (typically 0.075%) as a second- or third-line option for neuropathic pain, supporting its role in mixtures.
			Cabak et al. 2005.	
			Okan and Çağlıyan Türk 2020.	
Dexamethasone 1% / Lidocaine HCl 4% ultrasound gel	Lidocaine provides rapid-onset block. Perineural dexamethasone prolongs analgesia via anti-inflammatory effects.	Adjuvant for ultrasound-guided peripheral nerve blocks.	Aliste et al. 2017.	
			Choi et al. 2014	
			De Oliveira et al. 2014. Allen 2010	
Ketamine 4% / ketoprofen 10% / cyclobenzaprine 0.5% (PLO)	Targets multiple pain pathways: central sensitization, inflammation, and muscle spasm. PLO base enhances penetration.	Neuropathic pain syndromes (e.g., CRPS and post-herpetic neuralgia).	National Academies of Sciences, Engineering, and Medicine 2020.	Brutcher et al. 2019 (RCT) : Raises significant efficacy concerns for this class of multi-ingredient compounded creams for chronic pain.
				Dworkin et al. 2010 (guideline) : Establishes the standard pharmacological framework for neuropathic pain that topical combinations aim to address.

ing pro-inflammatory cytokines, and modulating edema, which is especially relevant for pain associated with inflammation and nerve compression (Venetikidou et al. 2025; Agrawal et al. 2022). Crucially, the feasibility of delivering such proteins via physical enhancement methods is not speculative. A papain-based preparation (Karipazim®) has been successfully administered via electrophoresis (iontophoresis) in clinical settings for the treatment of spinal osteochondrosis and related pain syndromes,

demonstrating a direct application of this concept (Moscow Polyclinic 2014). For compounding pharmacists, the key challenge of stabilizing these proteinaceous actives in a topical vehicle can be addressed through established techniques, such as the use of propylene glycol as a stabilizing agent, which has been shown to preserve papain activity in aqueous formulations (Bhattacharya and Bhattacharyya 2000). Therefore, proteolytic enzymes represent a viable and innovative category for inclusion in the “Oth-

Table 6. Experimental active ingredients for advanced topical pain management.

Molecule/formulation	Class/primary mechanism	Proposed delivery method	Primary indication	Key rationale/innovation
Ambroxol	Nav1.8 sodium channel blocker; TRPV1 receptor modulator.	Iontophoresis/topical	Neuropathic pain (NeP)	Targets peripheral sensitization via selective channel blockade, minimizing CNS side effects. Ideal for localized delivery. (Bernatoniene et al. 2023)
Bromelain	Proteolytic enzyme; anti-inflammatory, reduces cytokines (IL-1 β , TNF- α , iNOS).	Topical gel/phonophoresis	Neuropathic and musculoskeletal pain (e.g., CIPN)	Multi-target anti-inflammatory and tissue-healing action. Proven in animal models; used in oral supplements for CIPN. (Bernatoniene et al. 2023; Agrawal et al. 2022)
Cannabidiol (CBD)	Cannabinoid receptor modulator (CB1/CB2); TRPV1 agonist; antioxidant.	Iontophoresis/topical	Neuropathic pain	Multi-mechanism action reduces neuronal hyperexcitability and neuroinflammation. (Bernatoniene et al. 2023)
Ficin	Proteolytic enzyme (from fig tree latex); anti-inflammatory.	Topical gel/phonophoresis	Musculoskeletal pain and inflammation	Shares therapeutic rationale with bromelain/papain: exfoliating, anti-inflammatory, promotes tissue repair. Potential for cosmetic-dermatological crossover. (Venetikidou et al. 2025)
Melatonin	Endogenous hormone; MT1/MT2, opioid, adrenergic receptor modulator; potent antioxidant.	Topical/transdermal (systemic)	Neuropathic pain	Modulates pain signaling, central sensitization, and sleep quality. Enhances conventional analgesic efficacy. (Bernatoniene et al. 2023)
N-Acetyl-L-cysteine (NAC)	Antioxidant precursor; NMDA receptor modulator.	Phonophoresis/topical	Tendon repair and neuropathic pain	Mitigates oxidative stress in neuropathic pain. Promotes tenogenic differentiation, ideal for targeted deep tissue delivery. (Bernatoniene et al. 2023; Lu et al. 2023)
Naltrexone (thermosensitive gel)	Opioid antagonist (low-dose).	Microneedle-assisted transdermal	Neuropathic pain (potential)	Novel delivery platform (thermosensitive gel + microneedles) enables controlled release for complex pharmacology. (Tobin et al. 2021)
Papain	Proteolytic enzyme; debriding, anti-inflammatory.	Iontophoresis /topical gel	Musculoskeletal pain (e.g., spinal osteochondrosis)	(Abdullaevich and Myradovich 2016; Bhattacharya and Bhattacharyya 2000)
Proniosomal tramadol gel	Opioid agonist and SNRI in a proniosomal carrier.	Enhanced transdermal (proniosomes)	Neuropathic and musculoskeletal pain	Carrier system (proniosomes) provides stability and sustained release, improving topical efficacy. (Shah et al. 2019)

er Experimental Therapies” pipeline, where compounding is essential to formulate stable, iontophoresis- or phonophoresis-compatible gels that leverage their unique mechanisms for personalized pain management.

Conclusion

In summary, the integration of compounding pharmacy within sports medicine and physical therapy represents a critical advancement toward personalized, patient-centric care. By addressing the limitations of commercially available medications, compounding enables the precise tailoring of therapeutic formulations—ranging from topical analgesics to specialized preparations for iontophoresis and phonophoresis—that align with individual injury profiles, metabolic considerations, and performance requirements. This customization not only enhances localized drug delivery and minimizes systemic side effects but also supports rehabilitation adherence and functional recovery. The effective application of this practice, how-

ever, is fundamentally supported and shaped by its regulatory foundation. While the regulatory landscapes in the United States and the European Union share the common goal of safeguarding public health while enabling personalized therapy, their philosophical and structural approaches differ markedly. The U.S. model creates a distinct pathway for large-scale, non-patient-specific compounding through outsourcing facilities, acknowledging the industrial dimension of certain activities. Conversely, European models, as exemplified by Italy, Germany, and Spain, firmly root compounding within the professional and legal remit of the licensed pharmacy, emphasizing adherence to centralized formularies, detailed national preparation standards, and mandatory quality systems. This reflects a more integrated view of compounding as an intrinsic pharmaceutical service. Ultimately, the choice between these regulatory models represents a fundamental policy decision on delineating the boundary between a personalized healthcare service and drug manufacturing. As sports medicine continues to prioritize precision and efficacy, the role of compounding pharmacy remains in-

dispensable, and its sustainable integration relies on regulatory frameworks that ensure both quality and safety and the flexibility necessary to innovate and meet the unique needs of athletes and active individuals.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.

No AI tools were used in the preparation of this manuscript.

Funding

This study is financed by the European Union–NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project BG-RRP-2.0040009-C02.

Author contributions

Ivaylo Pehlivanov contributed to conceptualization, methodology, writing the original draft, and data curation. Velichka Andonova, Evgenia Vladeva, Detelina Nedyalkova-Petkova, Liliya Panayotova-Ovcharova, and Petar Petkov contributed to conceptualization, methodology, peer review, editing, and supervision.

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Data availability

All of the data that support the findings of this study are available in the main text.

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