

**NOVEL FORMULATIONS OF AMITRIPTYLINE: CONTROLLED-RELEASE,
TOPICAL, AND NANO-BASED DELIVERY SYSTEMS****Dr. B. Brahmam^{*1}, J. N. Suresh Kumar², S. K. Salma Ahmed³, V. Anil Kumar⁴, M. Madhu Latha⁵, S. K. Saleem⁶, Y. Akhila⁷**

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ABSTRACT

Amitriptyline is a tricyclic antidepressant commonly used to treat depression and, at lower doses, certain chronic pain conditions, including neuropathic pain. However, conventional oral tablets may cause side effects such as sedation and anticholinergic effects, and they are also associated with variable drug exposure and adherence difficulties. To overcome these limitations, researchers have explored controlled-release oral formulations, topical creams and gels, skin-permeation-enhancing systems, and nanoparticle-based formulations. An osmotic controlled-release oral system (OROS) has demonstrated a slower peak concentration with broadly comparable bioavailability to an immediate-release formulation.^[8,9] However, topical amitriptyline, alone or combined with ketamine, has shown inconsistent clinical benefits.^[3–7] Nano-amitriptyline hydrochloride has demonstrated improved in-vitro dissolution.^[11] Further studies are required to establish the stability, pharmacokinetics, safety and clinical efficacy of these novel formulations before they can be considered reliable therapeutic alternatives.

KEYWORDS: Amitriptyline hydrochloride, controlled-release formulations, nanoparticle-based formulations, neuropathic pain.**1. INTRODUCTION****1.1 Background**

Amitriptyline hydrochloride is a tricyclic antidepressant. It mainly inhibits serotonin and noradrenaline reuptake, and it also interacts with other receptors.^[15] Besides depression, it is used for selected conditions such as neuropathic pain and migraine prevention, depending on clinical guidance and individual assessment.^[1,2] Conventional oral tablets are affordable, easy to manufacture and widely used. However, they may cause adverse effects such as dry mouth, constipation, blurred vision, dizziness and sedation. The risk varies with dosage, patient characteristics and drug interactions. Overdose can cause serious toxicity, making safe prescribing and storage essential.^[1,2,3]

1.2 Why investigate novel formulations?

Novel formulations aim to improve drug release, absorption, distribution and patient convenience, reduce dosing frequency, target painful skin areas, improve local

drug delivery, or enhance drug dissolution.^[3,12,16] However, improved drug release in laboratory tests does not necessarily indicate a better clinical outcome or reduced toxicity. Topical formulations require careful, full evaluation because drug release from a cream does not guarantee sufficient penetration into the required skin layers.^[12,17] Increased skin permeation may also raise systemic drug exposure. Therefore, drug release, skin permeation, pharmacokinetics and clinical effectiveness must be assessed separately.^[4,5,6]

1.3 Aim and scope

Novel formulations modify the delivery of amitriptyline without changing its active pharmaceutical ingredient. Their benefits in drug delivery, convenience and exposure must be demonstrated through comparison with an appropriate reference formulation. This review examines conventional and investigational amitriptyline formulations, including oral controlled-release systems, topical creams and gels, dermal delivery vehicles, and

nano-sized drug particles. It discusses their formulation principles, available evidence, limitations and future research directions. General transdermal delivery studies help explain drug penetration and testing methods but do not directly establish the clinical effectiveness of specific amitriptyline products. Investigational approaches are distinguished from approved products, and self-compounding or unsupervised use is not recommended.^[7,8]

2. Pharmacological and Pharmaceutical Profile

2.1 Mechanism and therapeutic context

Amitriptyline inhibits serotonin and noradrenaline reuptake and also interacts with various receptors and ion channels, contributing to both its therapeutic and adverse effects.^[15] Oral amitriptyline is used for depression and selected neuropathic pain conditions, but its adverse effects may limit its use.^[1,2] Topical delivery has been investigated to target peripheral tissues while minimizing systemic exposure; however, this benefit requires further evidence. Amitriptyline hydrochloride is an ionisable salt whose solubility and partitioning influence drug delivery.^[14] In topical formulations, drug release from the vehicle and penetration through the skin are separate processes affected by pH, solvents, concentration, viscosity and excipients.^[12,19,20] Amitriptyline can be formulated as conventional tablets, controlled-release systems, creams, gels and engineered particles. Each dosage form requires appropriate quality testing, including dose uniformity, dissolution, stability, drug release, microbial quality where applicable, and particle size characterization for nanoparticle formulations.^[9,10]

2.2 Matching formulation goals with clinical needs

Oral controlled-release formulations aim to maintain suitable drug exposure while potentially reducing peak concentration and dosing frequency. Important pharmacokinetic parameters include C_{max} , T_{max} , AUC, half-life and variability. A slower peak alone does not guarantee improved tolerability or effectiveness. Topical formulations may be designed to retain the drug in specific skin layers rich in dermal nerve endings, rather than delivering it into the systemic circulation. Skin retention, permeation and systemic bioavailability must be evaluated separately. Improved dissolution of nanoparticles does not automatically establish better absorption or safety. Therefore, formulation development should begin with a clearly defined clinical objective.^[11]

3. Oral Formulations

3.1 Immediate-release tablets

Immediate-release tablets are an established, economical and widely used formulation of amitriptyline hydrochloride. They contain the active drug and suitable excipients to support manufacturing, disintegration, dissolution and stability. Their advantages include manufacturing simplicity and extensive clinical experience. However, systemic adverse effects and fluctuations in drug concentration may limit their use. The formulation does not eliminate the drug's inherent

risks, and tablets should be modified only according to the product instructions and professional advice. Liquid formulations may help patients who have difficulty swallowing tablets or require flexible dose adjustment; however, availability varies by market, and compounded liquids require evidence of uniformity, compatibility, stability, and suitable packaging and storage conditions. Preparation should be performed by qualified professionals using established formulas and controls. Patients should not prepare liquids from crushed tablets without professional guidance because dosing errors and stability problems may occur. Tablets should not be crushed or split unless the specific product instructions and a healthcare professional confirm that it is appropriate. Altering modified-release products may disrupt drug release. For liquid formulations, calibrated oral syringes provide more accurate measurement than household spoons. Conventional tablets provide a benchmark for cost, stability, reproducibility and patient convenience. Any novel formulation should demonstrate a meaningful clinical or practical advantage to justify its additional complexity.^[12]

3.2 Rationale for modified release

Modified-release formulations are designed to control the rate or timing of drug release. They may reduce peak plasma concentration, maintain drug exposure and simplify dosing. However, their clinical benefits depend on the formulation design and the drug's pharmacological properties.^[8,9] Other controlled-release approaches, such as pellets, have also been assessed in vitro and in vivo.^[13]

3.3 OROS amitriptyline

An osmotic controlled-release oral system (OROS) formulation has been developed for amitriptyline hydrochloride.^[8,9] A randomized, open-label, three-way crossover study compared the peak serum concentration (C_{max}) of a single 75 mg OROS dose with that of an immediate-release (IR) dose given in three divided doses and an IR dose given before bedtime. Relative bioavailability was compared with both the divided and the bedtime dosing. Anticholinergic effects, salivary secretion, visual acuity and subjective sedation were assessed. The results supported once-daily dosing, but the small size of the study does not support regulatory approval, changes in clinical practice, or superiority of the formulation.^[14]

3.4 Potential benefits and limitations

The OROS system releases the drug through the principles of osmosis and a membrane. Simplified once-daily dosing and lower peak drug levels are advantages of this system. However, these advantages may be offset by release variability, and batch-to-batch consistency needs to be ensured. Evaluation of food and drug interactions is also required. Release modification may improve tolerability, compliance and therapeutic outcome, but modified drug release and receptor activity do not always correlate.^[15]

4. Topical and Dermal Delivery

4.1 Drug release versus skin permeation

The vehicle must release the drug before skin permeation can occur, but the two processes must be assessed separately.^[12,22,23] A high drug release rate demonstrated in the laboratory does not indicate that the drug will be delivered to the site of action.^[16]

4.2 Comparison of compounding bases

Shakshuki and colleagues compared 1%, 5% and 10% amitriptyline hydrochloride formulations prepared in Lipoderm, an emollient cream and Mediflo 30 Pluronic lecithin organogel (PLO). After 24 hours, the 10% formulations showed drug release of 23.9%, 41.8% and 53.2%, respectively. Although the drug was released, the PLO base showed much lower cumulative permeation than the other bases. These findings show that drug release from a formulation does not mean the drug will pass through the skin, and both processes must be considered when choosing a vehicle.^[17]

4.3 Solvent and penetration-enhancer systems

Solvents and penetration enhancers can help improve drug solubility and movement into the skin. Their effects depend on the amount used and on the whole formulation. Alcohol, propylene glycol and lipid-compatible excipients have been studied for this purpose. Kung and colleagues examined amitriptyline delivery using solvent systems and penetration-enhancing vehicles; some isopropyl myristate-isopropanol combinations and propylene glycol systems improved permeation under the conditions tested. This laboratory result supports work on formulation improvement but does not prove that it works in clinical use. Penetration enhancers must also be checked for irritation, sensitization, stability, crystallization and possible systemic exposure.^[18]

5. Nanoparticle and Particle-Engineering Approaches

5.1 Rationale for particle engineering

Particle engineering can change surface area, crystallinity, wettability and dissolution rate. Smaller particles may dissolve faster because they have a greater surface area per unit mass. However, better dissolution does not always mean better absorption, effectiveness or safety.^[19]

5.2 Spray-freeze-dried nano-amitriptyline hydrochloride

Hu Y and colleagues prepared nano-amitriptyline hydrochloride using spray freeze-drying. The particles were reported to be amorphous, with a size of about 90 nanometres, and they showed better in-vitro dissolution than the regular material.^[11] Although this looks promising, these findings are only formulation improvements, not proven clinical benefits. More research should examine particle characteristics, solid-state stability, moisture, dissolution, purity and batch

consistency. Bioavailability and safety must also be checked before any real benefit can be confirmed.^[20,21]

5.3 Nanocarriers: research opportunities

Liposomes, polymeric nanoparticles, lipid nanoparticles, nanoemulsions and other nanocarriers are being investigated for drug delivery. These systems may affect drug solubility, release, stability and interaction with the body. However, their general potential does not mean that a specific amitriptyline formulation is effective. Development challenges include scale-up, stability, compatibility of ingredients, drug leakage, residual solvents, cost and batch consistency. For nanocarriers, studies must examine how the drug spreads in the skin, how it is released, whether it causes irritation and how much reaches the body. Claims about targeted delivery or reduced toxicity need experimental proof.^[22,23]

6. Stability Studies

Stability should be assessed on the formulation in its final packaging under appropriate temperature and humidity conditions.^[26] Important changes include chemical degradation, physical separation, changes in colour or odour, changes in viscosity, loss of solvent, drug crystallization, and recrystallization caused by moisture. The shelf life must be supported by data from the product packaging.^[26] The quality-by-design (QBD) approach starts by setting the quality target product profile and identifying critical material attributes and process conditions. These are then checked to make sure the product performs consistently.^[27] For topical formulations, the order of mixing, the amount of shear, temperature and polymer hydration affect uniformity and viscosity. Spray-freeze-drying conditions affect particle size and solid state.^[11] Regulatory requirements depend on the country, the route of administration and the intended use. New formulations need quality, safety, pharmacokinetic and clinical evidence. Compounded preparations should not be treated the same as approved products.^[24]

7. SUMMARY OF KEY STUDIES

Table 1: Key studies on novel amitriptyline formulations, their findings and limitations.

Study / source	Formulation and design	Main findings	Interpretation and limitations
Gupta et al., OROS studies ^[8,9]	OROS amitriptyline hydrochloride; randomized, open-label, three-way crossover comparing a single 75 mg OROS dose with divided and bedtime IR doses	Supported once-daily dosing; slower peak concentration with broadly comparable bioavailability; anticholinergic effects, salivary secretion, visual acuity and sedation assessed	Small study; does not support regulatory approval, change in clinical practice or superiority
Controlled-release pellets ^[10]	Controlled-release amitriptyline pellets; in vitro and in vivo assessment	Reported as a new controlled-release approach	Limited evidence presented; clinical benefit not established
Shakshuki et al. ^[13]	1%, 5% and 10% amitriptyline hydrochloride in Lipoderm, emollient cream and Mediflo 30 PLO; in-vitro release and permeation	10% formulations released 23.9%, 41.8% and 53.2% at 24 h; PLO showed much lower cumulative permeation	Drug release does not mean skin permeation; both must be assessed when choosing a vehicle
Kung et al. ^[12]	Amitriptyline in solvent systems and penetration-enhancing vehicles; laboratory permeation testing	Some isopropyl myristate–isopropanol and propylene glycol systems improved permeation	Laboratory result only; irritation, sensitization, stability and systemic exposure must be checked
Hu et al. ^[11]	Nano-amitriptyline hydrochloride prepared by spray freeze-drying	Amorphous particles of about 90 nm with better in-vitro dissolution than the regular material	Formulation improvement only; absorption, stability, safety and efficacy not shown
Topical amitriptyline clinical studies ^[3–7]	Topical amitriptyline, alone or combined with ketamine, in neuropathic pain	Clinical benefit inconsistent across studies	Small trials with mixed or unfavourable results; larger, well-designed trials needed

8. DISCUSSION AND OVERALL VIEW

Amitriptyline formulation research has several distinct goals. OROS technology controls how the drug is released in the body; topical formulations target specific skin areas; vehicle optimization improves drug release and movement through the skin; and spray-freeze-dried nanoparticles aim for faster dissolution. These approaches should therefore be judged against what they are designed to achieve. The strength of the evidence is not the same across approaches. Controlled-release oral formulations have data from human studies, whereas many topical studies use membranes or animal skin. Clinical trials of topical amitriptyline are small and have not given consistent results. Although nano-amitriptyline improves dissolution, it has not been shown to be better in terms of absorption or effectiveness.^[25]

Future research should clearly describe the formulation composition, how it was made, the testing methods, controls, sample size, variability and statistical analysis. Negative or inconclusive results should also be published to avoid repeating failed approaches. For pain studies, outcomes should include patient-reported pain, physical

function, sleep and medication use, rather than drug release in the laboratory alone.

Overall, no single formulation is best for everyone, because effectiveness depends on the route of delivery, the ingredients and how the product is made. Greater drug release from a product does not mean it works better on the skin, and faster nanoparticle dissolution does not mean better patient outcomes. Conclusions must be drawn only from the formulation that was tested. Studies of topical amitriptyline show the importance of going beyond laboratory results: controlled trials have given mixed or unfavourable results despite a plausible rationale.^[3–7] Better delivery systems need clinical testing for pain relief, systemic drug exposure and safety before their benefits can be established.^[26,27]

9. CONCLUSION

Conventional amitriptyline tablets remain affordable, well established and widely used, but their adverse effects, peak–trough fluctuations and dosing limitations have encouraged research into controlled-release, topical and nano-based formulations. Among these, the OROS

system has the strongest supporting data, showing once-daily dosing with a slower peak concentration and broadly comparable bioavailability, although the available study is small. Topical formulations and penetration-enhancer systems show promising laboratory results, but drug release does not guarantee skin permeation, and clinical benefit has been inconsistent. Nano-amitriptyline hydrochloride improves dissolution in vitro, but its absorption, stability, safety and efficacy remain unproven.

No single formulation is best for every patient, and each approach should be judged against its intended clinical goal. Future work should include well-designed comparative studies with clear reporting of formulation composition, methods and outcomes, and should measure pain relief, systemic exposure and safety rather than laboratory release alone. Until such evidence is available, these novel formulations should be regarded as investigational rather than established therapeutic alternatives, and self-compounding or unsupervised use is not recommended.

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