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Review article

Matrix tablets for extended-release orphenadrine citrate: a review on formulation approaches, polymer selection and RP-HPLC method development for quality control

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ABSTRACT

Orphenadrine citrate is a centrally acting skeletal muscle relaxant with anticholinergic properties and is frequently prescribed for painful musculoskeletal conditions. However, its conventional immediate-release formulation demands multiple dosing in a day due to short duration of action, which leads to poor patient compliance, plasma fluctuations, and side effects. This comprehensive review article explains the current knowledge on the formulation and optimisation of extended-release (ER) matrix tablets of Orphenadrine citrate with special emphasis on hydrophilic polymer systems, especially Hydroxypropyl Methylcellulose (HPMC). The review critically discusses formulation strategies, pre-compression and post-compression characterisation parameters and kinetics of drug release. Further, it offers a detailed study on analytical method development and validation by Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) for assay determination and blend uniformity testing. The incorporation of Quality by Design (QbD) concepts, such as Design of Experiments (DoE) for systematic optimisation, is discussed. While much progress has been made, several research gaps remain, including limited systematic optimisation studies, incomplete mechanistic release modelling and a lack of bio-relevant dissolution methods. This review provides a roadmap for the development of robust, commercially viable ER formulations of Orphenadrine citrate and thereby contributing to better patient outcomes and progress in sustained drug delivery.

Keywords: Orphenadrine citrate, Extended release, Hydrophilic matrix, Muscle relaxant, Quality by Design.

INTRODUCTION

Musculoskeletal disorders are a major global health burden, affecting an estimated 1.71 billion people worldwide and being the leading cause of disability (WHO, 2021). The treatment of painful musculoskeletal conditions such as acute muscle spasm, low back pain, cervical spondylosis and soft-tissue injuries often requires prolonged pharmacotherapy. Orphenadrine citrate, a centrally acting skeletal muscle relaxant chemically related to diphenhydramine, has been a cornerstone in the management of these conditions since its discovery in the 1940s [1, 2].

Orphenadrine citrate achieves its therapeutic effects through a multi-target action, mainly within the central nervous system. Its main mechanism of action is central anticholinergic modulation, by antagonising muscarinic acetylcholine receptors in the brainstem and spinal cord, thus suppressing abnormal polysynaptic reflex arcs and decreasing excessive firing of muscle spindles [3,4]. It also shows moderate NMDA receptor antagonism, which may reduce central sensitisation and provide analgesic effects, and mild local anaesthetic properties at higher concentrations [5].

However, the conventional immediate-release (IR) formulation of Orphenadrine citrate (usually 100 mg every 6 hours) has several therapeutic limitations despite its clinical efficacy. The plasma elimination half-life of the drug is 14-16 hours, but its active metabolite (N-desmethylorphenadrine) contributes to the pharmacological activity, resulting in a total duration of action of

only 4-6 hours after IR administration [6]. This requires three to four daily doses, which results in:

Poor patient compliance

Studies have shown that compliance drops by 15-20% for each extra daily dose. Patient compliance increases 30-40% with a change of frequency from three to once daily [7,8].

Fluctuating plasma concentrations

The "peak and valley" pattern of IR dosing leads to concentrations above the therapeutic window (risk of toxicity) and then below the minimum effective concentration (loss of therapeutic effect) [9].

Increased side effects

Dose-related side effects such as dry mouth, dizziness, drowsiness, constipation, urinary retention and blurred vision are associated with peak concentrations. Particular concerns are confusion and cognitive impairment in the elderly [10,11].

Inadequate night-time coverage

Musculoskeletal pain is worse at night due to prolonged immobility and reduced circulation. Patients with nocturnal muscle spasms suffer from disturbed sleep and require sustained overnight drug release [12].

Rationale for extended-release formulation

Extended-release (ER) medication delivery systems are designed to provide a controlled release of the active pharmaceutical ingredient over an extended period of time, typically 12 to 24 hours, thus maintaining therapeutic drug levels within a narrow range and minimising fluctuations in plasma concentration [13,14].

The development of an Orphenadrine citrate ER formulation has several attractive benefits:

Easier dosing schedule

Once-a-day dosing regimen simplifies the patient's medication routine, thus improving adherence and therapeutic results. Gradual concentration-time profile: ER dosing provides a gradual and prolonged plateau of drug concentration in the therapeutic range rather than peaks and valleys.

Fewer side effects

Peak concentrations are often below the threshold where side effects related to the concentration become problematic.

Improved quality of life

Patients can go about their day without having to constantly remind themselves to take their medication, thereby reducing the psychological burden of chronic illness [15].

Increased overnight coverage

ER formulations taken at bedtime provide 8 hours of therapeutic muscle relaxation during the night, allowing the body to rest and recover [16].

Current status and unmet need

A thorough review of pharmaceutical databases (Drugs @ FDA, EMA, CDSCO India) shows that no extended-release oral formulation of Orphenadrine citrate has been approved by regulators in any major market as of 2026. This represents a major unmet therapeutic need, especially for:

Elderly patients who form a considerable proportion of the musculoskeletal patient population and are especially susceptible to compliance problems due to polypharmacy and cognitive decline.

Patients with chronic musculoskeletal conditions (e.g., fibromyalgia, chronic low back pain, cervical spondylosis) who require continuous muscle relaxation throughout the day.

Patients with nocturnal muscle spasms (common in Parkinson's disease and multiple sclerosis) experiencing sleep disruption [17].

The present review aims to summarise the current knowledge in the formulation and optimisation of ER Orphenadrine citrate tablets with a comprehensive analysis of matrix systems, manufacturing approaches, characterisation parameters, and analytical method development. The integration of formulation science and analytical chemistry is considered essential for successful product development.

Physicochemical and biopharmaceutical properties of Orphenadrine Citrate.

Molecular characteristics

Orphenadrine citrate is the citrate salt of N, N-dimethyl-2-[(2-methylphenyl) phenylmethoxy] ethanamine with a molecular formula of C 18 H 23 NO · C 6 H 8 O 7 and a molecular weight of 461.5 g/mol [18]. The drug is a white to off-white crystalline powder with characteristic odour and bitter taste. The citrate salt improves the aqueous solubility relative to the base form. This is beneficial for tablet manufacture and dissolution.

Table 1: Physicochemical properties of Orphenadrine Citrate

Property	Value
Molecular Formula	$C_{18}H_{23}NO \cdot C_6H_8O_7$
Molecular Weight	461.5 g/mol
Physical Appearance	White to off-white crystalline powder
Melting Point	135-145°C
Solubility	Freely soluble in water and alcohol
pKa	~9.0
Log P	~3.0 (moderately lipophilic)
Half-life	14-16 hours

Dependence on pH and solubility

Orphenadrine citrate is a weak base drug with moderate lipophilicity (log P ~ 3.0). Its solubility is pH-dependent and this has significant consequences for the formulation of extended-release dosage forms. The drug is a weak base, so its solubility decreases as the pH increases along the gastrointestinal tract. This characteristic can lead to incomplete release in the distal small intestine and colon, and hence the need to use suitable polymer systems that can provide constant release independent of changes in environmental pH [19].

Pharmacokinetics considerations

Orphenadrine citrate is rapidly and completely absorbed from the gastrointestinal tract following oral administration. The drug undergoes extensive first-pass metabolism, mainly by N-

demethylation and aromatic hydroxylation, mediated by cytochrome P450 enzymes (in particular CYP2D6 and CYP3A4). The active metabolite N-desmethylorphenadrine contributes to the overall pharmacologic activity [20].

The volume of distribution is about 4 to 5 L/kg, and the drug distributes widely in the tissues. Plasma protein binding: Approximately 95% (mainly to alpha-1-acid glycoprotein and albumin). The elimination half-life is 14-16 hours, but the pharmacodynamic duration of action following IR administration is only 4-6 hours, probably due to rapid redistribution and the requirement to maintain threshold concentrations for therapeutic effect [6,21].

Principles and design of extended-release matrix systems:

ER system classification

Extended-release systems for drug delivery can be classified according to their release mechanism and physical design:

Matrix systems

Hydrophilic matrices (e.g. HPMC, PEO, xanthan gum)

Hydrophobic/lipophilic matrices (e.g. glyceryl behenate, ethyl cellulose)

Non-reactive matrices (e.g. polymethylmethacrylate)

Reservoir system

Tablets or pellets coated

Microencapsulation

Osmotic systems

Simple osmotic pump.

Osmotic pump push and pull

Ion-exchange resins

Among these, hydrophilic matrix systems are the most widely used due to its simplicity, cost-effectiveness, and proven reliability [22,23]. Such systems are based on polymers that absorb water, swell or erode to control the release of drugs for extended periods of time.

Hydrophilic matrix systems (HM)

Drug release mechanism

Hydrophilic matrix systems, especially those based on HPMC, control the drug release by combining three mechanisms:

Diffusion: The drug molecules dissolved in the gel layer diffuse through the hydrated polymer network.

Swelling: The polymer hydrates and swells in contact with aqueous media, forming a gel barrier that controls drug release.

Erosion: The hydrated polymer erodes slowly from the tablet surface with the release of drug together with polymer chains.

Mathematical models could be used to characterise the release mechanism, and the Korsmeyer-Peppas model is useful to determine whether Fickian diffusion, polymer relaxation or erosion controls the release [24].

Polymers selected: HPMC and others

The most commonly used hydrophilic polymer for ER formulations is Hydroxypropyl Methylcellulose (HPMC) due to its:

Good safety profile.

GRAS status for broad regulatory acceptance.

Release kinetics are predictable.

Broad spectrum of viscosity grades.

Compatible with many drugs.

Cost-effective and available.

HPMC is available in different viscosity grades (e.g. HPMC K4M, HPMC K15M, HPMC K100M) where the numerical designation indicates the viscosity of a 2% aqueous solution in centipoise (cP) [25]. The higher viscosity grade generally gives a more sustained drug release, but the relationship is complex and depends on the drug solubility, tablet geometry, and other formulation variables.

Other hydrophilic polymers studied for ER formulations include:

Polyethene oxide (PEO): High molecular weight grades can give very prolonged release.

Xanthan gum: a natural polysaccharide that has good release-retarding properties.

Sodium alginate: Forms a firm gel with calcium ions.

Carbopol (Carbomer): Provides pH-dependent release properties.

Manufacturing Approaches

There are two main methods of manufacturing extended-release tablets:

Direct compression

Direct compression has the advantages of simplicity, less processing time, less energy requirement and fewer manufacturing steps. However, it may be limited by poor flow properties or concerns about content uniformity, especially for high-dose drugs or drugs with poor compaction properties [26].

Wet granulation

Wet granulation is more complex but offers several advantages for ER formulations:

Better content uniformity.

Better flow characteristics.

Enhanced compaction characteristics.

Reduced environmental and dust exposure.

Greater control of drug distribution.

In a comparative study by Sousa et al. (2023), it was found that wet granulation had better content uniformity and tablet hardness, but both methods can be used to produce acceptable Orphenadrine citrate ER formulations [27].

Quality by design (QbD) concept

The Quality by Design (QbD) paradigm described in ICH Q8 (R2) encourages a systematic development of the product in terms

of sound science and quality risk management. Key features of the QbD approach are:

Quality target product profile (QTPP): Defining the product properties desired.

Critical quality attributes (CQA): The attributes that affect the quality of the product.

Critical material attributes (CMAs): Effect of material properties on CQAs.

Critical process parameters (CPPs): Identification of the process parameters that should be controlled.

Design of experiments (DoE): Statistical design of experiments for systematic optimisation.

Design space: Identification of the multidimensional combination of variables that ensures quality.

Table 2: Critical quality attributes for extended-release tablets

CQA	Measurement	Typical Target
Drug release at 1 hour	Dissolution testing	≤ 30%
Drug release at 4 hours	Dissolution testing	40-60%
Drug release at 8 hours	Dissolution testing	70-85%
Drug release at 12 hours	Dissolution testing	≥ 85%
Content uniformity	Blend/tablet assay	RSD ≤ 6%
Hardness	Tablet testing	6-12 kP
Friability	Roche friabilator	≤ 1%

Use of design of experiments (DoE)

A 3 2 full factorial design is a commonly used approach for optimisation of ER formulations, which investigates the effects of two independent variables at three levels each. The typical independent variables for Orphenadrine citrate ER tablets are:

HPMC K4M concentration

HPMC K15M concentration

Drug: polymer ratio

Filler/Binder Ratio

The usual dependent variables (responses) are:

Drug release at different time intervals (1, 4, 8, 12 hours)

Hardness of tablets

Crumbly

Uniformity of drug content

Then, response surface methodology (RSM) is used to find the optimum formulation that meets all target criteria [29].

Formulation optimization parameters

Pre-compression evaluation

Powders flow characteristics

The flow properties of the powder blend will have a direct effect on uniformity of tablet weight and content. Some of the key parameters are:

Angle of repose: Measured by the fixed funnel method. Interpretation:

Excellent: 25-30°

Good: 31 to 35

Fair: 36–40 °

Poor: >40 degrees

Carr's Index of Compressibility = [(Tapped Bulk Density – Bulk Density) / Tapped Bulk Density] × 100

5-15% Very Good

Good: 16% - 20%

Fair: 21-25%

Poor: >25%

Hausner's ratio = Tapped density / Bulk density

Excellent: 1.00 - 1.18

Good: 1.19 to 1.25

Fair: 1.26-1.34

Bad: >1.35

These parameters are generally improved for wet granulated formulations than for pure drug powder.

Drug and excipient compatibility

Compatibility studies by Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) are mandatory to confirm that there is no interaction of drug with excipients. Physical mixtures are stored under accelerated conditions (40°C ± 2°C / 75% RH ± 5%) for four weeks, and spectra are compared for identification:

New peaks develop

Loss of characteristic peaks

Significant shifts in peak positions

Post-compression evaluation

Physical characteristics

Variation of weight

USP states that for tablets of average weight 300 mg, not more than two tablets should vary by more than $\pm$7.5% from the average weight, and no tablet should vary by more than $\pm$15%.

Hardness

The hardness of ER tablets is generally in the range of 6-10 kP. Hardness affects the tablet integrity during handling and drug release kinetics.

Friability

The Roche friabilator test should not result in a weight loss of more than 1% of the tablet weight after 100 revolutions.

Thickness and diameter

Measured using a digital vernier calliper, reproducibility is important to ensure consistency in tablet volume and surface area.

Uniformity of blend and drug content

Blend uniformity

Ten different places of the blend need to be sampled to check for the uniformity of drug distribution. The relative standard deviation should be no more than 6% [32].

Drug Content: Individual tablet analysis by RP-HPLC should show that each tablet contains 90-110 per cent of the label claim with RSD ≤ 2%.

Dissolution testing *in vitro*

Dissolution testing is probably the most critical evaluation for ER formulations and provides a measure of drug release

behaviour. The standard USP Apparatus II (paddle method) used with dissolution medium of pH 6.8 phosphate buffer (simulating intestinal fluid) at 37°C ± 0.5°C and 50–100 rpm paddle speed [33].

Table 3: Typical release specifications for ER Orphenadrine Citrate tablets

Time Point	Cumulative drug release (%)
1 hour	15-30
4 hours	40-60
8 hours	70-85
12 hours	≥ 85

Modelling of release kinetics

Mathematical modelling of dissolution data aids in gaining insights about the drug release mechanism and prediction of in vivo performance. The commonly used models are:

Zero Order Model: Q = Q0 + k0t

The rate of release is constant and independent of concentration.

Good for ER formulations where constant delivery is optimum.

First Order Model: log Q = log Q0 - k1t / 2.303

The rate of release is proportional to the concentration of drug left.

Higuchi Model: Q = k H √t

Diffusion-controlled release from a matrix system.

Korsmeyer-Peppas Model: M_t/M_∞ = k t^n n ≤ 0.45: Diffusion controlled release 0.45 < n < 0.89: Anomalous (non-Fickian) transport n ≥ 0.89: Case II transport (erosion-controlled)

The release from hydrophilic matrix systems usually follows anomalous transport, indicating that both diffusion and erosion are involved.

Hixson-Crowell Model W0 1/3 - Wt 1/3 = kt

The release is controlled by surface area and particle size changes (erosion).

Analytical method development: RP-HPLC

Basic principles of RP-HPLC

The RP-HPLC (reversed-phase high-performance liquid chromatography) is the most popular liquid chromatography mode in pharmaceutical analysis today. In RP-HPLC, the stationary phase is non-polar (usually C18-bonded silica) and the mobile phase is polar (aqueous buffer with organic modifiers). The separation is based on hydrophobic interactions: the more non-polar the compounds are, the longer they are retained, while the more polar the compounds are, the faster they elute.

Control of mobile phase pH is critical to suppress silanol interactions and to obtain symmetrical peaks for basic drugs such as Orphenadrine citrate (pKa ~ 9.0). It is recommended to have a pH below the drug's pKa to ensure the drug is in its protonated (ionised) form, which reduces interaction with residual silanol groups on the stationary phase.

Parameters for method development

Selection of stationary phase

The most commonly used stationary phase for analysis of orphenadrine citrate is a C18 column (250 mm × 4.6 mm, 5 µm particle size). This column provides sufficient retention for moderately lipophilic basic drugs. Recent studies have also been carried out to use biphenyl column phases to solve the peak elution problems, especially when analysing Orphenadrine citrate along with polar drugs such as Paracetamol.

Composition of mobile phase

The mobile phase usually contains a mixture of acetonitrile or methanol with an aqueous buffer. Separation has been reported for the following studies on Orphenadrine citrate:

Ammonium acetate buffer (pH 5.5-6.5) with acetonitrile: methanol mixtures.

Phosphate buffer (pH 2.5-3.0) with acetonitrile.

Optimised an RP-HPLC method using a mobile phase consisting of 37% acetonitrile and 63% 29 mM $NaH_2PO_4 \cdot H_2O$ (pH 2.5) that enabled baseline separation of Paracetamol and Orphenadrine citrate.

Wavelength of detection

Detection was performed by UV scanning of Orphenadrine citrate at 215 nm (higher sensitivity) or 220 nm (less interference). The peak absorption of the drug was observed at about 220nm and 241nm.

Validation requirements for methods

The analytical methods for assay and blend uniformity determination should be validated for the following parameters according to the ICH Q2(R1) guidelines:

System suitability:

Theoretical plates (N): 2000 or more

Tailing factor: not greater than 2.0

Peak area %RSD from replicate injections ≤ 2.0

Linearity and range

Correlation coefficient (R2): ≥ 0.999

Range: 50 to 150% of target concentration

Accuracy

Recovery: 98-102% at three levels of concentration

Accuracy

%RSD: Not more than 2% for repeatability and intermediate precision

Limit of detection (LOD) and limit of quantification (LOQ)

LOD = 3.3 x σ/S (σ is the standard deviation of response, S is slope)

LOQ = 10 x S / σ

Specificity

No interference by placebo or degradation products

Strength

Small intentional changes in conditions do not affect the results

Recent trends in RP-HPLC method development

Recent studies have used Design of Experiments (DoE) principles to optimise RP-HPLC methods for Orphenadrine citrate. Plackett-Burman design was used to screen significant factors, followed by a Box-Behnken design to optimise an RP-HPLC method

for the simultaneous determination of five skeletal muscle relaxants and four analgesic drugs. The optimised method used ammonium acetate buffer (pH 5.56), acetonitrile and methanol in the ratio 30.5:29.5:40 v/v/v at a flow rate of 1.5 mL/min and showed good linearity ($R^2 > 0.999$), precision (%RSD < 2%) and accuracy (98-102% recovery).

RP-HPLC method with a biphenyl column phase for the resolution of issues of peak elution with systematic optimisation by means of Box-Behnken design for the assessment of acetonitrile percentage, pH and salt concentration. The method provided baseline separation of Paracetamol and Orphenadrine citrate with mobile phase composition of 37% acetonitrile and 63% 29 mM NaH2PO4.H2O (pH 2.5) with detection wavelength of 215 nm and flow rate of 1.5 mL/min. This method also involved greenness evaluation using the Analytical Greenness (AGREE) metric tool, which is a move toward greener analytical procedures.

Research gaps and future research directions

Despite significant progress in the formulation and analysis of ER Orphenadrine citrate tablets, some research gaps still exist:

Few systematic studies of optimisation

Although DoE has been employed in the development of an analytical method for Orphenadrine citrate, few studies have followed similar systematic approaches for the optimisation of formulation. Future research should integrate DoE-guided formulation optimisation, mechanistic release modelling and bio-relevant dissolution methods to define a comprehensive design space.

Comparative studies of polymers

The comparative performance of different polymer systems (HPMC, polyethene oxide, xanthan gum and lipophilic matrices) for Orphenadrine citrate has not been systematically studied. Consider the drug solubility and release profile requirements when selecting the polymer. Think about both in vitro and in vivo performance.

Releases not fully characterised mechanistically

Although dissolution profiles are routinely reported, mechanistic modelling with appropriate mathematical models is often superficial. Additional studies using more advanced modelling techniques and imaging methods are needed to fully study the relative contribution of diffusion vs. erosion to the release of Orphenadrine citrate.

Limited green analytical chemistry applications

Although recent studies have incorporated greenness assessment using the AGREE metric, this is not yet standard practice in pharmaceutical quality control. Future method development should incorporate sustainability considerations as a key design parameter.

Lack of bio-relevant dissolution techniques

Standard dissolution testing using phosphate buffers may not have good correlation to in vivo performance. The use of biorelevant media simulating fed/fasted gastrointestinal conditions would provide more meaningful release data and improve the in vitro-in vivo correlation (IVIVC).

Stability studies in real-life conditions

Routine stability studies are performed under ICH conditions, but real-life studies looking at the effect of temperature excursions, humidity variations and patient handling would provide confidence in the robustness of the product [27].

CONCLUSION

There is a major opportunity to improve patient outcomes in the management of painful musculoskeletal conditions through the development of extended-release Orphenadrine citrate tablets. Hydrophilic matrix systems, especially HPMC-based, are a proven, cost-effective, and regulatory-acceptable approach to sustained drug release over the period of 12-24 hours.

The application of Quality by Design principles, such as systematic optimisation using Design of Experiments, allows the definition of a design space that ensures critical quality attributes. The approach followed with RP-HPLC for the development and validation of analytical methods is rigorous, and the approach is comprehensive in terms of product development with scientific and industrial relevance.

Recent developments in RP-HPLC method development, such as the use of response surface methodology for chromatographic optimisation, use of alternative stationary phases, and greenness assessment, showcase the continuing evolution of analytical techniques that support formulation development.

Nevertheless, several research gaps remain, including the absence of systematic optimisation studies, incomplete mechanistic characterisation of release, and the lack of biorelevant dissolution methods. Future studies focusing on these gaps will improve the knowledge and optimisation of ER Orphenadrine citrate formulations.

The successful development and commercialisation of an ER formulation of Orphenadrine citrate would address a significant unmet therapeutic need, improving patient compliance, reducing side effects, and enhancing quality of life for millions of patients suffering from painful musculoskeletal conditions. As formulation science and analytical chemistry continue to evolve, the prospects for developing even more robust and sustainable extended-release products continue to improve, promising better patient care and therapeutic outcomes.

Conflict of interest statement

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