



EXTENDED-RELEASE MATRIX TABLETS OF TRAMADOL USING HYDROXYPROPYL METHYLCELLULOSE BLENDS

KARTHIK D PANDEY^{1*}, CARMEN MONTALBAN², ELIN SJOBERG³

Affiliation

¹Department of Pharmaceutical Technology, Sahyadri Institute of Pharmaceutical Education, Karad, India

²Department of Industrial Pharmacy, Navarre Plain Institute of Pharmacy, Pamplona, Spain

³Department of Pharmaceutical Technology, Norrland Institute of Clinical Pharmacology, Umea, Sweden

*Corresponding author: Karthik D Pandey, k.pandey@sipe.ac.in

ORCID iD: Karthik D Pandey 0000-0001-2569-3745; Carmen Montalban 0000-0001-3627-1329; Elin Sjöberg 0000-0001-1918-9999

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1. INTRODUCTION

Tramadol is a centrally acting analgesic used for moderate to moderately severe pain, and it has been on the market for more than four decades. Its immediate-release form is taken every four to six hours, which suits acute pain but is awkward for chronic conditions such as osteoarthritis or neuropathic pain [1, 2]. Peaks and troughs in plasma concentration can bring nausea and dizziness at the top of the curve and breakthrough pain at the bottom. Extended-release tablets address this by spreading absorption over twelve to twenty-four hours. Among the polymers available, hydroxypropyl methylcellulose

Abstract

Tramadol hydrochloride is a freely soluble opioid analgesic with a short half-life, which makes it a natural candidate for once- or twice-daily extended-release tablets. This review summarises published work on hydroxypropyl methylcellulose (HPMC) matrix systems and their use for tramadol, and it reports no new data. It covers the pharmacology that motivates modified release, the gel-layer mechanism of HPMC matrices, the influence of polymer grade, level, blending and diluents, and the dissolution testing and kinetic models used to judge performance. Published evidence shows that viscosity grade and polymer ratio can tune release predictably, whereas reporting of in vivo correlation, alcohol sensitivity and tablet robustness is limited.

(HPMC, hypromellose) has become the usual choice for such matrices, because it is non-ionic, tolerant of formulation variation and well accepted by regulators [3, 4].

This article reviews the published literature on tramadol extended-release matrix tablets made with HPMC blends. It is a narrative review and reports no new experimental data. The questions it asks are practical ones. How does an HPMC matrix actually control release of a highly soluble salt? Which variables move the profile most, and by how much? What tests, models and acceptance criteria are used to show that a tablet performs as intended? Evidence comes from general work on hydrophilic matrices, which is extensive, and from fewer reports on tramadol itself, so conclusions about tramadol are partly drawn by analogy from drugs with similar solubility such as propranolol, promethazine and diltiazem [5, 6, 7].

The review is organised in four parts. The first sets out why tramadol suits modified release and what limits the design. The second describes how HPMC matrices work. The third deals with formulation variables, including the blends of viscosity grades that give the topic its title, and the findings are brought together in table 1. The last covers evaluation, with dissolution methods, mathematical models and comparison statistics, and it ends with gaps in the evidence. Throughout, results are described qualitatively unless a number is firmly established, because absolute release percentages depend heavily on apparatus, tablet geometry and the exact lot of polymer used.

Table 1: Published findings on HPMC matrix variables relevant to tramadol

Variable Context	Reported finding	Ref.
Viscosity grade higher grade	Longer chains give a stronger gel layer and slower release.	[5, 8]
Polymer content critical level	Continuous gel forms above a threshold; release then becomes less sensitive.	[7, 9]
Grade blends low and high viscosity	Release changes smoothly with blend ratio; early gel formation limits burst.	[8, 10]
Soluble diluent lactose	Dissolves into the gel, opening channels and raising release rate.	[6, 7]
Insoluble diluent calcium phosphate	Can lengthen diffusion path; effect depends on drug solubility.	[6]

Variable Context	Reported finding	Ref.
Lubricant magnesium stearate	High level or long mixing retards wetting of the tablet surface.	[11]
Tablet geometry surface to volume	Surface-area-to-volume ratio correlates with release rate.	[6, 12]
Agitation and salts medium	Faster stirring and electrolytes alter gel thickness and cloud point.	[13, 14]
Ethanol dissolution medium	Alcohol changes release from hypromellose matrices in a grade-dependent way.	[10]
Power law exponent n value	Intermediate n indicates anomalous transport for soluble drugs.	[15, 16, 17]

2. TRAMADOL AND THE CASE FOR EXTENDED RELEASE

Tramadol is a racemic mixture whose analgesic effect arises from two linked mechanisms. The parent compound inhibits reuptake of noradrenaline and serotonin, while its O-desmethyl metabolite, formed mainly by CYP2D6, is a much stronger agonist at the μ -opioid receptor [18, 19, 20]. Neither action alone accounts for the clinical effect, as early receptor work already showed [21]. The practical consequence is that response varies with CYP2D6 status: poor metabolisers gain less analgesia from the same dose [22]. A formulation cannot correct this, but a smoother plasma profile may at least avoid compounding it with erratic peaks of the parent drug.

Pharmacokinetic properties favour modified release. Oral absorption is rapid and almost complete, with absolute bioavailability of an immediate-release dose commonly quoted at around 70 to 75 percent, a plasma half-life of about six hours and a metabolite half-life slightly longer [1, 2]. Tramadol hydrochloride dissolves freely across the physiological pH range, which is helpful for reproducibility but demanding for matrix design, since a freely soluble drug tends to diffuse out quickly once the tablet is wetted [5, 23]. The usual target is a profile that releases the dose steadily over twelve hours or more, without a large initial burst and without dependence on gastric or intestinal pH.

Safety considerations set limits. Tramadol lowers the seizure threshold and can cause

serotonin syndrome, particularly with other serotonergic drugs [24]. Daily doses are capped, and extended-release products contain a large dose in each tablet, up to several hundred milligrams, so a failure of the release mechanism matters more than with an immediate-release product [1, 24]. Dose dumping, meaning rapid release of the whole dose, is the principal technical hazard. Causes include fracture or crushing of the tablet, poor polymer hydration and interaction with ethanol, and each should be considered when a formulation is designed and judged [10, 25].

Clinical dosing for chronic pain illustrates the potential benefit. Reviews describe extended-release tramadol as giving a flatter concentration profile than the immediate-release form with fewer peak-related adverse effects, and as improving convenience and adherence when taken once or twice daily [1, 2]. Evidence for better analgesia, as distinct from better tolerability and convenience, is more modest. Pharmacokinetic equivalence of total exposure between modified and immediate-release products is generally the regulatory aim, with lower fluctuation as the intended advantage [25]. These points shape the formulation brief: matching exposure, smoothing the profile, resisting dose dumping and tolerating normal manufacturing variation.

3. HOW HPMC MATRICES CONTROL RELEASE

When an HPMC matrix tablet meets water, the outer polymer chains hydrate, swell and entangle to form a viscous gel layer. This layer is the barrier that controls release. Colombo and co-workers described the sequence of fronts that move through such a tablet: an inner dry core, a swelling front, a diffusion front where drug dissolves, and an erosion front at the gel surface [23]. Drug leaves by diffusing through the gel and by erosion of the gel itself. For a freely soluble drug in a high-viscosity polymer, diffusion usually dominates, while erosion becomes more important as drug solubility falls or the polymer viscosity is lower [13, 26].

Experimental work on matrix behaviour has relied on several simple measurements. Water

uptake and mass loss are followed by weighing tablets removed from the medium at intervals, giving separate curves for swelling and erosion [23, 26]. The thickness of the gel layer can be recorded by photography or imaging of tablets cut open after hydration, and dyes or mobile drug markers help to show the fronts. Tahara and co-workers combined such observations with release data and concluded that the gel layer thickness and the polymer erosion rate together explained the overall release of matrix tablets made from hypromellose 2910 [26]. These methods are low-cost, and they show why two formulations with similar dissolution profiles can still have quite different internal structures.

Several features of the polymer matter. Hypromellose is a mixed ether with methoxy and hydroxypropyl substituents, and grades are defined by substitution type and by the viscosity of a 2 percent solution, expressed in millipascal seconds [3, 4]. Grades with nominal viscosities of 100, 4000, 15000 and 100000 mPa·s are commonly used, the last three being the K-type grades employed for extended release. A higher viscosity grade has longer chains that entangle more strongly, so the gel is more resistant and the release slower [5, 8]. The substitution pattern controls how quickly hydration begins, which is important because a matrix must form its gel layer before the surface dissolves. Moisture content of the powder and its particle size distribution add to the variation seen between suppliers [3, 4].

Polymer content is the second major lever. Below a critical level the gel layer is discontinuous and the matrix disintegrates, and the release is fast and poorly controlled. Above it, a continuous gel forms and release becomes slower and less sensitive to small changes in content [7, 9]. Published work places this threshold at a fairly low proportion for high-viscosity grades, but it is not a universal number. Mitchell and colleagues showed that release rate depended on polymer concentration in a way that varied with drug solubility, and similar findings were reported for other freely soluble drugs [5, 9]. For tramadol, which is highly soluble, a polymer proportion of roughly a quarter to a half of

tablet weight is typical in such designs.

Release rate is also controlled by tablet geometry. For a matrix releasing by diffusion, the area available for release and the diffusion path length both matter, and early work found that tablet shape and size influenced the kinetics for a given composition [6]. Later studies showed that the surface-area-to-volume ratio correlates with release rate in a manner that can be used to scale between strengths [12]. Practically, this means lower and higher strength tablets of the same composition may release differently unless geometry is kept proportional. Regulators accept proportional compositions across strengths where release is shown to be similar, so the choice of geometry is as much a regulatory as a formulation issue [25].

4. POLYMER BLENDS AND FORMULATION VARIABLES

Blending different viscosity grades is a practical way to fine-tune a profile that no single grade quite delivers. A low-viscosity grade hydrates quickly and builds the gel early, which limits the initial burst, while a high-viscosity grade sustains the barrier over many hours [3, 7]. Mixtures therefore allow the formulator to move smoothly between the behaviours of the two, within limits. Studies of mixtures of K4M with K15M or K100M, and similar combinations with lower grades, report that release rate changes in a roughly continuous way with the blend ratio [8, 10]. Blends also reduce reliance on one very expensive or variable lot of a single grade, which is a quiet advantage in manufacturing.

Drug solubility interacts with every polymer variable, which is why findings for one drug do not always transfer. Early studies compared drugs of different solubility in identical HPMC matrices and showed that poorly soluble drugs were released mainly by erosion of the gel, while soluble drugs were released mainly by diffusion through it, with the rate rising as solubility rose [5, 6]. Maderuelo and colleagues summarised these relationships in a review of critical factors, stressing that the effect of polymer level and viscosity is strongest for soluble drugs, which is the situation for tramadol hydrochloride [7]. The design lesson is that data from

sparingly soluble models should not be used to set polymer levels for a soluble salt.

Filler choice is the next variable. Soluble diluents such as lactose dissolve into the gel and create channels, raising the release rate. Insoluble diluents such as dibasic calcium phosphate or microcrystalline cellulose behave differently: they can slow release by lengthening the diffusion path, although the effect depends on the drug [6, 7]. Ford and colleagues found that diluent type changed release kinetics noticeably for several drugs, and that the ranking depended on the solubility of the drug as much as on the diluent [6]. For tramadol, published designs usually favour a modest proportion of lactose or microcrystalline cellulose, adjusted until the profile reaches the target, while avoiding large soluble fractions that risk an early burst.

Other excipients and process steps have smaller but real effects. Lubricants such as magnesium stearate are hydrophobic and, at high levels or with prolonged mixing, retard wetting of the tablet surface [11]. Glidants influence flow but rarely release. Direct compression is the simplest route, but it demands adequate flow, and powder flow is checked by simple indices such as the Carr compressibility index and the Hausner ratio [27, 28]. Wet granulation can improve flow and uniformity at the cost of polymer pre-hydration and possible changes in matrix structure. Compression force within the usual range has less influence on release from HPMC matrices than on conventional tablets, because the gel, not the pore structure, controls release [5, 7].

Findings from the literature are brought together in table 1, and the grouping of its entries is shown in fig. 1. The entries emphasise that the largest and most consistent effects come from the polymer itself, namely viscosity grade, content and the ratio of grades in a blend, with diluents and tablet geometry in second place [5, 6, 8, 12]. Test conditions form a separate group: agitation, medium and ethanol content can change a profile as much as a formulation change [10, 14]. Kinetic descriptions are the fourth group, since most reports express their results through a handful of equations. Direct tramadol examples are few, so some entries

refer to model drugs of similar solubility.

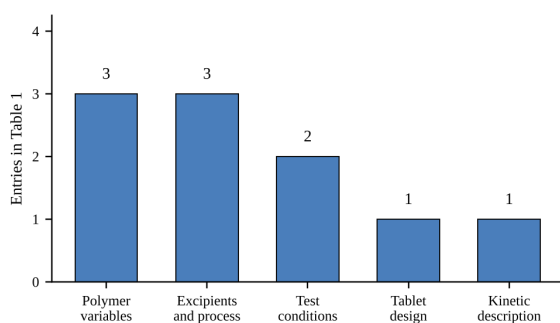


Fig. 1: Number of entries in table 1 by variable group

Alcohol sensitivity deserves its own comment because it is a regulatory concern for opioid products. Ethanol can affect HPMC gel formation, either strengthening or weakening it depending on concentration, and can also change drug solubility. In studies on a model drug, the presence of ethanol in the dissolution medium altered release from hypromellose matrices in a way that depended on polymer grade and alcohol concentration [10]. Guidance for modified-release products asks developers to examine this risk [25]. Higher-viscosity polymer and higher polymer content generally make a matrix more robust, but robustness is a property to be demonstrated for the particular tablet, not inferred from the general trend.

Combination with hydrophobic or ionic polymers is an alternative route to the same goal. Adding ethylcellulose, a carbomer or an anionic polymer such as sodium alginate can modify gel strength and, with ionic polymers, interactions with the charged drug. A basic drug such as tramadol, with a protonated amine at gastric pH, may interact with anionic polymers, which can slow release further but also introduce pH dependence. Because of that, many designs for tramadol stay with non-ionic HPMC, accepting a simpler formulation for easier control. Ionic interactions also complicate dissolution testing, since the buffer composition and ionic strength then affect the result as well as the polymer.

5. EVALUATION, KINETIC MODELS AND GAPS

The analytical side of dissolution testing is usually straightforward for tramadol. The

drug absorbs in the ultraviolet region near 270 nm, so spectrophotometry is common, although HPLC is preferred when excipients or degradation products might interfere. Sink conditions are easily met because the salt is so soluble, and the volume is normally 900 ml of medium [25, 29]. A practical point is that HPMC tablets float or stick to the vessel wall in some apparatus, which can cause erratic profiles; sinkers or baskets are used to prevent it. Sampling volumes must be replaced or corrected for, since over a twenty-four hour test the cumulative removal is not trivial.

Pre-compression and tablet tests come first. Powder blends are checked for flow, density and content uniformity, and tablets are tested for weight variation, hardness, thickness, friability and drug content, with limits set by pharmacopoeial requirements [27, 28]. For HPMC matrices, mechanical strength matters particularly, as a cracked or chipped tablet exposes extra surface and releases faster. Drug-polymer compatibility is commonly assessed by infrared spectroscopy and thermal analysis, though HPMC and tramadol hydrochloride are not known to interact adversely. Stability testing then follows regulatory expectations for modified-release products, with attention to moisture uptake, because HPMC is hygroscopic and equilibrium moisture can alter hydration behaviour [3, 29].

Dissolution testing is the central performance test. The paddle or basket method is used, typically at 37 °C and 50 to 100 revolutions per minute, with samples taken at intervals over twelve to twenty-four hours and assayed by ultraviolet spectrophotometry or HPLC [25, 29]. Many studies of extended-release tramadol use a sequence of media, such as acid for two hours followed by phosphate buffer, which approximates gastric then intestinal transit. Specification limits are normally set at several time points: an early point to exclude dumping, a middle point to define the shape and a late point to confirm near-complete release [25]. Regulatory guidance also encourages testing at several pH values and agitation rates to show that the profile is robust.

Kinetic models describe the profile mathematically and give a rough insight into

mechanism. The Higuchi equation relates cumulative release to the square root of time and applies to diffusion from a non-swelling matrix [30]. The power law of Korsmeyer and Peppas, written as $M_t/M_\infty = k t^n$, uses the exponent n to distinguish Fickian diffusion from anomalous transport and case II relaxation-controlled release; for cylinders, n values around 0.45 indicate Fickian diffusion, and values between 0.45 and 0.89 anomalous transport [15, 16, 17], while early work on compressed hydrophilic matrices had already shown release scaling with the square root of time in diffusion-controlled systems [31]. Alderman reviewed cellulose ethers as hydrophilic matrix formers, describing the gel layer through which drug must diffuse and which slowly erodes [32]. HPMC matrices of freely soluble drugs usually give anomalous transport, with n in the intermediate range.

These models are tools, not proofs. A good fit to a straight line over a limited range does not show that a particular mechanism operates, and the same data can often be described by several equations [33]. Colombo and colleagues, in an analysis of the gel layer of swellable matrices, described how swelling, diffusion and erosion fronts move together, and full mechanistic models, which account for swelling, diffusion and erosion together, are needed to predict release as a function of tablet size and composition [13]. Empirical models remain popular for convenience. The value of n depends on the portion of the curve fitted, normally up to 60 percent release, and on the geometry of the dosage form, so values quoted without such details are hard to interpret.

Comparing a test profile with a reference uses the difference factor f_1 and the similarity factor f_2 . An f_2 value between 50 and 100 is conventionally taken to indicate similar profiles, and the method assumes a minimum number of time points and low variability [34, 35]. It does not suit highly variable data, and more flexible approaches based on multivariate distance have been proposed. For extended-release tablets the regulator may also expect a level A in vitro-in vivo correlation, linking fraction dissolved with fraction absorbed, which allows dissolution to serve as a surrogate for bioequivalence after

minor changes [25]. Such correlations are seldom reported for tramadol matrices in academic papers, which usually stop at in vitro results.

The gaps are fairly clear. Many published reports rely on a single apparatus and condition, small numbers of tablets and a limited set of variables studied one at a time, so interactions between polymer grade, filler and geometry are underexplored [7, 10, 12]. Alcohol sensitivity, tablet crushing and the effects of food are rarely examined, although they are the central safety questions for an opioid extended-release tablet [10, 25]. Pharmacokinetic confirmation in humans is rare in the formulation literature. Statistical experimental design is applied in some work and would help to map interactions efficiently, and standardised reporting of grade, supplier, lot and apparatus would make results from different laboratories easier to compare.

Quality by design offers a framework for closing some of these gaps. A target product profile defines the desired release, critical material attributes such as polymer viscosity and particle size are linked to critical quality attributes such as dissolution, and a design space is mapped using designed experiments. Particle size of HPMC deserves a mention here: finer particles hydrate faster and form the gel layer more quickly, which can lower the initial burst, and particle size distributions differ between suppliers and lots [8]. Mapping such sources of variation early is cheaper than discovering them during scale-up.

6. CONCLUSION

Hydroxypropyl methylcellulose gives formulators a dependable way to extend the release of a freely soluble drug such as tramadol hydrochloride. Published work on hydrophilic matrices shows that viscosity grade, polymer content and the blending of grades are the main controls, that diluent and geometry refine the profile, and that the resulting release is usually anomalous transport through a swelling and eroding gel [5, 8, 13, 23]. These findings are consistent enough to be useful in planning a tablet, and they match what theory predicts for a

swelling, partly eroding gel barrier around a soluble drug.

The evidence is thinner where safety matters most. Few reports test alcohol sensitivity, crushing or food effects, and fewer still link dissolution with plasma concentrations in people [10, 25]. Wider use of experimental design, multi-condition dissolution testing and complete reporting of polymer supplier and lot would make the literature far more reliable. Until such data accumulate, published matrix designs for tramadol are best read as sound starting points, not finished products, and each new strength or polymer lot should be treated as something to be checked rather than assumed, in line with the evidence reviewed here.

7. ABBREVIATIONS

CYP2D6-Cytochrome P450 2D6, f1-Difference factor, f2-Similarity factor, HPLC-High-performance liquid chromatography, HPMC-Hydroxypropyl methylcellulose (hypromellose), ICH-International Council for Harmonisation, mPa·s-Millipascal second, μ -Mu (opioid receptor subtype)

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All the authors have contributed equally.

10. CONFLICT OF INTERESTS

Declared none

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