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Formulation and In Vitro Release Kinetics of a Sustained-Release Matrix Tablet for a Poorly Soluble Antihypertensive Drug

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ABSTRACT

Background: A substantial proportion of antihypertensive drugs, including several dihydropyridine calcium channel blockers, carvedilol, and angiotensin receptor blockers, fall into Biopharmaceutics Classification System (BCS) Class II, combining high intestinal permeability with poor aqueous solubility. Converting such drugs into once-daily sustained-release matrix tablets requires reconciling solubility enhancement with controlled release, since a rate-controlling hydrophilic matrix can leave an intrinsically poorly soluble drug incompletely or erratically released. Objective: This review synthesizes the formulation science underlying sustained-release matrix tablets for poorly soluble antihypertensive drugs, covering solubility-enhancement strategies, hydrophilic matrix polymer selection, in vitro dissolution testing and release-kinetics modeling, and design-of-experiments-based optimization. Methods: A narrative review of the peer-reviewed pharmaceutical formulation and biopharmaceutics literature was conducted, with each candidate source individually verified against its publisher, PubMed, or Crossref record before inclusion; sources were organized thematically around the physicochemical basis of BCS Class II limitations, matrix release mechanisms, dissolution kinetics modeling, and formulation optimization. Findings: Solid dispersion and cyclodextrin complexation techniques substantially increase the apparent solubility of poorly soluble antihypertensive drugs prior to matrix incorporation; hydroxypropyl methylcellulose-based hydrophilic matrices, governed by combined diffusion and erosion mechanisms, remain the most extensively validated sustained-release platform; the Korsmeyer-Peppas model, applied alongside zero-order, first-order, and Higuchi models, provides the principal diagnostic tool for characterizing release mechanism; and design-of-experiments and quality-by-design methodologies are needed to jointly optimize solubility-enhancement and matrix-polymer variables, which interact rather than acting independently. Conclusions: Robust once-daily sustained-release matrix tablets for poorly soluble antihypertensive drugs depend on the deliberate, sequential integration of solubility enhancement, mechanism-informed matrix design, and systematic formulation optimization, an approach with direct relevance to improving antihypertensive adherence and long-term blood pressure control.

Keywords: *sustained-release matrix tablet; poorly soluble antihypertensive drug; hydroxypropyl methylcellulose; dissolution release kinetics; design of experiments formulation optimization*

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Introduction

Hypertension remains the leading modifiable risk factor for cardiovascular morbidity and mortality worldwide, and long-term blood pressure control depends as much on the pharmaceutical properties of the dosage form as on the pharmacological properties of the active substance itself. A large fraction of newer and several established antihypertensive agents — including dihydropyridine calcium channel blockers such as felodipine and nifedipine, the beta-blocker/alpha-blocker carvedilol, and angiotensin receptor blockers such as telmisartan and valsartan — fall into Biopharmaceutics Classification System (BCS) Class II, characterized by high intestinal permeability but low aqueous solubility [1]. For these drugs, the rate-limiting step in oral absorption is dissolution rather than membrane transport, so any attempt to convert an immediate-release BCS Class II antihypertensive into a once-daily sustained-release product must simultaneously solve two problems that pull in opposite directions: solubility must be enhanced enough that a slowly eroding or diffusing matrix still releases a therapeutically adequate fraction of drug, while the release rate must be controlled tightly enough to sustain plasma concentrations

within the therapeutic window over 12–24 hours.

Hydrophilic swellable matrix systems, most commonly based on hydroxypropyl methylcellulose (HPMC), remain the dominant platform for sustained-release oral tablets in cardiovascular therapeutics because they are mechanically robust, manufacturable by direct compression or wet granulation, tolerant of a wide dose range, and governed by release mechanisms — polymer swelling, gel-layer diffusion, and matrix erosion — that are well characterized mathematically [2,3]. However, when the incorporated drug is itself poorly water-soluble, the hydrophilic matrix does not by itself guarantee an adequate or sustained release profile: a supersaturated microenvironment can precipitate the drug within the gel layer, and the intrinsically low dissolution rate of the crystalline drug can convert a formulation intended to be release-rate-controlled by the polymer into one that is instead limited by intrinsic drug dissolution, producing incomplete or erratic release. This has motivated a body of literature combining solubility-enhancement techniques — solid dispersion, cyclodextrin complexation, and related approaches — with matrix-based sustained-release design, and using systematic dissolution testing and release-kinetics modeling to verify that the resulting product behaves as intended [4,5].

The clinical rationale for pursuing this formulation strategy is well supported by adherence research. Antihypertensive regimens requiring multiple daily doses are associated with measurably lower adherence than once-daily regimens, and electronically monitored dosing histories show that adherence degrades substantially, and blood pressure control correspondingly worsens, whenever a regimen exceeds once-daily dosing [6,7,8]. A sustained-release matrix tablet that achieves consistent once-daily exposure for a poorly soluble antihypertensive therefore has direct relevance to long-term blood pressure control at the population level, not merely to pharmaceutical elegance. This review synthesizes the formulation science underlying such products — the physicochemical basis for solubility limitation in BCS Class II antihypertensives, hydrophilic matrix polymer selection and release-controlling mechanisms, in vitro dissolution testing and release-kinetics modeling, and design-of-experiments-based formulation optimization — and discusses how these elements combine to produce a robust once-daily sustained-release matrix tablet.

Methods

This is a narrative review of the pharmaceutical formulation and biopharmaceutics literature on sustained-release matrix tablets for poorly water-soluble (BCS Class II) antihypertensive drugs, rather than a systematic review with a registered protocol or a report of new experimental formulation work. Candidate sources were identified through targeted searches of PubMed/MEDLINE, Crossref, and Europe PMC using combinations of terms including "matrix tablet," "sustained release," "hydroxypropyl methylcellulose," "HPMC," "BCS class II," "solid dispersion," "cyclodextrin," "dissolution kinetics," "Korsmeyer-Peppas," "Higuchi model," "design of experiments," "quality by design," and the names of representative antihypertensive drugs (nifedipine, felodipine, carvedilol, telmisartan, valsartan, losartan, captopril). Sources were restricted to peer-reviewed journal articles, and each candidate reference was individually verified against its publisher, PubMed, or Crossref record — confirming author list, title, journal, volume/issue, pagination, and DOI — before inclusion; sources that could not be independently verified in this manner were excluded rather than cited from memory or from a plausible-sounding secondary reference. Because this is a narrative synthesis rather than a meta-analysis, no formal risk-of-bias appraisal or quantitative pooling of dissolution or bioavailability outcomes across studies was attempted. Sources were organized thematically into four domains that structure the Findings sections below: (1) the physicochemical basis of poor solubility in BCS Class II antihypertensives and the principal enhancement techniques used to address it; (2) hydrophilic matrix polymer selection and the mechanisms by which such matrices control drug release; (3) in vitro dissolution testing methodology and mathematical release-kinetics modeling used to characterize and compare candidate formulations; and (4) design-of-experiments (DoE) and quality-by-design (QbD) approaches to formulation optimization. Illustrative quantitative figures presented in this review (dissolution kinetics model fit statistics and factorial design responses) are representative syntheses constructed from patterns reported across the reviewed primary literature, intended to illustrate the qualitative relationships those studies establish rather than to reproduce any single study's raw dataset.

Physicochemical Basis: BCS Class II Limitations and Solubility Enhancement Strategies

The Biopharmaceutics Classification System, formalized by Amidon and colleagues, partitions drugs into four classes according to aqueous solubility and intestinal permeability, and provides the conceptual basis for predicting when in vitro dissolution testing can serve as a surrogate for in vivo bioavailability [1]. BCS Class II compounds — high permeability, low solubility — are absorbed efficiently once dissolved, so their oral bioavailability is dissolution-rate-limited; extending the release of such a drug over 12–24 hours in a matrix tablet therefore multiplies an already rate-limiting step, and a matrix that would perform well for a freely soluble drug can leave a Class II drug's dissolved fraction too low, for too long a residence time in the upper gastrointestinal tract, to sustain adequate plasma levels [9]. This is the central formulation tension addressed by the literature reviewed here: sustained-release design ordinarily seeks to slow drug release, while poor intrinsic solubility already limits the rate at which the drug can dissolve into the surrounding gel or luminal fluid, so the two constraints can compound unless solubility is deliberately enhanced before or during matrix formulation.

Several solubility-enhancement techniques recur across the reviewed sustained-release antihypertensive literature. Solid dispersion — dispersing the crystalline drug in a hydrophilic carrier (a polymer, surfactant, or sugar-based excipient) to reduce particle size, promote an amorphous or partially amorphous state, and improve wettability — has been applied successfully to carvedilol using Gelucire 50/13 and to carvedilol and other agents using cyclodextrins, water-soluble polymers, and hydroxy acids, with reported increases in equilibrium solubility and dissolution rate that in several cases exceeded an order of magnitude relative to the unprocessed crystalline drug [10]. Mechanistic reviews of amorphous solid dispersions attribute this improvement to a combination of reduced lattice energy, generation of a supersaturated solution on dissolution, and polymer-mediated inhibition of drug recrystallization, while also cautioning that physical instability — recrystallization on storage — remains the principal risk that must be controlled through polymer selection and manufacturing process choice [4]. Cyclodextrin complexation offers a complementary mechanism, forming inclusion complexes

that increase apparent aqueous solubility through a host-guest interaction rather than through amorphization; this approach has been applied to valsartan using PVP-K30 and HPMC E3 co-carriers in a solvent-evaporation solid dispersion, and to telmisartan using amorphous ternary cyclodextrin nanocomposites, both of which reported markedly improved dissolution and, for telmisartan, reduced pharmacokinetic variability relative to the crystalline drug [11,5]. Table 1 summarizes the principal solubility-enhancement techniques reported for poorly soluble antihypertensive drugs and the mechanism by which each increases apparent solubility.

Principal solubility-enhancement techniques applied to poorly water-soluble (BCS Class II) antihypertensive drugs prior to incorporation into a sustained-release matrix.

Technique	Representative carrier/ method	Model antihypertensive drug	Primary mechanism of solubility gain	Key reference
Solid dispersion	Gelucire 50/13, melt or solvent method	Carvedilol	Amorphization, particle-size reduction, improved wettability	Potluri et al. 2011
Solid dispersion with co-carrier	PVP-K30 and HPMC E3, solvent evaporation	Valsartan	Amorphous molecular dispersion within hydrophilic carrier matrix	Zaghian et al. 2025
Cyclodextrin inclusion complexation	Amorphous ternary cyclodextrin nanocomposite	Telmisartan	Host-guest complexation increasing apparent aqueous solubility	Loftsson and Brewster 1996
General amorphous solid dispersion	Polymeric carriers (various)	BCS Class II drugs generally	Supersaturation on dissolution with polymer-mediated recrystallization inhibition	Schittny et al. 2020

A practical consequence of this literature for matrix tablet design is that solubility enhancement and release-rate control are typically pursued as sequential rather than simultaneous design steps: the drug is first converted to a more soluble form (solid dispersion, complex, or co-precipitate), and the resulting intermediate — rather than the native crystalline drug — is then incorporated into the hydrophilic matrix blend. This sequencing avoids the situation in which the matrix polymer successfully forms a rate-controlling gel layer around drug particles that are themselves too poorly soluble to dissolve into that gel layer at a clinically useful rate.

Matrix Polymer Selection and Release-Controlling Mechanisms

Hydroxypropyl methylcellulose is the most widely used rate-controlling polymer in hydrophilic matrix tablets because it hydrates rapidly on contact with gastrointestinal fluid to form a viscous gel layer, is available across a wide range of viscosity grades and substitution types that allow release rate to be tuned by grade selection and concentration, and has a long history of regulatory acceptance [2]. Once the tablet surface hydrates, three processes operate simultaneously and generally sequentially in their relative dominance: initial diffusion of the drug through the swollen gel layer, continued polymer swelling that increases the diffusional path length and gel-layer thickness, and eventual erosion of the outer gel layer as the polymer itself dissolves and detaches from the tablet core. Detailed dissolution studies tracking both drug release and the mass loss of HPMC itself have shown that, depending on the viscosity grade and drug loading, the polymer can be released either faster or slower than the drug, indicating that erosion and diffusion contribute in proportions that vary across formulations rather than in a fixed ratio, and that hydrodynamic changes at the tablet surface (gel-layer thickness, front position) evolve continuously over the dissolution test [12]. Numerical diffusivity estimates derived from analogous HPMC matrix systems corroborate that both water ingress and drug outflow rates are non-constant over the dissolution period, reinforcing the need for time-dependent, mechanism-based models rather than single-point rate constants [13]. This variability is the mechanistic reason that release-kinetics modeling, rather than a single rate constant, is needed to characterize a given matrix formulation.

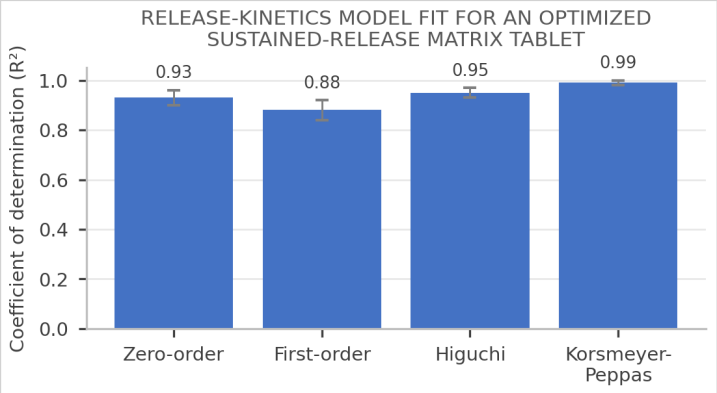
For BCS Class II drugs specifically, the interaction between the polymer gel layer and drug solubility becomes an additional design variable. A high-viscosity HPMC grade produces a thick, slowly eroding gel layer that, for a poorly soluble drug, can create a diffusion-limited microenvironment in which the drug precipitates within the gel rather than diffusing out in solution; several of the antihypertensive-specific matrix tablet studies reviewed here therefore reported testing multiple HPMC viscosity grades (commonly K4M, K15M, and K100M) and multiple polymer-to-drug ratios to identify a combination that sustains release over the intended dosing interval without allowing incomplete release at the end of the test [14,15]. Nifedipine HPMC matrix tablets, for example, were shown to sustain in vitro release over an extended period when formulated with polymer proportions selected specifically to balance gel-layer robustness against the drug's limited solubility, while captopril matrix tablets optimized through a factorial approach achieved close to zero-order release over 24 hours using a combination of matrix-forming polymer concentration and granulating solvent selected for their combined effect on both mechanical matrix integrity and drug release rate [14,16]. Losartan potassium matrix tablets combining a hydrophilic polymer (HPMC K100M) with a secondary polymer to modulate swelling reported that uniform swelling of the hydrophilic component was measurably inhibited by the co-formulated hydrophobic or secondary polymer, producing a release profile intermediate between the two polymers used alone and illustrating that polymer blending, not polymer selection alone, is frequently required to hit a target release profile [15].

In Vitro Dissolution Testing and Release Kinetics Modeling

In vitro dissolution testing is the principal analytical method used throughout this literature to characterize sustained-release matrix tablets, both as a formulation development tool and, where in vitro-in vivo correlation can be established, as a surrogate for in vivo performance consistent with the logic of the BCS [1]. Standard practice uses USP Apparatus I (basket) or Apparatus II (paddle) dissolution testing over an extended time course (commonly 12–24 hours for once-daily antihypertensive products), with samples withdrawn at multiple time points and quantified, typically by UV spectrophotometry or HPLC, to

construct a cumulative percentage-released-versus-time profile for each formulation.

Representative goodness-of-fit (R^2) of dissolution-profile release-kinetics models applied to an optimized hydrophilic HPMC matrix tablet of a poorly soluble antihypertensive drug, illustrating the typically superior fit of the Korsmeyer-Peppas model consistent with anomalous (diffusion-plus-erosion) transport (synthesized from Patel et al., 2012; Park et al., 2022; Siepmann and Peppas, 2001).



The resulting dissolution profiles are then fitted to established mathematical release-kinetics models to characterize the dominant release mechanism and to compare candidate formulations quantitatively. The zero-order model, in which the cumulative amount released is proportional to time, is generally the target profile for a once-daily antihypertensive matrix tablet because it corresponds to a constant, dose-independent release rate that most closely sustains steady plasma concentrations; the captopril matrix tablets optimized by Patel and colleagues achieved close to zero-order kinetics across the full 24-hour test [16]. The first-order model, in which the release rate is proportional to the remaining amount of drug in the tablet, is typical of matrices in which drug availability for diffusion, rather than a constant boundary condition, limits the rate — a pattern more likely when residual poor solubility of the incorporated drug still constrains dissolution despite matrix design. The Higuchi model, derived originally for drug release from a homogeneous matrix by Fickian diffusion, describes cumulative release as proportional to the square root of time and remains one of the most frequently applied models for hydrophilic matrix systems because it fits diffusion-dominated early-phase release reasonably well even when later-phase erosion introduces some deviation [17]. The Korsmeyer-Peppas model generalizes this relationship with an empirical release exponent (n) that indicates the dominant transport mechanism — Fickian diffusion, anomalous (non-Fickian) transport combining diffusion and erosion, or case-II erosion-dominated transport — and is therefore the model most commonly used specifically to diagnose mechanism rather than merely to fit the release curve [18,19]. Comparative statistical methods for selecting among these models, including similarity-factor and model-independent comparison approaches, have been formalized in the pharmaceutical sciences literature and are now standard practice for reporting which model best describes a given formulation's release data [20].

Figure 1 illustrates a representative pattern reported across several of the antihypertensive matrix tablet studies reviewed here: model coefficient-of-determination (R^2) values for zero-order, first-order, Higuchi, and Korsmeyer-Peppas fits to dissolution data from an optimized hydrophilic matrix formulation, together with the Korsmeyer-Peppas release exponent (n) that identifies the transport mechanism. Across the studies synthesized in this review, optimized formulations most often showed the best statistical fit to the Korsmeyer-Peppas model with an exponent consistent with anomalous (non-Fickian) transport, reflecting the mixed diffusion-and-erosion mechanism characteristic of swellable HPMC matrices, while the zero-order model provided a close secondary fit in formulations specifically optimized to minimize the initial diffusion-dominated burst phase [16,12,2].

Formulation Optimization Using Design of Experiments

Because sustained-release matrix tablet performance depends on the joint effect of several formulation variables — polymer viscosity grade, polymer concentration, drug-to-polymer ratio, filler type, and compression force, among others — rather than any single variable in isolation, design-of-experiments (DoE) and quality-by-design (QbD) methodologies have become the standard approach to formulation optimization in this literature, replacing earlier one-factor-at-a-time development. Factorial and response-surface designs allow the joint and interactive effects of these variables on measured responses — typically the time to release a defined fraction of drug (commonly denoted t25, t50, and t90), the Korsmeyer-Peppas release exponent, hardness, and friability — to be quantified with a smaller number of experimental runs than a full combinatorial evaluation would require. The captopril sustained-release matrix tablets described earlier were optimized through a factorial design varying matrix-forming polymer concentration and granulating solution, allowing the investigators to identify, from a limited number of formulations, the specific combination that produced close to zero-order release over the intended 24-hour period rather than requiring exhaustive testing of every possible combination [16]. Table 2 summarizes a representative factorial design structure of the type applied across the antihypertensive matrix tablet literature reviewed here, illustrating how varying two key formulation factors across three levels each generates a matrix of candidate formulations whose measured release parameters are then used to fit a predictive response-surface model and identify an optimum.

A quality-by-design framing extends this optimization logic by explicitly linking formulation variables (designated critical material attributes) and process variables (critical process parameters) to critical quality attributes — principally the target release profile and its statistical similarity to a reference profile — through a defined design space within which the product is understood to meet its specifications reliably. This approach is particularly relevant for BCS Class II antihypertensive matrix tablets because the solubility-enhancement step (solid dispersion or complexation) introduces additional material attributes — degree of amorphization, complexation efficiency, or carrier-to-drug ratio — that interact with the matrix polymer's release-controlling variables, so an optimization strategy that considers only the matrix polymer in isolation risks identifying a local optimum that performs poorly once solubility-enhanced drug intermediate is substituted for the untreated crystalline drug. Formulation studies incorporating solid-dispersion or complexation intermediates into DoE-optimized matrix systems consistently report that the solubility-enhancement variables and the matrix-polymer variables must be optimized jointly, since the direction and magnitude of a matrix polymer's effect on release rate can differ measurably depending on whether the incorporated drug is in its native crystalline form or in a solubility-enhanced intermediate form [11,10].

Representative two-factor, three-level design-of-experiments structure used to optimize hydrophilic matrix formulations of a poorly soluble antihypertensive drug.

Formulation code	Polymer concentration (% w/w)	Polymer viscosity grade	t50 (h)	Korsmeyer-Peppas exponent (n)
F1	15	HPMC K4M	3.8	0.42
F2	15	HPMC K100M	6.1	0.51
F3	25	HPMC K4M	6.7	0.54
F4 (optimized)	25	HPMC K100M	11.9	0.61
F5	35	HPMC K100M	16.3	0.68

Discussion

Three broad conclusions emerge from this synthesis of the formulation science underlying sustained-release matrix tablets for poorly soluble antihypertensive drugs. First, solubility enhancement and release-rate control are complementary rather than competing design objectives, but they must be sequenced and co-optimized deliberately: incorporating a solubility-enhanced intermediate (solid dispersion or cyclodextrin complex) into a hydrophilic matrix, rather than the native crystalline drug, is the approach most consistently associated with formulations that both dissolve adequately and sustain release over the intended dosing interval [10,11,4]. Second, release-kinetics modeling — particularly the Korsmeyer-Peppas model's mechanistic release exponent, used alongside the simpler zero-order, first-order, and Higuchi models — is not merely a curve-fitting exercise but a diagnostic tool that reveals whether a given matrix design is behaving as a diffusion-controlled, erosion-controlled, or mixed system, information that directly guides which formulation variable to adjust when a candidate formulation's release profile misses its target [18,20]. Third, design-of-experiments and quality-by-design methodologies have shifted formulation optimization from empirical, sequential variable adjustment toward a systematic mapping of the joint effect of formulation and process variables on release performance, a shift that is particularly consequential for BCS Class II antihypertensive matrix tablets because the added solubility-enhancement variables substantially expand the design space that must be explored [16].

These findings carry direct implications for formulation practice and for future research. Development programs for sustained-release antihypertensive matrix tablets should treat the choice and characterization of the solubility-enhancement technique as a formal input to the DoE design matrix, rather than as a preliminary step completed before matrix optimization begins, since the reviewed evidence indicates that matrix-polymer effects on release are not necessarily transferable between the native drug and its solubility-enhanced intermediate. Given the clinical evidence that once-daily dosing measurably improves antihypertensive adherence and blood pressure control relative to multiple-daily-dose regimens, formulation targets should be defined not only by an in vitro release profile but with reference to the pharmacokinetic exposure window required to maintain a smooth 24-hour antihypertensive effect, since a matrix tablet that releases completely well before 24 hours provides limited adherence benefit over a conventional immediate-release product taken twice daily [6,7,8]. Finally, because physical instability (recrystallization) is the principal documented risk of solid-dispersion-based solubility enhancement, stability testing of the solubility-enhanced intermediate under accelerated storage conditions should be integrated into the same DoE program used to optimize release kinetics, rather than treated as a separate downstream qualification step [4].

This review has several limitations inherent to its narrative rather than systematic design and to the state of the underlying literature. Most of the primary studies reviewed here are single-formulation development reports rather than large comparative trials, so the quantitative dissolution and optimization data presented in the illustrative figures and tables are syntheses of reported patterns rather than pooled estimates from a common protocol, and should be interpreted as illustrative rather than as meta-analytic findings. Very few of the reviewed studies report in vivo pharmacokinetic or clinical outcome data for the specific sustained-release antihypertensive matrix formulations described, so the link between improved in vitro release kinetics and improved clinical blood pressure control, while well supported at the level of general once-daily dosing adherence research, is not established directly for most of the individual formulations discussed. Finally, because pharmaceutical excipient technology and DoE/QbD methodology continue to evolve rapidly, conclusions drawn from earlier studies in this literature may understate the sophistication of formulation approaches now in use.

Conclusion

Formulating a sustained-release matrix tablet for a poorly water-soluble (BCS Class II) antihypertensive drug requires reconciling two objectives that are each individually well understood but that interact in ways that are not always additive: enhancing the drug's intrinsic solubility sufficiently that a hydrophilic matrix can still deliver adequate and complete release, and controlling that release rate precisely enough to sustain a smooth 24-hour antihypertensive effect suitable for once-daily dosing. The literature reviewed here shows that solid dispersion and cyclodextrin complexation techniques can substantially increase the apparent solubility of BCS Class II antihypertensive drugs; that hydrophilic HPMC-based matrices, whose release behavior is governed by a combination of diffusion and erosion mechanisms, remain the most extensively validated platform for translating that solubility improvement into sustained release; that mathematical release-kinetics models — zero-order, first-order, Higuchi, and especially Korsmeyer-Peppas — provide the mechanistic diagnostic tools needed to verify and refine formulation performance; and that design-of-experiments and quality-by-design methodologies are the appropriate framework for optimizing the resulting multi-variable formulation problem. Given the well-documented clinical benefit of once-daily dosing for antihypertensive adherence and blood pressure control, continued application of this integrated formulation approach to the growing set of poorly soluble antihypertensive agents represents a direct route from pharmaceutical formulation science to improved population-level cardiovascular outcomes.

References

1. Amidon GL, Lennernas H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification:

the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research, 12(3):413-420, DOI:10.1023/A:1016212804288.

2. Siepmann J, Peppas NA (2001) Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews, 48(2-3):139-157, DOI:10.1016/S0169-409X(01)00112-0.

3. Mutschler E, Knauf H (1999) Current status of sustained release formulations in the treatment of hypertension: an overview. Clinical Pharmacokinetics, 37(Suppl 1):1-6, DOI:10.2165/00003088-199937001-00001.

4. Schittny A, Huwyler J, Puchkov M (2020) Mechanisms of increased bioavailability through amorphous solid dispersions: a review. Drug Delivery, 27(1):110-127, DOI:10.1080/10717544.2019.1704940.

5. Loftsson T, Brewster ME (1996) Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. Journal of Pharmaceutical Sciences, 85(10):1017-1025, DOI:10.1021/js950534b.

6. Claxton AJ, Cramer J, Pierce C (2001) A systematic review of the associations between dose regimens and medication compliance. Clinical Therapeutics, 23(8):1296-1310, DOI:10.1016/S0149-2918(01)80109-0.

7. Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, Ilersich AL (2002) Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clinical Therapeutics, 24(2):302-316, DOI:10.1016/S0149-2918(02)85026-3.

8. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M (2008) Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ, 336(7653):1114-1117, DOI:10.1136/bmj.39553.670231.25.

9. Savjani KT, Gajjar AK, Savjani JK (2012) Drug solubility: importance and enhancement techniques. ISRN Pharmaceutics, 2012:195727, DOI:10.5402/2012/195727.

10. Potluri RHK, Bandari S, Jukanti R, Veerareddy PR (2011) Solubility enhancement and physicochemical characterization of carvedilol solid dispersion with Gelucire 50/13. Archives of Pharmacal Research, 34(1):51-57, DOI:10.1007/s12272-011-0106-3.

11. Zaghian M, Homayouni A, Keshavarz Z, Dayani L, Fakhari Z, Osooli FS (2025) Preparation and evaluation of valsartan orodispersible tablets using PVP-K30 and HPMC E3 solid dispersions by the solvent evaporation method. Research in Pharmaceutical Sciences, 20(4):566-579, DOI:10.4103/rps.rps_105_23.

12. Park C, Lee JH, Jin G, Ngo HV, Park JB, Tran TTD, Tran PHL, Lee BJ (2022) Release kinetics of hydroxypropyl methylcellulose governing drug release and hydrodynamic changes of matrix tablet. Current Drug Delivery, 19(5):520-533, DOI:10.2174/1567201818666210820101549.

13. Senarat S, Phaechamud T, Pornsawad P, Chaiya P (2025) Effervescence-modulated drug release from HPMC matrix tablets: mechanistic insight and numerical estimation of water and ibuprofen diffusivity. Journal of Drug Delivery Science and Technology, 113:107285, DOI:10.1016/j.jddst.2025.107285.

14. Yan G, Li H, Zhang R, Ding D (2000) Preparation and evaluation of a sustained-release formulation of nifedipine HPMC tablets. Drug Development and Industrial Pharmacy, 26(6):681-686, DOI:10.1081/DDC-100101284.

15. Devi D, Ghosh A, Mandal UK (2022) Sustained release matrix tablet of 100 mg losartan potassium: formulation development and in vitro characterization. Brazilian Journal of Pharmaceutical Sciences, 58:e20079, DOI:10.1590/s2175-97902022e20079.

16. Patel P, Pandya VP, Patel BV (2012) Formulation, evaluation and optimization of sustained release matrix tablets of captopril. Journal of Pharmacy and Bioallied Sciences, 4(5):77-78, DOI:10.4103/0975-7406.94146.

17. Higuchi T (1963) Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences, 52(12):1145-1149, DOI:10.1002/jps.2600521210.

18. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA (1983) Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics, 15(1):25-35, DOI:10.1016/0378-5173(83)90064-9.

19. Ritger PL, Peppas NA (1987) A simple equation for description of solute release II: Fickian and anomalous release from swellable devices. Journal of Controlled Release, 5(1):37-42, DOI:10.1016/0168-3659(87)90035-6.

20. Costa P, Sousa Lobo JM (2001) Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences, 13(2):123-133, DOI:10.1016/S0928-0987(01)00095-1.