

STUDY ON FORMULATION, CHARACTERIZATION AND MODIFICATION OF SUSTAINED RELEASE BILAYER MATRIX TABLETS OF PROPRANOLOL HCl AND NIFEDIPINE FOR ANTIHYPERTENSIVE THERAPY

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ABSTRACT

Background: Sustained-release (SR) bilayer matrix tablets allow two release segments, or two drugs, to be combined in one dosage unit. Propranolol hydrochloride (BCS class I) and nifedipine (BCS class II) are complementary antihypertensives, but their contrasting solubility makes the design of a shared SR system challenging.

Objective: To critically analyse published formulation, characterization and modification data on SR bilayer/matrix tablets of propranolol HCl and SR hydroxypropyl methylcellulose (HPMC) tablets of nifedipine, and to derive an evidence-based design framework for a combined bilayer tablet.

Methods: Quantitative data on composition, micromeritics, tablet quality, drug release, swelling, release kinetics, particle size, similarity factor (f_2) and bioequivalence were extracted from five key studies. Published dissolution data (HPMC K15M and Kollidon® SR matrices, 1–4 h) were re-analysed using zero-order, first-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models, and Hausner ratios were derived from reported compressibility indices.

Results: In the bilayer propranolol tablet, 20 mg sodium starch glycolate released 99.72% of the loading dose in 10 min, while the SR layer containing 40% HPMC K15M (F9) released 98.41% over 12 h ($f_2 = 60.5$; Peppas $n = 0.622$; anomalous transport). Re-analysis showed that release from low-polymer matrices was best described by the Higuchi model ($R^2 \geq 0.989$), whereas higher Kollidon® SR levels gave near-linear release (zero-order $R^2 = 0.998$ – 0.999). For nifedipine, raw-drug particle size governed release similarity: the batch whose in-tablet D90 (147 μm) matched the reference (150 μm) gave $f_2 = 78.2$ and was bioequivalent under fasting and fed conditions.

Conclusion: Polymer grade and level control the propranolol layer, while particle size and solubilisation control the nifedipine layer. A proposed propranolol–nifedipine bilayer composition and a characterization protocol are presented for experimental verification.

Keywords: Bilayer tablet; Sustained release; Propranolol hydrochloride; Nifedipine; HPMC K15M; Kollidon® SR; Release kinetics; Similarity factor; Hypertension

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1. INTRODUCTION

Hypertension is the leading modifiable risk factor for cardiovascular disease, stroke and chronic kidney disease. The World Health Organization estimates that about 1.3 billion adults aged 30–79 years live with hypertension, and that only about one in five of them has blood pressure under control [1]. Poor control is linked to multiple daily doses, pill burden and the need for more than one drug class. Current guidelines therefore recommend long-acting agents and, for most patients, combinations of drugs with complementary mechanisms [2,3]. A meta-analysis of 354 randomised trials showed that combining low doses of two antihypertensive classes lowers blood pressure more, with fewer adverse effects, than increasing the dose of one agent [4].

Propranolol hydrochloride is a non-selective β -adrenoceptor antagonist. It is highly soluble and highly permeable (BCS class I), but it undergoes extensive, saturable first-pass metabolism, giving an oral bioavailability of about 25% and an elimination half-life of 3–6 h [5]. Conventional tablets must therefore be taken two to four times a day. Nifedipine is a dihydropyridine calcium-channel blocker that lowers peripheral vascular resistance. It is practically insoluble in water (BCS class II), light-sensitive and has a short half-life of about 2 h; immediate-release nifedipine produces abrupt vasodilation and reflex tachycardia [6]. Combining the two drugs is pharmacologically rational: β -blockade blunts the reflex sympathetic activation caused by the vasodilator, while nifedipine counteracts the rise in peripheral resistance that can accompany β -blockade [2,6].

Hydrophilic matrix tablets, most commonly based on HPMC, are the simplest and most widely used way to obtain sustained release. On contact with fluid the polymer hydrates to form a gel layer. Release of a soluble drug is then controlled mainly by diffusion through this gel, and release of a poorly soluble drug mainly by erosion of the matrix [7–9]. Bilayer tablets extend this concept. They can combine an immediate-release (IR) loading dose with an SR maintenance

layer, or place two incompatible or differently behaving drugs in separate layers [10]. However, bilayer tablets bring their own problems, including layer separation, cross-contamination at the interface, differences in compaction behaviour and weight control of each layer [10].

Several studies have developed SR bilayer or matrix tablets of propranolol HCl [11–13], and others have developed SR HPMC tablets of nifedipine [14,15]. These data have not yet been brought together to guide a combined propranolol–nifedipine product. The present study therefore (i) compiles and critically compares published formulation and characterization data for the two drugs, (ii) re-analyses the published dissolution data using standard kinetic models, (iii) examines the formulation modifications that shift release behaviour, and (iv) proposes a rational composition and characterization framework for an SR propranolol–nifedipine bilayer matrix tablet.

2. MATERIALS AND METHODS

2.1 Study design and data sources

This is a literature-based comparative study with secondary data analysis. No new laboratory experiments were performed. Primary research articles reporting the formulation and evaluation of SR bilayer or matrix tablets of propranolol HCl, and SR HPMC tablets of nifedipine, were identified. Studies were included if they reported quantitative formulation compositions together with at least one of the following: micromeritic properties, post-compression quality parameters, *in vitro* drug release, release kinetics, similarity factor or *in vivo* bioequivalence. Five studies met these criteria and form the core dataset: two bilayer propranolol studies [11,12], a comparative HPMC/Kollidon® SR propranolol matrix study [13], an HPMC nifedipine SR study [14] and a Raman-mapping-guided nifedipine SR development and bioequivalence study [15].

2.2 Data extraction

From each study, the following were extracted: formulation composition (mg per tablet or layer), bulk and tapped density, angle of repose, compressibility index, drug content, weight variation, hardness, friability, cumulative drug release against time, swelling, kinetic model parameters, particle size distribution (D10, D50, D90), f_2 values and pharmacokinetic parameters. Values are reported as published. Where a source reported only the mean, no standard deviation was assumed. All values carry the citation of their source study.

2.3 Secondary kinetic analysis

The cumulative release data for eight propranolol HCl matrix formulations (PrH1–PrH4 with HPMC K15M and PrK1–PrK4 with Kollidon® SR, in increasing polymer proportion; pH 6.8 phosphate buffer) [13] were available for 1, 2, 3 and 4 h. These data were fitted by least-squares linear regression to the following models [16–20]:

$$\text{Zero order: } Q_t = Q_0 + k_0 t \quad (1)$$

$$\text{First order: } \log(100 - Q_t) = \log Q_0 - k_1 t / 2.303 \quad (2)$$

$$\text{Higuchi: } Q_t = k_H t^{1/2} \quad (3)$$

$$\text{Hixson–Crowell: } Q_0^{1/3} - Q_R^{1/3} = k_{HCT} t \quad (4)$$

$$\text{Korsmeyer–Peppas: } M_t/M_\infty = k_{KP} t^n \quad (5)$$

Here Q_t is the percentage released at time t , Q_R the percentage remaining and n the release exponent. The Korsmeyer–Peppas model was applied only to data points with $M_t/M_\infty \leq 0.60$ and only when at least three such points were available. For cylindrical matrices, $n \leq 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ anomalous (non-Fickian) transport and $n \geq 0.89$ case-II (relaxation/erosion-controlled) transport [18,19]. The time to 50% release ($t_{50\%}$) was obtained by linear interpolation. Dissolution efficiency over 0–4 h (DE_{4h}) was calculated as the area under the release curve (trapezoidal rule) divided by the area of the rectangle for 100% release over the same period [20]. Calculations were carried out in Python 3 (NumPy/SciPy).

2.4 Derived flow parameters and similarity factor

The Hausner ratio (HR) was derived from the reported compressibility (Carr's) index (CI) as $HR = 100 / (100 - CI)$ and interpreted using the pharmacopoeial flowability scale [21,22]. The similarity factor used in the source studies to compare dissolution profiles is defined as [23]:

$$f_2 = 50 \times \log \{ [1 + (1/n) \sum (R_t - T_t)^2]^{-0.5} \times 100 \} \quad (6)$$

Here R_t and T_t are the percentages released by the reference and test products at each time point. A value of f_2 between 50 and 100 indicates similar profiles [23].

2.5 Data presentation

All figures were redrawn by the authors from the numerical values reported in the cited studies; they are not reproductions of the original authors' graphs. Figure 1 is a conceptual design schematic, not an image of a manufactured tablet.

3. RESULTS AND DISCUSSION

3.1 Physicochemical basis for a propranolol–nifedipine bilayer system

Table 1 compares the properties of the two drugs that determine SR design. Propranolol HCl is soluble at all physiological pH values, so the main risk is dose dumping through fast diffusion. A high-viscosity polymer and a sufficiently thick gel layer are needed. Nifedipine release is limited by dissolution, so a polymer that erodes at a controlled rate, together with control of drug particle size or a solid-dispersion carrier, is required. These opposite needs are best met by placing each drug in its own layer, each with its own matrix design (Figure 1).

Table 1: Properties of propranolol HCl and nifedipine relevant to sustained-release design

Property	Propranolol HCl	Nifedipine
Pharmacological class	Non-selective β -blocker	Dihydropyridine Ca^{2+} -channel blocker

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Property	Propranolol HCl	Nifedipine
BCS class	I (high solubility, high permeability)	II (low solubility, high permeability)
Aqueous solubility	Soluble	Practically insoluble; light-sensitive
Elimination half-life	≈ 3–6 h	≈ 2 h (IR)
Oral bioavailability	≈ 25% (first-pass)	≈ 45–55% (CYP3A4 first-pass)
Dominant SR mechanism in HPMC	Diffusion through gel layer	Matrix erosion / dissolution
Key design variable	Polymer viscosity grade and level	Particle size, carrier, polymer level

Sources: [5,6,7,9].

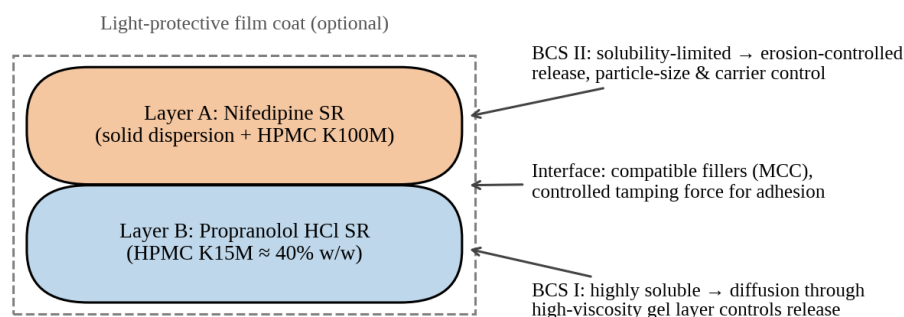


Figure 1: Proposed architecture of a propranolol HCl–nifedipine SR bilayer matrix tablet

3.2 Formulation design of propranolol HCl bilayer tablets

Gangireddy *et al.* [11] developed a bilayer tablet consisting of a 200 mg IR layer (25 mg propranolol HCl) and a 250 mg controlled-release (CR) layer (55 mg propranolol HCl), giving 80 mg per tablet. The IR layer tested three levels of the superdisintegrant sodium starch glycolate (SSG; Table 2). The CR layer compared polyethylene oxide (PEO WSR 1105) and HPMC K15M at 10–50% of layer weight, with microcrystalline cellulose (MCC) used to keep the layer weight constant (Table 3; Figure 2). Patra *et al.* [12] used a similar IR/SR approach, with SSG in the fast-release layer and water-insoluble polymers (ethylcellulose, Eudragit® RLPO and RSPO) in the sustaining layer. They obtained an initial burst followed by release over 12 h.

Table 2: Composition of the immediate-release layer (mg per tablet)

Ingredient	IR1	IR2	IR3
Propranolol HCl	25	25	25
Sodium starch glycolate	10	15	20
Microcrystalline cellulose	155	150	145
Magnesium stearate	5	5	5
Talc	5	5	5
Total	200	200	200

Source: Gangireddy *et al.* [11].

Table 3: Composition of the controlled-release layer (mg per layer)

Code	Propranolol HCl	PEO WSR 1105	HPMC K15M	MCC	Mg stearate	Talc	Total
F1	55	25	—	160	5	5	250
F2	55	50	—	135	5	5	250
F3	55	75	—	110	5	5	250
F4	55	100	—	85	5	5	250
F5	55	125	—	60	5	5	250
F6	55	—	25	160	5	5	250
F7	55	—	50	135	5	5	250
F8	55	—	75	110	5	5	250

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Code	Propranolol HCl	PEO WSR 1105	HPMC K15M	MCC	Mg stearate	Talc	Total
F9	55	—	100	85	5	5	250
F10	55	—	125	60	5	5	250

Source: Gangireddy *et al.* [11]. Polymer levels correspond to 10, 20, 30, 40 and 50% of CR-layer weight.

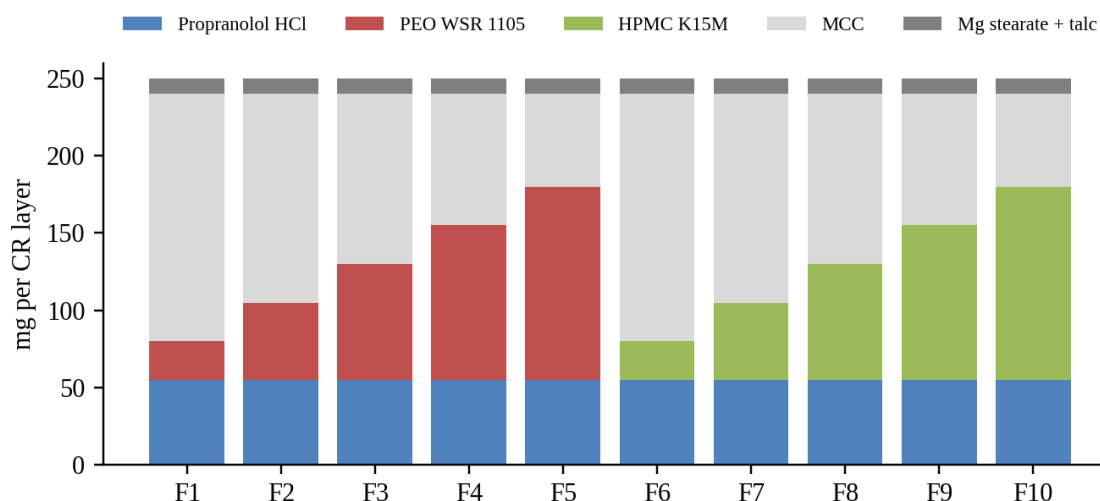


Figure 2: Composition of CR-layer formulations F1–F10, showing replacement of MCC by increasing PEO WSR 1105 (F1–F5) or HPMC K15M (F6–F10); redrawn from [11]

This design changes one variable at a time: drug load and lubricant levels are fixed, and polymer replaces filler. Any change in release can therefore be attributed to polymer type and level. MCC is a sensible diluent for both layers because its plastic deformation supports bonding at the layer interface. Using the same filler in both layers also reduces the mismatch in elastic recovery that often causes bilayer tablets to split along the interface [10].

3.3 Pre-compression characteristics

The reported micromeritic properties and the Hausner ratios derived in this study are shown in Table 4. Angles of repose of 25.9–29.8° and compressibility indices of 10.2–11.4% place the blends in the 'excellent' to 'good' flow classes [21,22]. The derived Hausner ratios of 1.11–1.13 support this. Good flow is especially important for bilayer compression, because each layer is filled volumetrically in turn and poor flow shows up directly as layer-weight variation and dose non-uniformity.

Table 4: Pre-compression parameters of the propranolol HCl bilayer blends

Parameter	Reported range	Flow interpretation [21,22]
Bulk density (g/mL)	0.33–0.39	—
Tapped density (g/mL)	0.43–0.45	—
Angle of repose (°)	25.9–29.8	Excellent (25–30°)
Compressibility index (%)	10.16–11.36	Excellent to good (≤ 10 / 11–15)
Hausner ratio (derived)	1.11–1.13	Excellent to good (1.00–1.11 / 1.12–1.18)

Measured values from Gangireddy *et al.* [11]; Hausner ratio calculated in the present study from the reported compressibility index.

3.4 Post-compression quality of propranolol HCl matrix tablets

Table 5 summarises the physical evaluation of the HPMC K15M (PrH) and Kollidon® SR (PrK) matrix tablets of Sahoo *et al.* [13], each containing 80 mg of propranolol HCl. Drug content ranged from 80.1 to 81.6 mg per tablet (100.1–102.0% of label claim). Hardness was 5.1–5.4 kg/cm² and friability 0.72–0.91%, all within the usual limit of 1%. Friability was therefore acceptable, but the margin was narrow. The bilayer tablets of Gangireddy *et al.* [11] had lower friability (0.13–0.15%) and a drug content of 101.3%, which suggests that bilayer compression with MCC produced mechanically stronger compacts. Neither polymer affected tablet integrity, which is consistent with the good plasticity of both HPMC and the polyvinyl acetate–povidone blend in Kollidon® SR.

Table 5: Post-compression parameters of propranolol HCl matrix tablets (80 mg)

Formulation	Drug content (mg/tablet)	Weight variation (%)	Hardness (kg/cm ²)	Friability (%)
PrH1	81.2	±4.9	5.2	0.91
PrH2	80.3	±4.6	5.1	0.81

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Formulation	Drug content (mg/tablet)	Weight variation (%)	Hardness (kg/cm ²)	Friability (%)
PrH3	80.8	±5.2	5.4	0.83
PrH4	80.2	±4.6	5.3	0.75
PrK1	80.1	±4.4	5.4	0.85
PrK2	80.3	±4.8	5.2	0.76
PrK3	80.9	±4.3	5.1	0.72
PrK4	81.6	±4.5	5.3	0.89

Source: Sahoo et al. [13]. Mean values; standard deviations as reported in the original article.

3.5 Performance of the immediate-release layer

The IR layer is meant to reach therapeutic plasma levels quickly before the SR layer takes over. Table 6 and Figure 3a show that release at 10 min rose from 85.92% to 99.72% as SSG increased from 10 to 20 mg (5–10% of layer weight). SSG swells rapidly and extensively, so faster disintegration and near-complete release of the highly soluble drug at the 20 mg level is expected. IR3 was therefore chosen as the loading layer. For a combined propranolol–nifedipine product, an IR component may not be needed, or may even be undesirable, for nifedipine, because an abrupt rise in nifedipine concentration triggers reflex tachycardia [6]. Any loading dose should therefore come from propranolol only.

Table 6: Effect of sodium starch glycolate on IR-layer release

Formulation	SSG (mg; % of layer)	Drug release at 10 min (%)
IR1	10 (5%)	85.92 ± 1.23
IR2	15 (7.5%)	91.12 ± 0.22
IR3	20 (10%)	99.72 ± 1.37

Source: Gangireddy et al. [11]; mean ± SD.

3.6 Sustained-release layer: optimization, swelling and kinetics

Among the CR layers, formulation F9 (40% HPMC K15M) was selected as optimal. It released 98.41% of propranolol HCl over 12 h, and its profile was similar to the target ($f_2 = 60.5$; Table 7). Water uptake in the HPMC series (F6–F9) rose from 109% to 136% as polymer content increased. This reflects a thicker, more hydrated gel layer, which lengthens the diffusion path and slows release. Of the kinetic models, Korsmeyer–Peppas gave the best fit ($R^2 = 0.991$), followed by Higuchi (0.987), first order (0.975) and zero order (0.932) (Table 8; Figure 3b). The release exponent $n = 0.622$ indicates anomalous (non-Fickian) transport, in which diffusion of the dissolved drug through the gel is combined with relaxation and slow erosion of the polymer chains [18,19]. This is the typical behaviour of a soluble drug in a high-viscosity HPMC matrix [8,9].

Table 7: Characteristics of the optimized SR layer (F9)

Parameter	Published result
HPMC K15M level	40% of layer weight (100 mg)
Cumulative drug release at 12 h	98.41%
Similarity factor (f_2)	60.5
Water uptake (swelling), F6–F9	109–136%
Peppas release exponent (n)	0.622
Release mechanism	Anomalous (non-Fickian) transport

Source: Gangireddy et al. [11].

Table 8: Release-kinetics parameters of the optimized formulation F9

Model	Rate constant	R^2
Zero order	17.472	0.932
First order	0.201	0.975
Higuchi	64.334	0.987
Korsmeyer–Peppas	$n = 0.622$	0.991

Source: Gangireddy et al. [11].

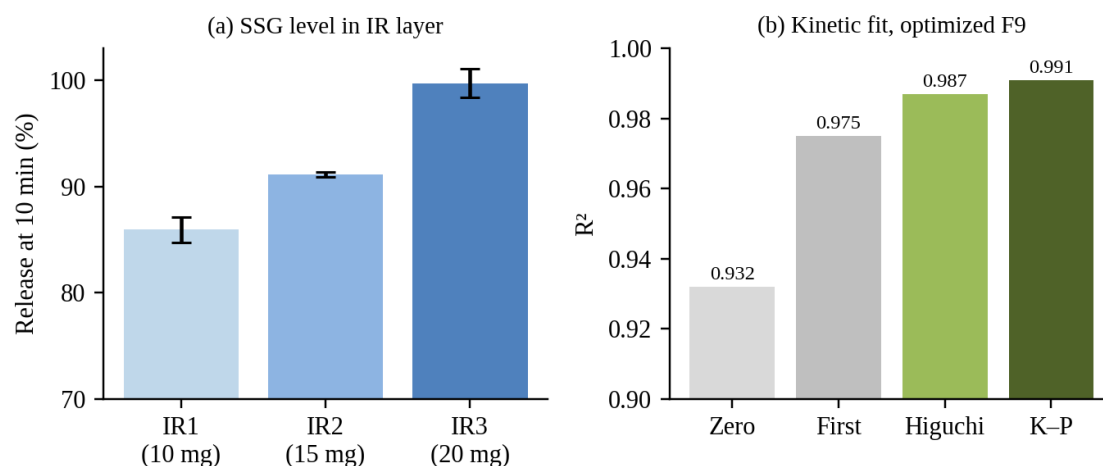


Figure 3: (a) Effect of SSG level on IR-layer release at 10 min; (b) coefficients of determination of kinetic models for the optimized SR layer F9; redrawn from [11]

PEO WSR 1105 (F1–F5) was a less efficient retardant than HPMC K15M at the same level. The lower-viscosity grade forms a gel that erodes faster, which is why HPMC K15M was selected [11]. The ethylcellulose/Eudragit® system of Patra *et al.* [12] also followed Higuchi kinetics with non-Fickian diffusion over 12 h. This shows that insoluble polymers can give similar overall kinetics, although they depend less on gel formation and more on the porosity and tortuosity of an inert skeleton.

3.7 HPMC K15M versus Kollidon® SR: secondary kinetic analysis

Figure 4 plots the published 1–4 h dissolution data of the PrH and PrK matrices [13]. At the lowest polymer levels (PrH1, PrK1), about 98% of the drug was released within 4 h, so these matrices provide little sustained release. Increasing either polymer lowered the 4 h release to 30.6–53.4%. At equivalent levels, Kollidon® SR retarded release slightly more than HPMC K15M (e.g., PrK4 30.56% versus PrH4 39.36%). Table 9 and Figure 5 give the results of our re-analysis.

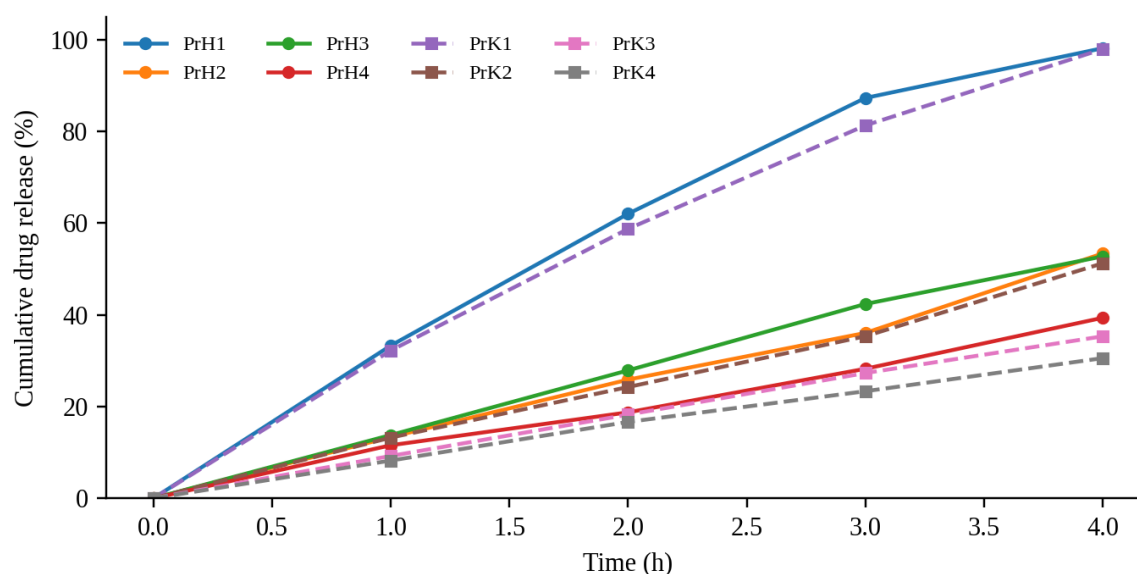


Figure 4: Cumulative release of propranolol HCl from HPMC K15M (PrH) and Kollidon® SR (PrK) matrix tablets in pH 6.8 phosphate buffer (1–4 h); redrawn from [13]

Table 9: Secondary kinetic analysis of published propranolol HCl release data (1–4 h)

Code	Zero order k_0 (%/h); R^2	First order k_1 (h^{-1}); R^2	Higuchi k_H (%/h ^{1/2}); R^2	Hixson–Crowell R^2	Peppas n ; R^2	$t_{50\%}$ (h)	DE _{4h} (%)
PrH1	21.99; 0.966	1.190; 0.937	66.75; 0.989	0.990	n.d.	1.58	57.9
PrH2	13.03; 0.988	0.201; 0.962	38.60; 0.964	0.973	0.973; 0.994	3.80	25.5
PrH3	13.14; 0.995	0.203; 0.998	39.44; 0.996	0.999	0.981; 0.998	3.73	27.6
PrH4	9.29; 0.991	0.126; 0.978	27.46; 0.963	0.983	0.874; 0.986	> 4	19.6
PrK1	21.98; 0.990	1.133; 0.888	66.25; 0.999	0.965	n.d.	1.67	55.3
PrK2	12.51; 0.991	0.189; 0.968	37.05; 0.966	0.977	0.958; 0.994	3.92	24.6

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Code	Zero order k_0 (%/h); R^2	First order k_1 (h ⁻¹); R^2	Higuchi k_H (%/h ^{1/2}); R^2	Hixson–Crowell R^2	Peppas n ; R^2	$t_{50\%}$ (h)	DE _{4h} (%)
PrK3	8.74; 0.999	0.113; 0.999	26.14; 0.994	1.000	0.974; 1.000	> 4	18.1
PrK4	7.37; 0.998	0.092; 0.999	22.09; 0.996	0.999	0.943; 0.998	> 4	15.9

Calculated in the present study from release data reported by Sahoo *et al.* [13]. *n.d.*: not determined (fewer than three points with release $\leq 60\%$). DE_{4h}: dissolution efficiency over 0–4 h. The analysis covers only the first 4 h and should be read as describing early-phase behaviour.

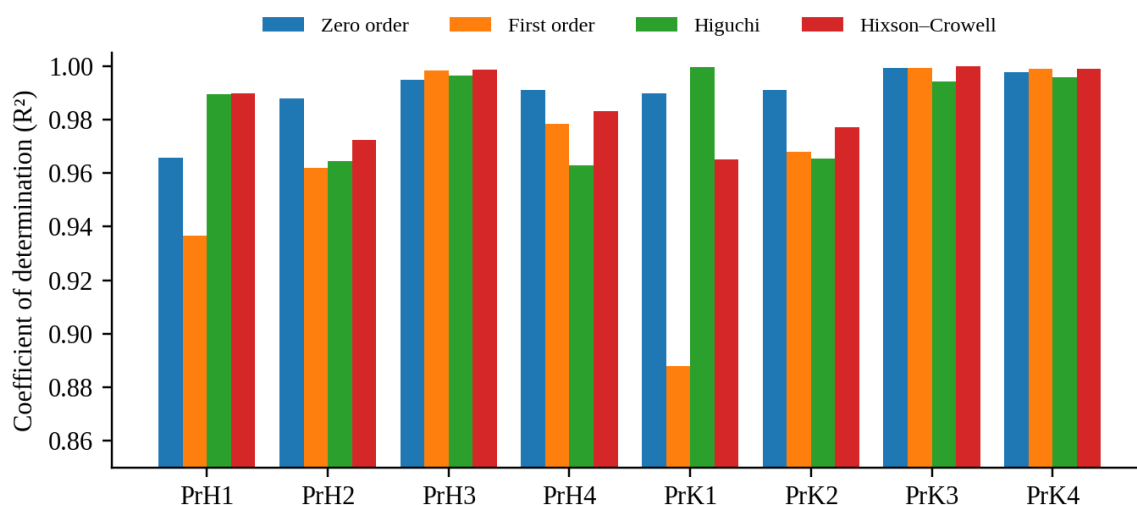


Figure 5: Goodness of fit (R^2) of four release models to the early-phase (1–4 h) propranolol HCl release data; calculated in the present study from data in [13]

Three trends emerge. First, the fast-releasing matrices PrH1 and PrK1 were best described by the Higuchi square-root-of-time model ($R^2 = 0.989$ and 0.999). This is the expected result for diffusion from a matrix whose gel barrier is too thin to limit release for long. Second, as polymer content increased, the profiles became almost linear: PrK3 and PrK4 fitted zero order with $R^2 = 0.999$ and 0.998 . This agrees with the original authors' conclusion that Kollidon® SR at 40% gave zero-order release over 12 h, whereas HPMC K15M at 40% followed first-order kinetics [13]. Third, the Korsmeyer–Peppas exponents for the sustained matrices (0.874–0.981) lie close to or above the case-II threshold of 0.89. In the early phase, therefore, release is dominated by polymer relaxation rather than by pure Fickian diffusion.

These exponents are higher than the $n = 0.622$ reported for the full 12 h profile of the bilayer F9 [11]. This is expected, because the early portion of a hydrating matrix is dominated by gel-front movement, and n usually falls as the diffusion path lengthens. The near-identical $t_{50\%}$ values of PrH2, PrH3 and PrK2 (3.80, 3.73 and 3.92 h) show that the two polymers can be interchanged to reach a given early release rate. Where a constant input rate is the goal, as for a once-daily antihypertensive, Kollidon® SR or a Kollidon® SR–HPMC blend is the better modification.

3.8 Nifedipine sustained-release matrix tablets

Because nifedipine is poorly soluble, its release from HPMC matrices depends on both erosion and diffusion. An early HPMC study used a nifedipine solid dispersion in HPMC K15M/K100 tablets to extend release to 24 h. Release was described by the Hixson–Crowell and Higuchi models, consistent with a mechanism that depends on both matrix erosion and diffusion [14]. More recently, Sun *et al.* [15] used Raman mapping to reverse-engineer the reference product Adalat®-L. They found that the particle size of nifedipine inside the tablet was the critical quality attribute. The core composition they used is shown in Table 10. They then prepared four batches from raw drug of decreasing particle size (Table 11).

Table 10: Composition of a nifedipine SR tablet core (mg per tablet)

Ingredient	Amount (mg)	Function
Nifedipine	20.0	Active
Polysorbate 80	0.4	Wetting agent
Microcrystalline cellulose	26.0	Diluent/binder
Lactose	8.0	Diluent
Corn starch (blending)	12.4	Diluent/disintegrant
Corn starch (as paste)	12.4	Binder
Magnesium stearate	0.8	Lubricant
Total	80.0	

Source: Sun *et al.* [15].

Table 11: Particle size of nifedipine in raw drug and in prepared tablets

Batch	Raw drug D90 (μm)	Raw drug D50 (μm)	Raw drug D10 (μm)	In-tablet D90 / D50 / D10 (μm)
A	145.2 $\pm$ 0.6	69.3 $\pm$ 0.6	12.1 $\pm$ 0.5	Not reported
B	96.1 $\pm$ 0.7	38.2 $\pm$ 0.6	8.4 $\pm$ 0.6	173 / 118 / 52.2
C	62.0 $\pm$ 0.6	26.3 $\pm$ 0.2	5.5 $\pm$ 0.3	147 / 121 / 47.5
D	38.9 $\pm$ 0.5	18.8 $\pm$ 0.4	6.1 $\pm$ 0.4	108 / 103 / 32.7
Adalat®-L (reference)	—	—	—	150 / 118 / 30.7

Source: Sun et al. [15]; mean $\pm$ SD for raw drug.

A notable finding is that the particle size measured inside the tablet was much larger than that of the raw drug (e.g., Batch C: raw D90 62.0 μm , in-tablet D90 147 μm). Fine nifedipine agglomerates during wet granulation. The raw-drug specification therefore has to be set with this growth in mind, and processing can itself be used to adjust the effective particle size. Batch C, whose in-tablet particle size was closest to that of the reference, gave the highest similarity factor ($f_2 = 78.2$). Batch A, made from the coarsest raw drug, failed the similarity test ($f_2 = 44.2$) (Table 12; Figure 6). In a crossover study in healthy volunteers ($n = 28$), Batch C was bioequivalent to Adalat®-L under both fasting and fed conditions, with all 90% confidence intervals within 80–125% [15].

Table 12: Dissolution similarity and bioequivalence of nifedipine SR batches versus Adalat®-L

Parameter	Batch A	Batch B	Batch C	Batch D
f_2 (vs reference)	44.2	54.9	78.2	52.3
Interpretation	Not similar	Similar	Similar (closest)	Similar
Fasting C_{max} ratio, % (90% CI)	—	—	102.75 (92.15–114.56)	—
Fasting $\text{AUC}_{0-\infty}$ ratio, % (90% CI)	—	—	93.48 (87.55–99.80)	—
Fed C_{max} ratio, % (90% CI)	—	—	89.67 (81.95–98.11)	—
Fed $\text{AUC}_{0-\infty}$ ratio, % (90% CI)	—	—	95.28 (88.97–102.04)	—

Source: Sun et al. [15]. Dissolution medium: pH 4.0 acetate buffer with 0.05% polysorbate 80, paddle 50 rpm. —: not tested in vivo.

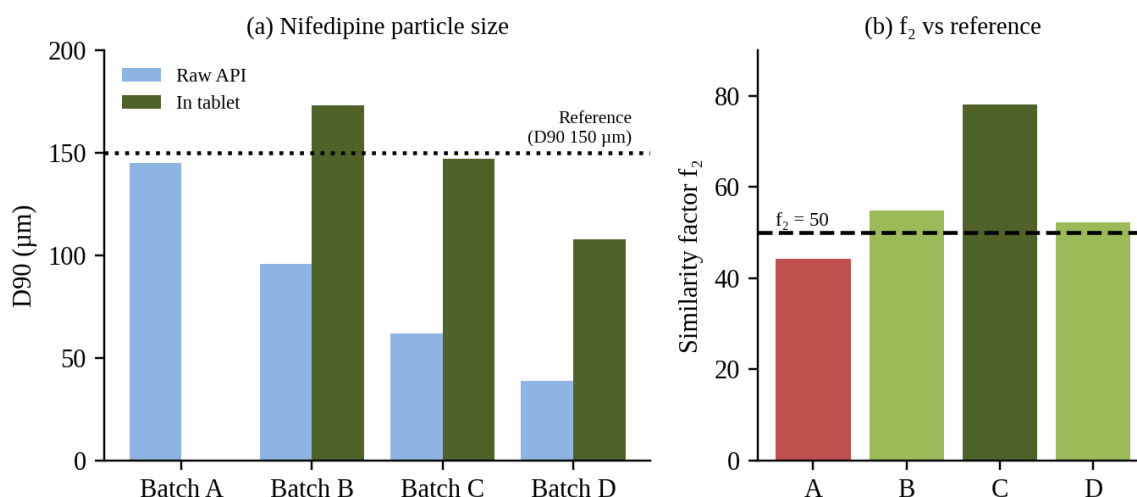


Figure 6: (a) D90 of nifedipine in raw drug and in tablets relative to the reference product; (b) similarity factor of each batch versus Adalat®-L; redrawn from [15]

3.9 Modification strategies

The combined evidence identifies several formulation levers that can be used to tune an SR bilayer tablet of these two drugs:

- **Polymer level and viscosity grade.** In the propranolol layer, increasing HPMC K15M from 10% to 40% turned a fast-releasing matrix into a 12 h system [11]. Moving to K100M, or blending in Kollidon® SR, should extend release towards 24 h and make it more linear (Section 3.7). For nifedipine, a lower-viscosity or partly eroding grade (e.g., K4M/K15M blends) avoids incomplete release of the poorly soluble drug [14].
- **Polymer type.** Kollidon® SR, an insoluble polyvinyl acetate–povidone matrix, gives release that depends less on pH and is closer to zero order [13]. PEO provides faster gelation but weaker retardation than HPMC [11]. Insoluble polymers such as ethylcellulose and Eudragit® RS/RL can be used to reduce the initial burst [12].
- **IR/SR partitioning.** An SSG-based IR layer ($\approx 10\%$ SSG) gives near-complete release of propranolol within 10 min [11]. The IR fraction (here 25 of 80 mg) should be chosen from the target C_{max} and not simply maximised.

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- **Solubility and particle-size engineering for nifedipine.** Solid dispersions (e.g., with PVP, PEG or poloxamer), micronisation with control of agglomeration, and surfactants such as polysorbate 80 regulate the dissolution-limited step [14,15,24]. Particle size in the tablet, not only in the raw drug, should be specified [15].
- **Layer interface and compression.** Using a plastic diluent (MCC) in both layers, applying a low tamping force to the first layer and matching the moisture content of the two layers all help to prevent delamination [10].
- **Photostability.** Nifedipine degrades on exposure to light, so an opaque film coat (e.g., containing titanium dioxide or iron oxide) and light-protected processing are required [6].

3.10 Proposed propranolol HCl–nifedipine bilayer formulation and characterization framework

Based on the evidence above, a starting composition for a once-daily bilayer tablet is proposed in Table 13 (Figure 1). Layer B is derived from the optimized propranolol SR layer F9 [11], scaled to 80 mg of drug at 40% HPMC K15M. Layer A contains nifedipine as a solid dispersion within an HPMC matrix [14,15], with iron oxide added so that the layers can be told apart and to give some protection from light. This composition is a hypothesis to be tested experimentally. It has not been manufactured or tested, and polymer levels should be optimized by a statistical design, for example a 3² factorial or Box–Behnken design, with release at 2, 8, 12 and 24 h and f_2 against marketed SR products as responses.

Table 13: Proposed starting composition of an SR propranolol HCl–nifedipine bilayer tablet (for experimental verification)

Layer / ingredient	mg per tablet	Function / rationale
Layer A – nifedipine SR (200 mg)		
Nifedipine–PVP K30 solid dispersion (1:2)	60.0 (≡ 20 mg nifedipine)	Improves solubility [24]
HPMC K100M	60.0 (30%)	Erosion-controlled matrix [14]
Microcrystalline cellulose	70.0	Diluent; interfacial bonding
Iron oxide red	2.0	Layer identification; light protection
Magnesium stearate / talc	4.0 / 4.0	Lubricant / glidant
Layer B – propranolol HCl SR (250 mg)		
Propranolol HCl	80.0	Active
HPMC K15M	100.0 (40%)	Diffusion-controlled gel matrix [11]
Microcrystalline cellulose	60.0	Diluent
Magnesium stearate / talc	5.0 / 5.0	Lubricant / glidant
Total tablet weight	450.0	

The characterization programme needed to verify the proposed tablet is given in Table 14. Two points deserve emphasis. First, a single dissolution method must provide sink conditions for nifedipine without dumping propranolol. A pH-change method (0.1 N HCl for 2 h, then pH 6.8 phosphate buffer) with a surfactant (e.g., 0.5% sodium lauryl sulphate) and light-protected vessels, combined with a validated HPLC method that measures both drugs simultaneously, is recommended. Second, drug–excipient compatibility (FTIR, DSC) must be confirmed for both drugs, because the two layers are in direct contact.

Table 14: Recommended characterization of the proposed bilayer tablet

Test	Method	Suggested acceptance criterion
Pre-compression flow	Angle of repose, Carr's index, Hausner ratio	Angle ≤ 30°; CI ≤ 15%; HR ≤ 1.18
Compatibility	FTIR, DSC (and XRD for solid dispersion)	No new peaks/shift; amorphous nifedipine maintained
Physical quality	Weight variation, thickness, hardness, friability	Pharmacopoeial limits; friability < 1%
Layer adhesion	Axial/diametral breaking test at interface	No delamination on handling
Assay / content uniformity	Simultaneous RP-HPLC (UV ≈ 235 and 290 nm)	95–105% of label claim for each drug
In vitro release	USP apparatus II, pH 1.2 → 6.8 with surfactant, 24 h	Target profile; f_2 ≥ 50 vs reference
Swelling / erosion	Gravimetric water uptake and mass loss	Reproducible gel formation
Release kinetics	Zero, first, Higuchi, Hixson–Crowell, Peppas models	Identify mechanism; n for each drug
Stability	ICH Q1A(R2): 40 °C/75% RH, 6 months, light-protected	No significant change in assay or release

Criteria follow pharmacopoeial and ICH guidance [21–23,25].

3.11 Consolidated literature benchmarks

Table 15 summarises the benchmarks against which the experimental results for a propranolol–nifedipine bilayer tablet can be judged.

Table 15: Literature benchmarks for sustained-release propranolol HCl and nifedipine tablets

Parameter	Propranolol HCl benchmark	Nifedipine benchmark
Duration of release	12 h (bilayer, 40% HPMC K15M) [11]	Up to 24 h (HPMC K15M/K100) [14]
Optimal polymer	HPMC K15M; Kollidon® SR for zero order [11,13]	HPMC K15M/K100 [14]
Drug content	80.1–81.6 mg per 80 mg tablet [13]; 101.3% [11]	Formulation-specific
Friability	0.72–0.91% [13]; 0.13–0.15% [11]	Formulation-specific
Release mechanism	Higuchi/first order; anomalous transport ($n = 0.622$) [11]	Erosion + diffusion (Hixson–Crowell, Higuchi) [14]
Similarity factor	$f_2 = 60.5$ (F9) [11]	$f_2 = 78.2$ (Batch C) [15]
Critical attribute	Polymer level and gel strength	In-tablet particle size ($D_{90} \approx 150 \mu\text{m}$) [15]
In vivo	—	Bioequivalent to Adalat®-L, fasting and fed [15]

4. LIMITATIONS

This study is based on published data and includes no new laboratory measurements. The comparisons are therefore limited by differences between the source studies in apparatus, media, drug load and analytical methods. The secondary kinetic analysis used only the first four hourly time points available [13]. With so few points, R^2 values are high for several models and do not discriminate well between them, so the fitted parameters should be read as describing early-phase behaviour, not the whole 12 h profile. The proposed bilayer composition has not been manufactured or tested, and its release behaviour, stability and bioavailability must be established experimentally.

5. CONCLUSION

The published evidence shows that SR propranolol HCl tablets are governed mainly by polymer grade and level. An SSG-based IR layer (10% SSG) delivers the loading dose within 10 min, and an SR layer containing 40% HPMC K15M sustains release for 12 h by anomalous, diffusion-dominated transport. Re-analysis of the comparative matrix data showed that raising the polymer level, particularly of Kollidon® SR, moves release from Higuchi-type towards near zero-order kinetics, which suits once-daily dosing. For nifedipine, the in-tablet particle size and the use of solubilising carriers are the critical quality attributes: matching the reference D_{90} of about $150 \mu\text{m}$ gave $f_2 = 78.2$ and bioequivalence. Because the two drugs need opposite release mechanisms, a bilayer design with separately engineered layers is the most rational way to combine them. The proposed composition and characterization framework provide a starting point for experimental development of an SR propranolol–nifedipine bilayer matrix tablet for hypertension.

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