

Immediate-Release Rosuvastatin Calcium and Sustained-Release Gliclazide Bilayer Tablet: Formulation and In Vitro Evaluation

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Abstract: Type 2 diabetes mellitus (T2DM) commonly coexists with dyslipidemia, creating a need to manage glycemic and lipid risk. This study developed a bilayer tablet with an immediate-release (IR) solid-dispersion layer of poorly water-soluble rosuvastatin calcium and a hydrophilic matrix-based sustained-release (SR) layer of gliclazide. Rosuvastatin solid dispersions were prepared by solvent evaporation using polyvinylpyrrolidone K30, polyethylene glycol 6000, or hydroxypropyl methylcellulose (HPMC) E5 at drug-to-carrier ratios of 1:1, 1:2, and 1:3. The selected dispersion used HPMC E5 at 1:3. Gliclazide matrix tablets were prepared with HPMC K4M, K15M, or K100M; the formulation containing 50 mg HPMC K100M was selected. In vitro, the optimized bilayer released 99% of rosuvastatin within 60 min and 90% of gliclazide over 12 h. Gliclazide release was best fitted by the Higuchi model ($R^2 = 0.9973$), while the Korsmeyer-Peppas exponent ($n = 0.8212$) was consistent with anomalous release. Dissolution profiles remained close to initial values after 3 months of accelerated storage at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$. These results support the in-vitro feasibility of the bilayer design; pharmacokinetic, clinical, and longer-term stability conclusions cannot be drawn from these experiments.

Keywords: Rosuvastatin calcium; Gliclazide; solid dispersion; sustained-release matrix; bilayer tablet

1. Introduction

Worldwide, an estimated 589 million adults aged 20-79 were living with diabetes in 2024 [1]. T2DM frequently coexists with dyslipidemia, which is commonly characterized by elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and a greater proportion of small, dense low-density lipoprotein (LDL) particles. Together, these conditions contribute to cardiovascular risk and create a need to manage glycemic and lipid risk.

Rosuvastatin calcium, an HMG-CoA reductase inhibitor used to manage dyslipidemia, and gliclazide, a second-generation sulfonylurea used in T2DM, were selected for this study. The dosage-form design assigns a rapidly dissolving immediate-release layer to rosuvastatin and a sustained-release HPMC matrix to gliclazide. These are formulation objectives; their clinical relevance was not evaluated in this study.

Solid dispersion technology is used to improve dissolution of poorly soluble drugs by dispersing the drug in a hydrophilic carrier [2]. Studies of rosuvastatin have used PVP, PEG, HPMC, and other polymers, including Eudragit EPO dispersions [3], solid-dispersion-loaded orodispersible films [4], fast-dissolving films [5], and solid-dispersion-based multilayer tablets [6]. Solid-dispersion formulations have also been reported for gliclazide [13]. For sustained release, hydrophilic HPMC matrices can modulate gliclazide release through polymer hydration and drug diffusion [7], [8], [9]. Release behavior depends on polymer viscosity and content, matrix porosity, and tablet geometry [7], [8].

Bilayer tablets can combine separate drug layers in a single dosage unit while accommodating different release profiles [10], [11]. Previous work includes rosuvastatin/atenolol bilayer tablets with a solid-dispersion-based immediate-release layer [12] and bilayer systems containing gliclazide [10], [11]. The present study designed and assessed a bilayer combining an immediate-release rosuvastatin solid dispersion with an HPMC-based sustained-release gliclazide layer. The study focused on formulation screening, tablet properties, in-vitro dissolution and release kinetics, and short-term accelerated stability; pharmacokinetics and clinical outcomes were not evaluated.

The present study therefore aimed to design, optimize, and evaluate such a bilayer tablet, encompassing: (i) preparation and screening of Rosuvastatin calcium solid dispersions using three hydrophilic carriers; (ii) development of a directly compressed immediate-release Rosuvastatin layer; (iii) development of an HPMC-based sustained-release Gliclazide matrix layer; (iv) manufacture and physicochemical/dissolution evaluation of the resulting bilayer tablet; (v) analysis of Gliclazide release kinetics and mechanism; and (vi) short-term accelerated stability assessment of the optimized formulation.

2. Materials and Methods

2.1 Materials

Rosuvastatin calcium and gliclazide were obtained as gift samples. Polyvinylpyrrolidone (PVP) K30, polyethylene

glycol (PEG) 6000, and hydroxypropyl methylcellulose (HPMC) E5 were used as solid-dispersion carriers. Lactose DCL21 and microcrystalline cellulose (MCC) PH102 served as diluents for the immediate-release (IR) layer; croscopovidone, croscarmellose sodium, and sodium starch glycolate were used as superdisintegrants. MCC PH101 and lactose monohydrate served as diluents for the sustained-release (SR) layer, with PVP K90 as the granulating binder and HPMC K4M, K15M, and K100M as matrix-forming polymers. Colloidal anhydrous silica and magnesium stearate were used as glidant and lubricant, respectively, and ferric oxide red as the IR-layer colorant. Materials were of pharmaceutical grade and used as received; other reagents were of analytical grade.

2.2 Preformulation and Analytical Method Development

Organoleptic properties, shake-flask solubility in water, methanol, ethanol, and pH 1.2, 6.8, and 7.4 buffers, and melting point by the capillary method were assessed for both drugs. A UV-visible spectrophotometric method was developed for quantification of rosuvastatin (λ_{max} 243 nm) and gliclazide (λ_{max} 226 nm) in methanol. Linearity was assessed over 2-10 $\mu\text{g/mL}$.

2.3 Drug-Excipient Compatibility

Fourier-transform infrared (FTIR) spectra of the pure drugs and their respective formulation blends were recorded using the KBr pellet method from 4000 to 400 cm^{-1} and compared for retention of characteristic absorption bands.

2.4 Preparation of Rosuvastatin Calcium Solid Dispersions

Solid dispersions were prepared by solvent evaporation. Rosuvastatin and the selected carrier (PVP K30, PEG 6000, or HPMC E5) were dissolved separately in methanol, combined with continuous stirring, and evaporated at 40-45 $^{\circ}\text{C}$. The resulting mass was dried in a hot-air oven at 40 $^{\circ}\text{C}$, pulverized, and passed through sieve No. 60. Nine formulations (SD1-SD9) were prepared at drug-to-carrier ratios of 1:1, 1:2, and 1:3 for each carrier and screened for solubility and dissolution relative to the pure drug.

2.5 Formulation of the Immediate-Release Rosuvastatin Layer

The optimized solid dispersion, in an amount equivalent to 10 mg rosuvastatin, was blended with lactose DCL21, MCC PH102, the corresponding superdisintegrant, ferric oxide red, colloidal anhydrous silica, and magnesium stearate. The blend was compressed by direct compression using a single-punch tablet press to a target weight of 100 mg.

2.6 Formulation of the Sustained-Release Gliclazide Matrix Layer

Gliclazide (30 mg/tablet) matrix granules were prepared by wet granulation using MCC PH101 and lactose monohydrate as diluents, aqueous PVP K90 as binder, and HPMC K4M, K15M, or K100M (25, 37.5, or 50 mg/tablet) as the rate-controlling polymer (nine formulations, SR1-SR9). Granules

were dried, sized through sieve No. 20/22, lubricated with colloidal anhydrous silica and magnesium stearate, and compressed to a target weight of 250 mg.

2.7 Manufacture of the Bilayer Tablet

The optimized SR granules (250 mg) were lightly pre-compressed in the die, the optimized IR blend (100 mg) was added, and both layers were compressed together using a bilayer tablet press fitted with 9.5 mm caplet punches to a target total tablet weight of 350 mg.

2.8 Evaluation of Powder Blends and Tablets

Pre-compression flow properties (angle of repose, bulk and tapped density, Carr's index, and Hausner ratio) were determined for all blends and granules. Compressed tablets were assessed for appearance, thickness, weight variation, hardness, friability, drug-content uniformity, and IR-layer disintegration time using standard procedures. Bilayer-specific parameters, including layer separation or delamination, interlayer adhesion, and layer-weight uniformity, were also assessed.

2.9 In Vitro Dissolution Studies

Dissolution testing used USP Apparatus II (paddle, 50 rpm, 37 ± 0.5 $^{\circ}\text{C}$, 900 mL). For the bilayer tablet, 0.1 N HCl (pH 1.2) was used for 2 h, followed by phosphate buffer (pH 6.8) for 10 h. At predetermined sampling times, 5 mL samples were withdrawn, filtered, and replaced with fresh medium. Samples were analyzed spectrophotometrically at the appropriate λ_{max} , and cumulative percentage release was corrected for the volume withdrawn at each sampling point.

2.10 Drug Release Kinetics

Dissolution data for the optimized SR gliclazide layer were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The model with the highest correlation coefficient (R^2) was taken as the best fit. The Korsmeyer-Peppas exponent (n), calculated from the initial approximately 60% of release, was used to interpret the transport mechanism.

2.11 Stability Studies

Optimized bilayer tablets were stored under accelerated conditions (40 ± 2 $^{\circ}\text{C}/75 \pm 5\%$ RH) for 3 months in accordance with ICH Q1A(R2). Physical appearance, weight, hardness, friability, drug content, and dissolution were assessed at 1, 2, and 3 months against initial values.

2.12 Statistical Analysis

Unless otherwise stated, results are expressed as mean $\pm$ standard deviation (SD) of three independent determinations ($n = 3$; $n = 20$ for weight variation).

3. Results and Discussion

3.1 Preformulation and Analytical Method

Both drugs were described as white-to-off-white crystalline powders. Melting-point checks were reported as consistent with literature ranges (rosuvastatin calcium, approximately 159-161 °C; gliclazide, approximately 163-171 °C). The UV calibration curves were linear over 2-10 µg/mL (rosuvastatin: $y = 0.052x + 0.001$, $R^2 = 0.999$; gliclazide: $y =$

$0.045x + 0.001$, $R^2 = 0.999$) and were used for subsequent quantification.

3.2 Drug–Excipient Compatibility

The FTIR spectra of the pure drugs and formulation blends are shown in Figure 1. The main characteristic bands were retained in the rosuvastatin (Figure 1A, B) and gliclazide (Figure 1C, D) blends. Minor intensity changes and broadening were reported, with no major band loss or new bands. These results suggest no major interaction detectable by FTIR under the test conditions.

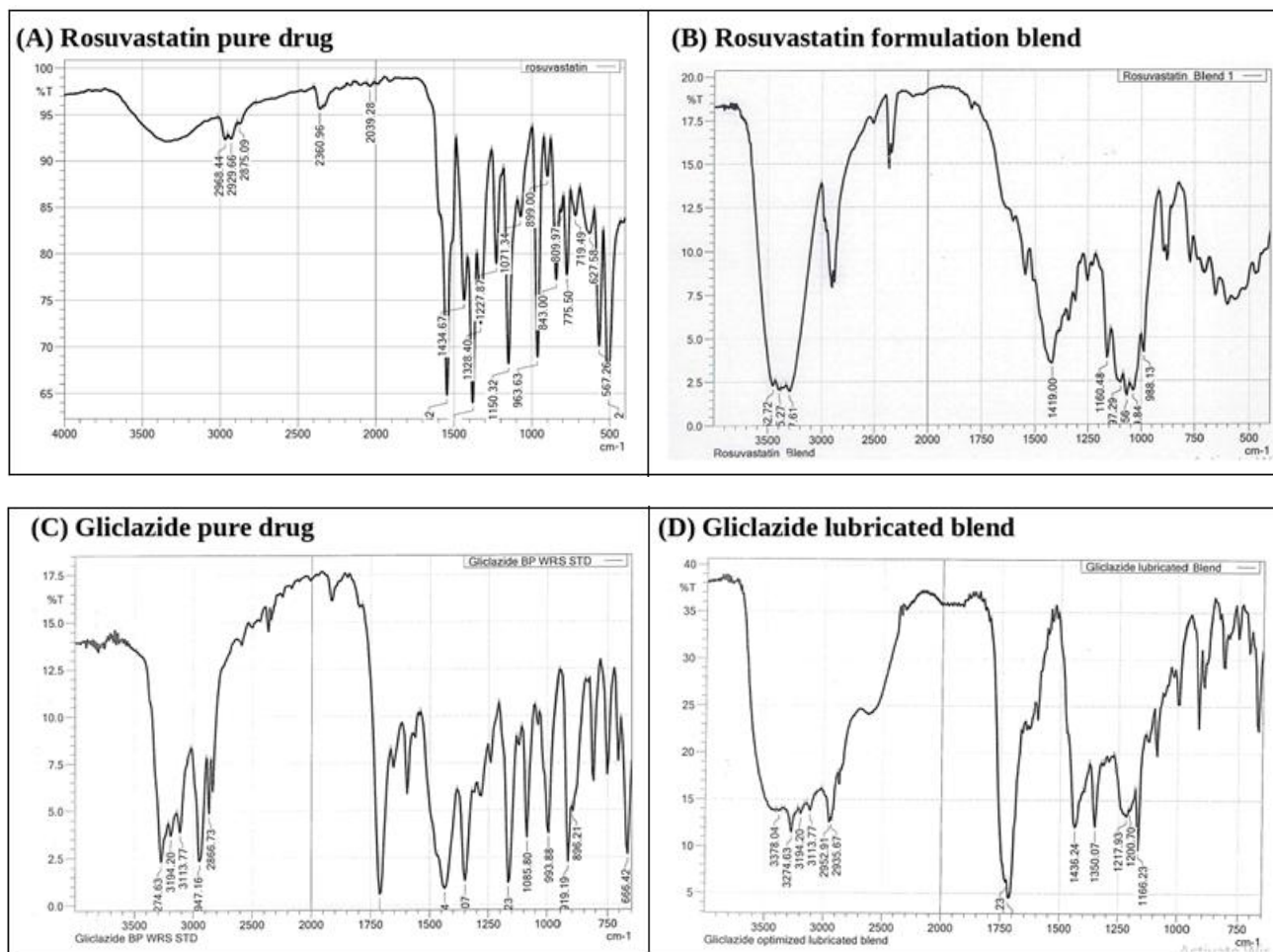


Figure 1: FTIR spectra of (A) pure rosuvastatin, (B) rosuvastatin formulation blend, (C) pure gliclazide, and (D) gliclazide lubricated blend

3.3 Optimization of the Rosuvastatin Solid Dispersion and Immediate-Release Layer

The dissolution profiles showed increasing rosuvastatin release as the carrier proportion increased from 1:1 to 1:3 for all three carriers (Figure 2A). SD9 (rosuvastatin:HPMC E5, 1:3) had the fastest reported profile, with 42% release at 5 min and 99% at 60 min, and was selected as the optimized IR formulation. The IR tablets met the reported limits for weight variation, hardness, and friability; SD9 had a disintegration time of 28 s. Improved wetting and dispersion may contribute to the profile; amorphization was not established by FTIR alone.

3.4. Optimization of the Gliclazide Sustained-Release Matrix Layer

Dissolution of the nine SR formulations showed the expected relationship between HPMC level or viscosity grade and release rate (Figure 2B), consistent with greater gel-layer thickness and diffusional resistance at higher polymer content and viscosity [8]. SR9 (50 mg HPMC K100M) showed the most controlled profile among the screened formulations (17% at 1 h and 90% at 12 h) and was selected. The reported post-compression results indicated increasing hardness and decreasing friability with increasing polymer content.

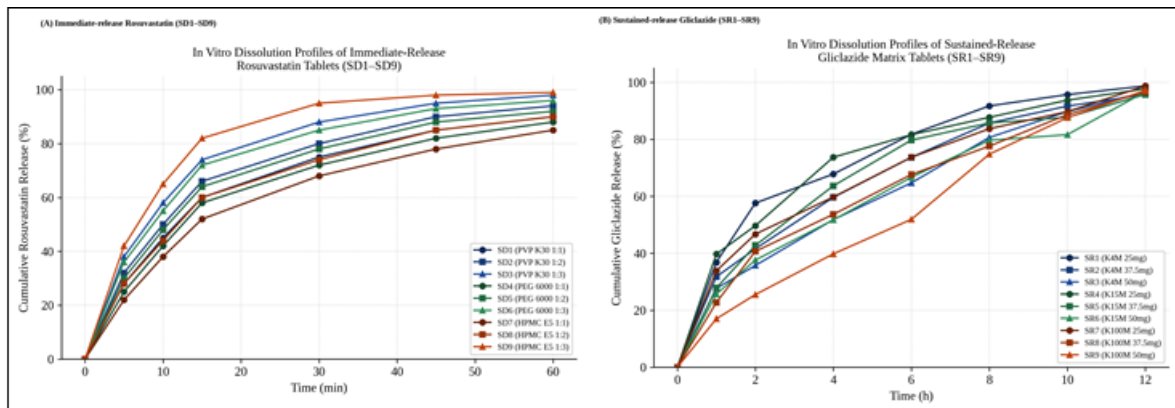


Figure 2: In-vitro dissolution screening of (A) immediate-release rosuvastatin formulations SD1-SD9 and (B) sustained-release gliclazide formulations SR1-SR9

3.5 Evaluation of the Optimized Bilayer Tablet

The optimized bilayer tablet (SD9 IR layer + SR9 SR layer, 350 mg total) was caplet-shaped (14.0×6.0 mm) with distinguishable red (IR) and white-to-off-white (SR) layers. No visible capping, lamination, or layer separation was reported. Key post-compression results are summarized in Table 1.

Table 1: Post-compression evaluation of the optimized bilayer tablet (mean $\pm$ SD; n = 3, except mean tablet weight, n = 20).

Parameter	Result
Thickness (mm)	5.8 ± 0.10
Hardness (kg/cm ²)	6.5 ± 0.20
Friability (%)	0.62 ± 0.04
Mean tablet weight (mg)	350 ± 3.0

Rosuvastatin content (%)	99.2 ± 0.65
Gliclazide content (%)	99.0 ± 0.71
IR-layer disintegration time (s)	30 ± 3
Layer separation	None observed
Interlayer adhesion	Satisfactory

The optimized bilayer showed rapid rosuvastatin release from the IR layer (85% at 15 min, 99% at 60 min, and approximately 100% by 2 h) and gradual gliclazide release from the SR layer (14% at 1 h, 62% at 6 h, and 90% at 12 h; Figure 3). The profiles indicate that both release objectives were observed in the integrated dosage form. A formal comparison with the corresponding single-layer tablets would be needed to establish whether one layer affects release from the other. A previously reported rosuvastatin/atenolol bilayer achieved 92.3% rosuvastatin release within 60 min [12].

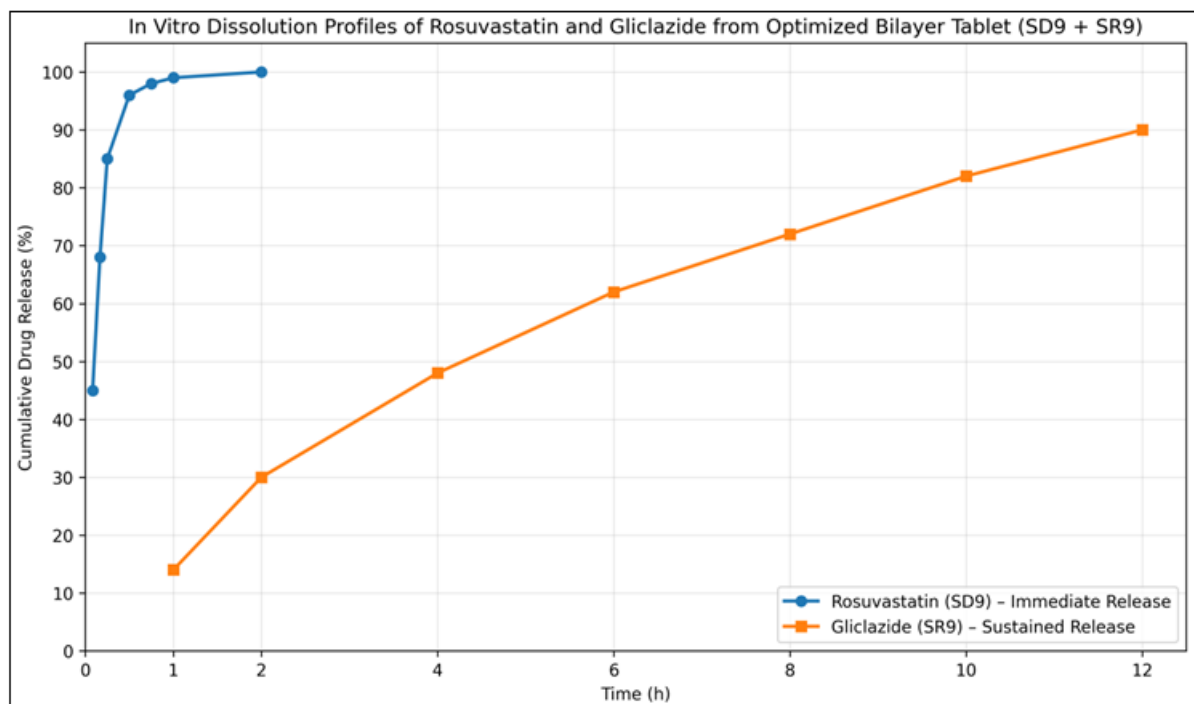


Figure 3: In-vitro dissolution profiles of rosuvastatin (immediate-release layer, SD9) and gliclazide (sustained-release layer, SR9) from the optimized bilayer tablet

3.6. Drug Release Kinetics

Gliclazide release from the optimized SR layer was fitted to four kinetic models (Figure 4, Table 2). The Higuchi model gave the highest R^2 (0.9973), followed by first-order (0.9841), Korsmeyer-Peppas (0.9818), and zero-order (0.9603) models. The fitted Korsmeyer-Peppas exponent ($n = 0.8212$) was consistent with anomalous (non-Fickian) release under the tested conditions, suggesting contributions from diffusion and polymer relaxation or erosion.

Table 2: Drug-release kinetic models for the optimized gliclazide SR9 layer

Model	Key parameter	R^2
Zero-order	$K_0 = 6.635\%/\text{h}$	0.9603
First-order	$K_1 = 0.185\text{ h}^{-1}$	0.9841
Higuchi	$K_H = 30.495\%/\text{h}^{1/2}$	0.9973
Korsmeyer-Peppas	$n = 0.8212$	0.9818

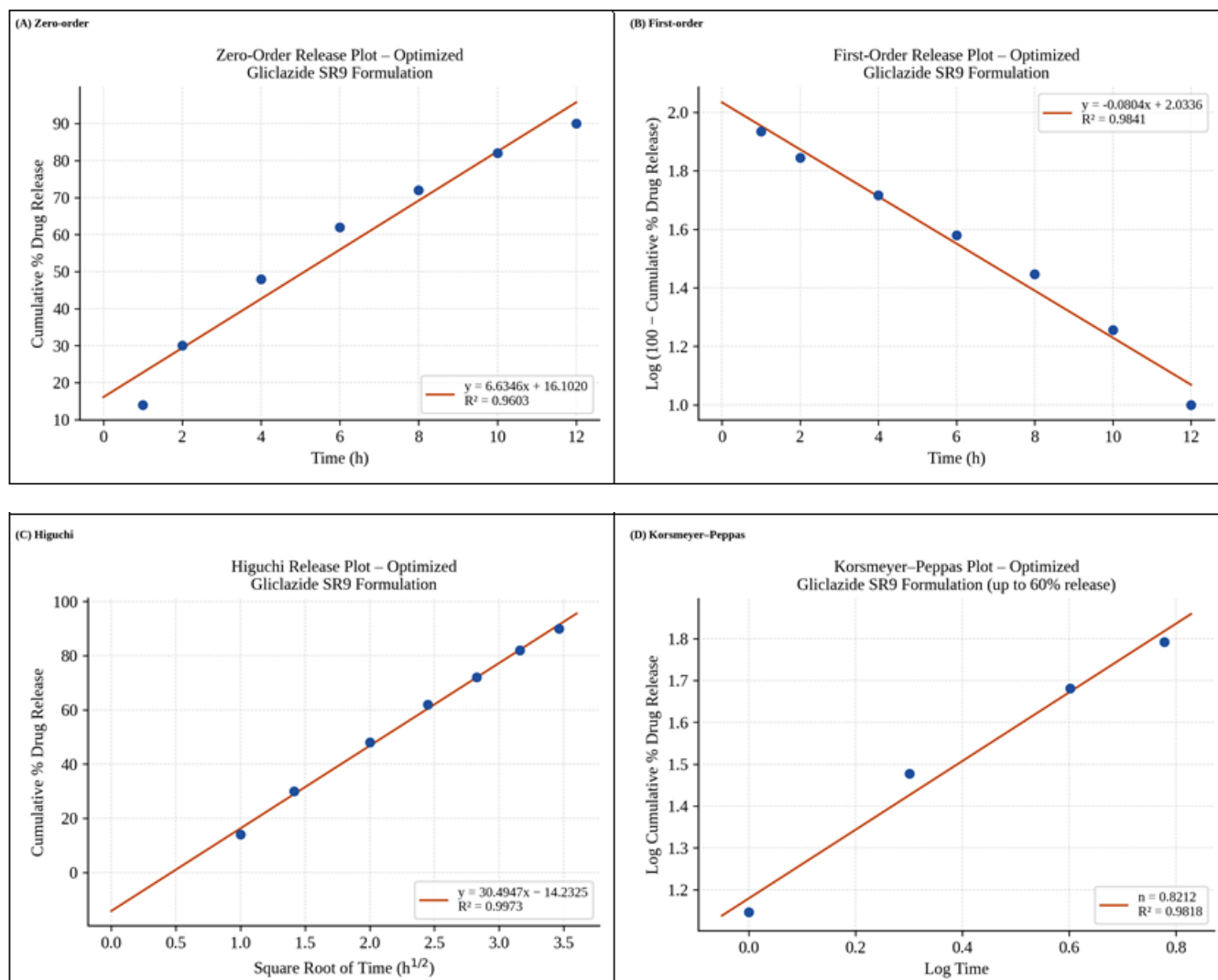


Figure 4: Drug-release kinetic model fits for the optimized gliclazide SR9 layer: (A) zero-order, (B) first-order, (C) Higuchi, and (D) Korsmeyer-Peppas plots

3.7 Stability of the Optimized Bilayer Tablet

During accelerated storage ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$, 3 months), dissolution profiles remained close to their initial values (rosuvastatin: 98.3% at 60 min after 3 months versus

99.0% initially; gliclazide: 90.8% at 12 h versus 90.0% initially; Figure 5). No visible physical degradation of either layer was reported. These observations support short-term in-vitro stability under the tested conditions; longer-term and real-time data are required to establish shelf life

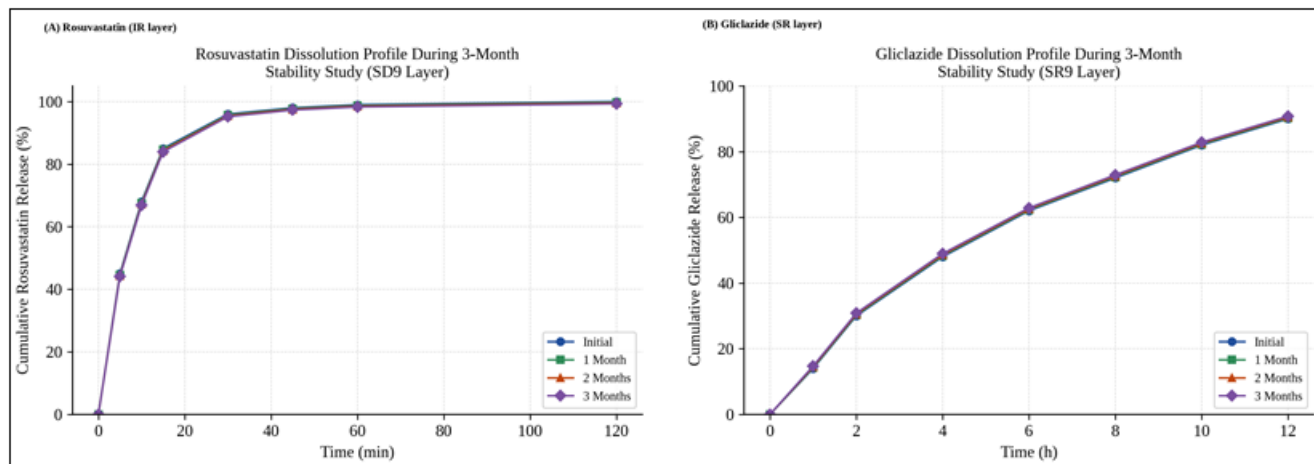


Figure 5: Dissolution profiles of (A) rosuvastatin and (B) gliclazide from the optimized bilayer tablet at initial, 1-, 2-, and 3-month time points during accelerated stability testing ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$)

4. Conclusions

A bilayer tablet combining a solid-dispersion-based immediate-release rosuvastatin calcium layer with an HPMC matrix-based sustained-release gliclazide layer was designed and evaluated. The selected rosuvastatin dispersion used HPMC E5 at a 1:3 drug-to-carrier ratio, while the selected gliclazide matrix contained 50 mg HPMC K100M. In vitro, the optimized tablet released 99% of rosuvastatin within 60 min and 90% of gliclazide within 12 h. Higuchi fitting gave the highest R^2 for gliclazide release, and the Korsmeyer-Peppas exponent was consistent with anomalous release under the tested conditions. No layer separation was reported, and dissolution profiles remained close to initial values after 3 months of accelerated storage. The findings support in-vitro feasibility only; pharmacokinetic, clinical, and definitive shelf-life conclusions require further study.

Acknowledgments

The authors thank Sai Mirra Innopharm Pvt. Ltd., India, for resources, facilities, and technical assistance. They also acknowledge the management and principal of Pallavan Pharmacy College for institutional support and encouragement.

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