

Design and evaluation of bilayer sildenafil sublingual tablets combining fast-dispersible and mucoadhesive layers

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ABSTRACT

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This study focused on the development and evaluation of a bilayer sildenafil tablet for sublingual administration. The aim was to design a sublingual tablet that provides both rapid onset and sustained drug delivery for treating erectile dysfunction. Bilayer tablets (total weight approximately 300 mg, containing 40 mg sildenafil citrate) were prepared by direct compression. The upper layer (200 mg) was designed as a fast-dispersible layer and a lower layer was a mucoadhesive layer (100 mg). The physical properties, *in vitro* drug release, and mucoadhesion of the formulations were evaluated. Mucoadhesion was tested on mucin-coated substrates using a modified falling liquid technique. The fast-dispersible layer disintegrated in 3.30 min. Among the evaluated polymers, HPMC showed the best adhesion and gel integrity for over 120 min compared with HPC-SL and Carbopol 940. Increasing concentration and the molecular weight of HPMC enhanced the structural durability of the mucoadhesive gel mass and effectively delayed drug release. The bilayer tablet design successfully pairs a quick-acting layer with a slow-releasing, adhesive layer. Based on these results, using an HPMC matrix is a practical approach to control sublingual sildenafil release for erectile dysfunction management.

Keywords: sildenafil; fast-dispersible; mucoadhesive property; sublingual tablet; erectile dysfunction

1. INTRODUCTION

Erectile dysfunction (ED) is a common condition affecting 322 million men worldwide (Sarnoski et al., 2026). The risk of developing ED increases as men age, especially for those with health issues like diabetes or cardiovascular disease. Oral phosphodiesterase-5 inhibitors, mainly sildenafil citrate, are widely used as first-line therapy (Goldstein et al., 1998). These drugs help achieve an erection by boosting nitric oxide levels, which relaxes blood vessels during sexual stimulation. However, conventional oral sildenafil formulations are limited by

low absolute bioavailability due to extensive first-pass hepatic metabolism, a slow onset of action, and important interactions with organic nitrates, which contraindicate their use in patients with cardiovascular risk profiles (Dighe & Tank, 2019).

To overcome these problems, several oral delivery systems have been investigated, including orodispersible films (Radicioni et al., 2017), sublingual tablets (Sheu et al., 2016), and orodispersible tablets (Deveci et al., 2004). These systems were designed to disintegrate in the oral cavity. This allowed the drug release to be absorbed while bypassing hepatic first-pass metabolism. Thus, the drug

bioavailability was increased resulting fast therapeutic onset. Sildenafil has been incorporated into mucoadhesive systems, such as vaginal thermosensitive gels (Soliman et al., 2017) and buccal-adhesive nanofibers (Alamer et al., 2024) to prolong mucosal residence and enhance therapeutic effect.

Despite these advantages, standard single-layer tablets cannot easily provide both a fast onset and a long-lasting effect. Orodispersible systems may disintegrate too quickly to sustain drug plasma concentrations. On the other hand, mucoadhesive systems might retard the drug and the initial effects, which is a major problem for an “on-demand” ED treatment. A bilayer tablet is a design to address this problem. The first layer quickly releases a loading dose of the drug, while the second layer sustains drug release by forming a swelling, adhesive matrix (Abbasi et al., 2016; Shirsand et al., 2012). This design is suited to the oral cavity, where saliva usually washes formulations away quickly. By combining both release patterns within one tablet, the bilayer offers a much more effective treatment. However, sublingual drug delivery remains underexplored for sildenafil, despite offering a direct route into systemic circulation that bypasses first-pass metabolism and can accelerate the onset of action. This study addresses that gap directly. A single bilayer tablet designed for sublingual placement separates the two-release method into distinct layers. It delivers both an immediate and a sustained release profile in one dosage form tailored to how sildenafil is used clinically.

This study therefore aimed to develop and evaluate a new bilayer sublingual tablet for sildenafil citrate. The 300-mg tablets (containing 40 mg of the active drug) were prepared by direct compression. The upper, fast-dispersible layer was designed to disintegrate quickly for fast absorption in the sublingual area. For the lower mucoadhesive layer, the hydrophilic polymers were incorporated to prolong mucosal contact and sustain drug release. The effects of mucoadhesive polymer type, concentration, and molecular weight on physical properties, *ex vivo* mucoadhesion (assessed by a modified falling liquid technique), and *in vitro* drug release were investigated.

2. MATERIALS AND METHODS

2.1 Materials

Sildenafil citrate USP standard was obtained from Rakshit Drugs Pvt. Ltd. (Sangareddy, Telangana, India). Hydroxypropyl methylcellulose (HPMC), in grades K100LV, K15M, and K100M, was supplied by Colorcon Asia Pacific Pte. Ltd. (Merchant Square, Singapore). Hydroxypropyl cellulose-SL (HPC-SL) was procured from Nippon Soda Co. Ltd. (Tokyo, Japan). Carbomer 940 (Carbopol®) and talcum powder were sourced from Hong Huat Company Ltd. (Bangkok, Thailand). Crospovidone (Kollidon® CL, BASF, Ludwigshafen, Germany) was kindly provided as a gift sample by Jebsen & Jessen Technology (Bangkok, Thailand). Mannitol (Univar®) was purchased from Ajax Finechem Pty Ltd. (Auckland, New Zealand). Microcrystalline cellulose (Avicel® PH-101) was obtained from FMC BioPolymer (Philadelphia, USA). Lactose monohydrate (FlowLac® 100) was supplied by Meggle Pharma (Wasserburg am Inn, Germany). All chemicals and excipients were of pharmaceutical grade.

2.2 Tablet preparation and bilayer tablet formulation

Bilayer tablets, each comprising a fast-dispersible layer and a mucoadhesive layer, were prepared by direct compression using a manual hydraulic press (Specac Ltd., Orpington, Kent, United Kingdom). The fast-dispersible layer (200 mg) was designed for rapid disintegration in the oral cavity to provide a quick-release component, while the mucoadhesive layer (100 mg) was formulated to achieve prolonged contact with the sublingual mucosa for sustained drug delivery.

The fast-dispersible layer mixture consisted of sildenafil citrate (20 mg), microcrystalline cellulose (25 mg), lactose monohydrate (48 mg), polyethylene glycol 4000 (2 mg), mannitol (100 mg), and crospovidone (5 mg), giving a total layer weight of 200 mg. The fast-dispersible upper layer composition was kept constant across all formulations. The mucoadhesive layer compositions varied across formulations according to the experimental design and are detailed in Table 1. Bilayer tablets were assembled by sequential compression. First, 100 mg of the mucoadhesive powder was loaded into a die fitted with 9.53 mm flat-faced punches. This powder was lightly pre-compacted to form a stable base layer. Next, 200 mg of the fast-dispersible mixture was carefully poured on top of this base. The entire two-layer assembly was then compressed using a force of 5 kN for 30 s.

Table 1. Composition of the mucoadhesive layer

Ingredients (mg)	F0	F1	F2	F3	F4	F5	F6	F7
Sildenafil	20	20	20	20	20	20	20	20
HPMC K100LV	-	20	-	-	-	-	10	30
HPMC K15M	-	-	-	-	20	-	-	-
HPMC K100M	-	-	-	-	-	20	-	-
HPC-SL	-	-	20	-	-	-	-	-
Carbopol 940	-	-	-	20	-	-	-	-
Lactose	68	48	48	48	48	48	58	38
Microcrystalline cellulose	10	10	10	10	10	10	10	10
Talcum	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1

2.3 Physical properties evaluation

The physical characteristics of the bilayer sildenafil tablets were evaluated in terms of weight variation, thickness, and hardness. Weight uniformity was determined by individually weighing 20 tablets from each batch using a calibrated analytical balance. Tablet thickness was measured for 10 randomly selected tablets from each formulation using a digital micrometer (Mitutoyo Corporation, Kawasaki, Japan). Hardness was assessed using a digital tablet hardness tester (TBH 125; Erweka GmbH, Langen, Germany), whereby 10 tablets per batch were subjected to diametral compression until fracture.

2.4 Mucoadhesive properties evaluation

The mucoadhesive characteristics of the bilayer tablets were evaluated using a modified falling liquid technique, adapted from Wattanaphraya et al. (2021). Glass slides were prepared by wrapping with cellophane membrane and coating with a 4% (w/v) mucin solution to simulate the biological mucous membrane. The mucin-coated

substrates were then incubated in a desiccator for 15 min at ambient conditions to permit equilibration and optimize polymer–mucin interactions prior to testing. Figure 1 shows the mucoadhesion testing apparatus using the falling liquid technique. Each mucoadhesive tablet layer ($n = 6$) was gently placed onto the mucin-coated surface. The entire assembly was then mounted on an adjustable stand at a 45° angle. Artificial saliva

(phosphate-buffered saline, pH 6.8) was pre-warmed to $37 \pm 0.5^\circ\text{C}$ to mimic normal oral temperature. This fluid was continuously delivered onto the tablet surface at a controlled flow rate of $2.0 \pm 0.1\text{ mL/min}$ using a calibrated peristaltic pump. The adhesion of the tablets was monitored visually at regular intervals. Finally, the total retention time, along with any signs of detachment or matrix erosion, was carefully recorded for each formulation.

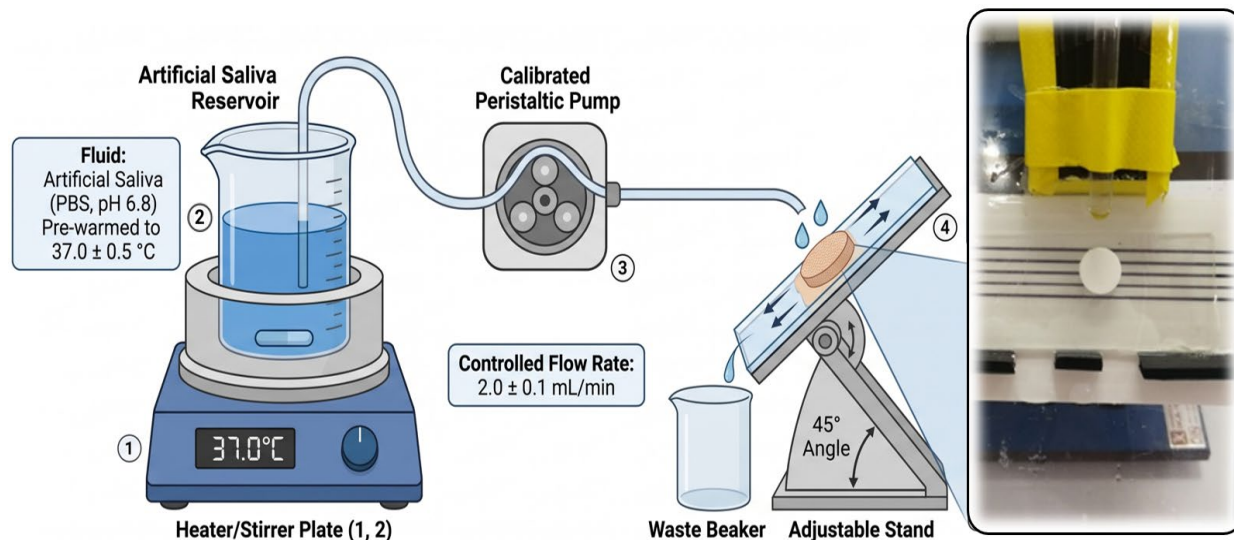


Figure 1. Schematic illustration of mucoadhesion testing apparatus by falling liquid technique

2.5 *In vitro* drug release studies

Drug release profile of the bilayer sildenafil tablets were conducted using a modified dissolution method adapted from Trirattanapintusorn et al. (2019) to approximate the low-volume, low-agitation environment of the sublingual cavity. Tablets ($n = 3$) were placed individually in a Petri dish containing 20 mL of reverse osmosis water as the dissolution medium. Water was selected as the medium for this assay rather than simulated saliva to provide a controlled baseline for matrix diffusion without the complex ionic interactions of salivary buffers. The medium was maintained at 37°C and agitated at 10 rpm using an orbital shaker to simulate the hydrodynamic conditions of the oral cavity. At predetermined time intervals (5, 15, 30, 60, and 120 min), 5 mL aliquots were withdrawn and immediately replaced with an equal volume of fresh pre-warmed medium. Considering that the saturation solubility of sildenafil citrate in water is 4 mg/mL at 37°C (Jung et al., 2011). This continuous 5 mL replacement at frequent initial intervals successfully maintained a pseudo-sink state by preventing local saturation and preserving the concentration gradient required for steady drug diffusion. Withdrawn samples were filtered through a $0.45\text{ }\mu\text{m}$ membrane filter prior to analysis to remove any particulate matter. The absorbance of the collected samples was measured at 293 nm using a UV-Vis spectrophotometer (UV-1800; Shimadzu Corporation, Kyoto, Japan). Drug concentrations and cumulative drug release were calculated for each time point.

2.6 Statistical analysis

Statistical analysis was conducted using a one-way analysis of variance (ANOVA) followed by Tukey's post hoc test to evaluate multiple comparisons among the different formulations. An independent sample *t*-test was used where appropriate for specific pairwise comparisons. A *p*-value of less than 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Design of bilayer sildenafil sublingual tablets combining fast-dispersible and mucoadhesive layers

The bilayer sildenafil citrate tablets in this study combined two separate layers into a single 300-mg tablet (containing 40 mg of active drug). Because sublingual administration bypasses first-pass hepatic metabolism, this lower dose is sufficient to achieve a systemic exposure comparable to standard 25–100 mg oral tablets (Deveci et al., 2004). This bilayer design aimed to provide both a fast onset of action and prolonged sublingual retention (Figure 2), with the total drug payload split equally (20 mg each) between the layers. The 200-mg upper layer was designed as the fast-dispersible layer. It disintegrated rapidly—in an average of 3.30 ± 0.42 min—when exposed to a small volume of saliva. This allowed the initial dose to release immediately for quick absorption. In contrast, the 100-mg lower layer contained mucoadhesive polymers. Once this layer contacted the sublingual mucosa, it hydrated to form a cohesive gel. This gel attached to the sublingual tissue and slowly released the remaining drug.

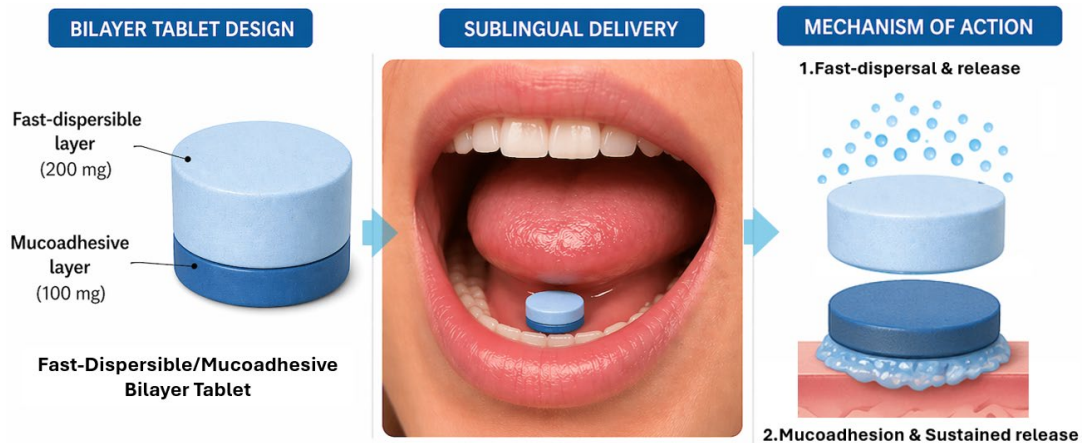


Figure 2. Schematic of the fast-dispersible/mucoadhesive bilayer tablet design and sublingual delivery mechanism

3.2 Physical properties

Table 2 summarizes the physical properties of the bilayer tablets. All formulation batches showed excellent uniformity in both weight (298.80–301.32 mg) and thickness (3.47–3.60 mm), confirming the powder blends were suitable for direct compression. Hardness values ranged from 9.47 ± 4.18 N (F0, no polymer) to 19.61 ± 2.35 N (F7, 30 mg HPMC K100LV), reflecting the influence of polymer type and concentration on interparticulate bonding. The formulations

containing HPMC exhibited higher crushing strength compared to HPC-SL or Carbopol 940. Increasing concentration of HPMC K100LV, particularly in F7, clearly increased the tablet's hardness. This observation aligns with existing literature (Mawla et al., 2023), which links higher polymer concentrations to greater plastic deformation. Thus, the higher polymer content provides a greater matrix of deformable material that consolidates more effectively during direct compression.

Table 2. Physical properties of bilayer sildenafil tablets containing different mucoadhesive polymers and concentrations

Formulation	Mucoadhesive polymer	Weight (mg)	Thickness (mm)	Hardness (N)
F0	No polymer	301.32 ± 0.67	3.55 ± 0.05	9.47 ± 4.18
F1	HPMC K100LV, 20 mg	299.18 ± 0.98	3.56 ± 0.03	12.75 ± 3.43
F2	HPC-SL, 20 mg	299.12 ± 1.13	3.56 ± 0.11	11.28 ± 2.35
F3	Carbopol 940, 20 mg	300.48 ± 1.22	3.54 ± 0.07	11.59 ± 2.64
F4	HPMC K15M, 20 mg	298.80 ± 1.02	3.60 ± 0.06	13.73 ± 2.06
F5	HPMC K100M, 20 mg	299.69 ± 1.93	3.53 ± 0.07	11.77 ± 2.55
F6	HPMC K100LV, 10 mg	299.00 ± 1.19	3.60 ± 0.08	11.36 ± 2.84
F7	HPMC K100LV, 30 mg	299.05 ± 1.60	3.47 ± 0.04	19.61 ± 2.35^a

Note: ^a $p < 0.05$ compared with F0 (one-way ANOVA)

3.3 Effect of polymer type on mucoadhesive properties and drug release

To evaluate the influence of mucoadhesive polymer type on tablet performance, formulations were developed using HPMC K100LV (F1), HPC-SL (F2), and Carbopol 940 (F3). These polymers are commonly used in mucosal delivery because they are biocompatible, form films or gels upon hydration, and exhibit good swelling and mucoadhesive behavior (Luca et al., 2025; Phan et al., 2020; Wattanaphraya et al., 2021).

Results from the modified falling liquid test showed that mucoadhesive properties depended on the polymer type (Figure 3). The inset images above each bar show the macroscopic appearance of the mucoadhesive layer after the test, illustrating differences in swelling, erosion, and gel coherence. The formulation containing HPMC K100LV (F1) provided the strongest and longest-lasting adhesion. In fact, these tablets stayed attached to the mucin surface for the entire 120-min observation period. As seen in Figure 3, the HPMC rapidly hydrated into a thick, cohesive gel. While the matrix did gradually erode under the continuous flow of

artificial saliva—leaving only a small remnant by the end of the test—it never lost its grip on the substrate. In contrast, the other two polymers did not perform as well. The HPC-SL tablets (F2) washed away and detached after about 60 min. Interestingly, while the Carbopol 940 tablets (F3) quickly formed a strong gel matrix, they lost their adhesion and completely detached within just 30 min. This macroscopic performance is likely linked to the distinct chemical structures of the polymers. Based on previous studies, the abundance of hydroxyl groups in HPMC is thought to facilitate rapid water absorption, allowing the polymer chains to uncoil and form a dense network of hydrogen bonds with the mucin glycoproteins (Mady et al., 2024). HPC-SL has a different substitution pattern that limits its water uptake and chain entanglement compared to HPMC (Sarode et al., 2013), which explains its lower adhesion time. Carbopol 940 is highly pH-sensitive and typically requires a higher pH environment to achieve its strongest mucoadhesive gelation (Sulaiman et al., 2018). In our simulated oral conditions (pH 6.8), it simply could not swell properly to maintain long-term adhesion.

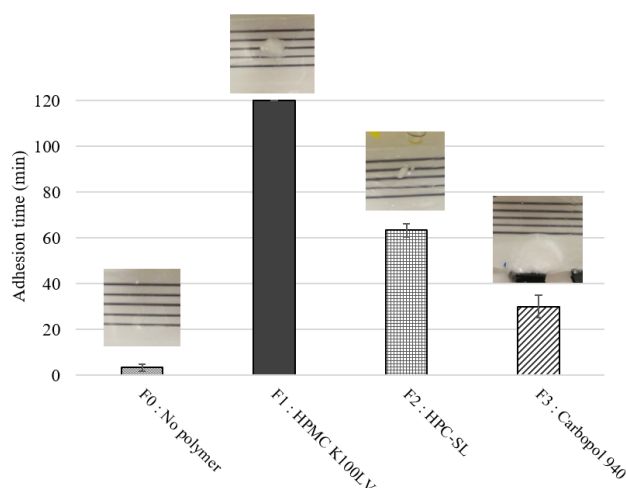


Figure 3. Mucoadhesion time of bilayer sildenafil tablets containing different mucoadhesive polymers

Regarding *in vitro* drug release (Figure 4), the non-polymer formulation (F0) exhibited rapid dissolution. The fast-dispersible layer released nearly all of its 20 mg sildenafil dose within the first 20 min. Meanwhile, the remaining 20 mg in the mucoadhesive layer released gradually over 120 min. The inclusion of matrix-forming polymers (HPMC and HPC-SL) significantly prolonged sildenafil release, reaching about 80% cumulative release by 120 min. This sustained release profile is governed by the gradual hydration and relaxation of the polymer gel layer, which dictates how quickly the dissolved drug can diffuse out of the matrix (Kriangkrai et al., 2024). On the other hand, Carbopol 940 clearly exhibited drug release retardation (only 25% of the sildenafil released at 120 min). This happens because Carbopol forms a dense gel barrier, which limits water penetration and drug diffusion (Ambarish et al., 2024).

Collectively, these findings demonstrated that HPMC was the most suitable mucoadhesive polymer for the bilayer tablet system. It provided a good balance: it prolonged mucosal retention for over 120 min while still allowing the drug to release at a controlled, steady rate. In contrast, HPC-SL quickly eroded under the simulated saliva flow, meaning it would not stay in the mouth long enough to provide a sustained therapeutic effect. Carbopol 940 exhibited low mucosal retention time under salivary conditions, and its tight gel trapped too much of the drug inside, making it impractical for this specific delivery route. Therefore, HPMC was selected as the optimal polymer matrix for further formulation development. Subsequent investigations focused on adjusting its concentration and molecular weight to tune both the adhesion strength and the drug release profile.

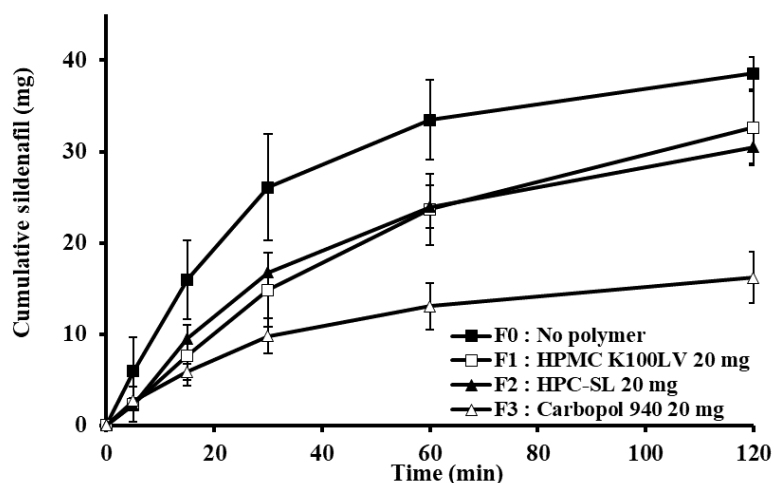


Figure 4. *In vitro* drug release profiles of bilayer sildenafil tablets incorporating different mucoadhesive polymers (20 mg)

The sublingual sildenafil tablet was reported in the previous studies. Deveci et al. (2004) showed that 20 mg sublingual sildenafil reduced onset to 15.5 min but the effect lasted only around 40 min on average. Sheu et al. (2016) developed direct-compression sublingual tablets using superdisintegrants such as Ac-Di-Sol and Kollidon

CL, achieving disintegration times of 0–7 min *in vitro* and an onset of 1.9 min in rabbits.

The bilayer tablet developed here addresses both limitations. The fast-dispersible upper layer disintegrated in 3.30 min and released nearly 100% of its 20 mg. This was comparable to earlier sublingual formulations. The

mucoadhesive layer adhered for over 120 min, resisting salivary washout and sustaining release of the remaining 20 mg throughout.

3.4 Effect of HPMC K100LV concentration on mucoadhesive properties and drug release

Increasing the concentration of HPMC K100LV significantly enhanced both tablet adhesion and resistance to erosion

(Figure 5). While a 10 mg polymer load (F6) eroded completely by 60 min, higher concentrations (20 mg and 30 mg) sustained mucosal attachment for over 120 min. This concentration-dependent improvement occurred because an increased availability of polymer chains allows the matrix to continuously swell and interpenetrate more deeply into the mucosal layer, forming a more robust and long-lasting adhesive bond (Mady et al., 2024).

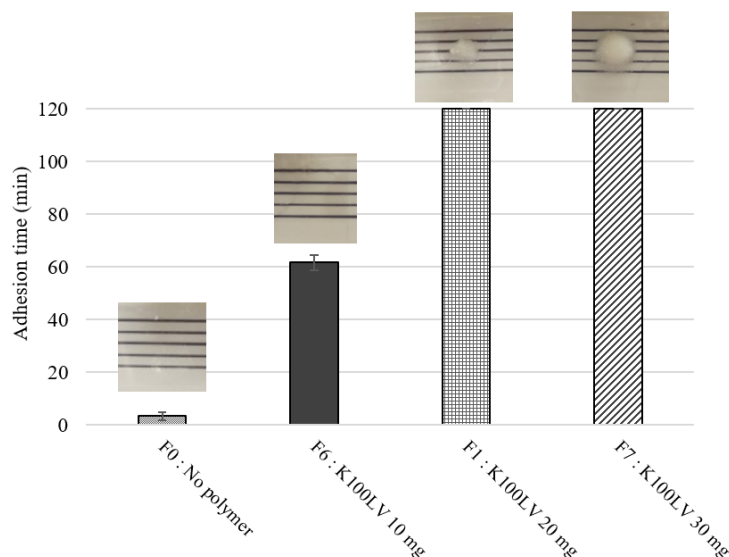


Figure 5. Effect of HPMC K100LV concentration on the mucoadhesion time of bilayer sildenafil tablets

Drug release profiles (Figure 6) further supported this concentration-dependent behavior. Incorporating the mucoadhesive polymer delayed the sildenafil release. The 10 mg of HPMC K100LV (F6) provided noticeably lower drug release than the non-polymer formulation (F0). However, the cumulative drug release reached almost 100% of drug content by 120 min. As shown in the release profiles (Figure 6), higher HPMC K100LV concentrations effectively retarded sildenafil release. As the polymer concentration increased, the hydrated matrix became more viscous and tortuous. This created a thicker gel

barrier that reduced solvent penetration and slowed the diffusion of the dissolved drug out of the matrix (Kavanagh & Corrigan, 2004; Kriangkrai et al., 2024). However, drug release from formulations containing 20 mg (F1) and 30 mg (F7) HPMC K100LV was not significantly different ($p > 0.05$). This suggested that there was a threshold effect: further increases in polymer content do not proportionally retard drug release. Based on these findings, 20 mg of HPMC K100LV was selected as an optimal concentration to maintain adhesion while delivering the sustained release profile.

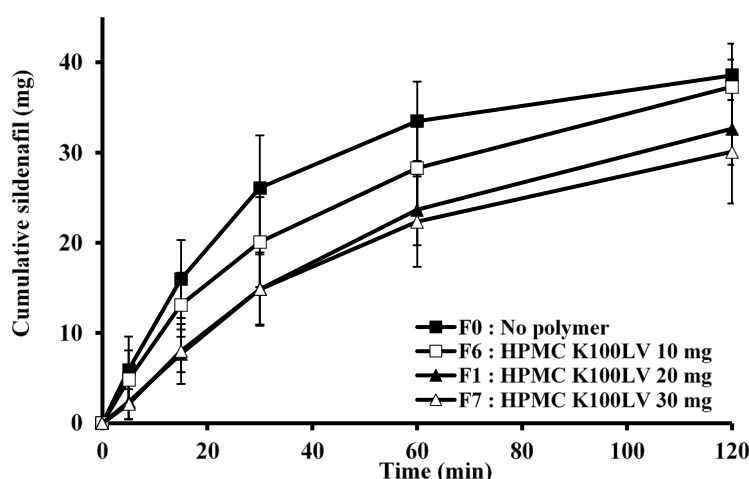


Figure 6. *In vitro* drug release profiles illustrating the effect of HPMC K100LV concentration (10 mg, 20 mg, and 30 mg)

3.5 Effect of HPMC molecular weight on mucoadhesive properties and drug release

To evaluate the effect of polymer chain length on mucoadhesive properties and drug release, the molecular weight (MW) of HPMC was varied using grades K100LV, K15M, and K100M. The MW of HPMC directly influenced gel cohesion and resistance to salivary erosion. While the polymer-free control (F0) detached within 5 min, all HPMC grades maintained firm adhesion for 120 min (Figure 7). Notably, higher MW grades (K15M

and K100M) produced larger residual tablet volumes, indicating superior structural integrity. The longer polymer chains in these high-MW grades facilitated greater chain entanglement and more extensive hydrogen bonding with mucin glycoproteins, creating a denser, tougher hydrated network that better resists salivary wash-off (Kavanagh & Corrigan, 2004; Mady et al., 2024). These results agree with the principle that HPMC grades exceeding ~100,000 Da provide a good balance of gel strength and mucoadhesive properties (Park et al., 2022).

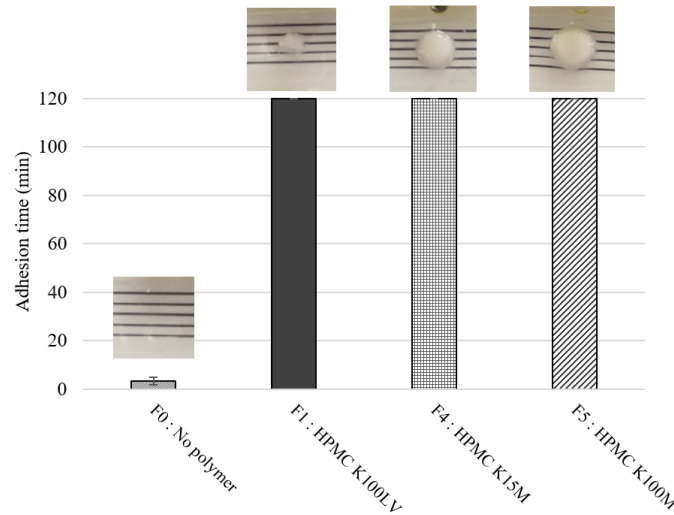


Figure 7. Effect of HPMC molecular weight on the mucoadhesion time of bilayer sildenafil tablets

In vitro drug release profiles also reflected this influence of MW on matrix behavior (Figure 8). The low and intermediate molecular weight HPMC performed similarly, the highest MW grade (K100M) inducing a pronounced retardation of drug release. This relationship between molecular weight and release rate is driven by polymer chain dynamics. Upon hydration, the substantially longer polymer chains of the K100M grade undergo more extensive entanglement, resulting in a denser, highly cohesive microenvironment. This aligns with previous

studies showing that increasing MW from K100LV to K4M/K15M/K100M grades reduced drug release rate; K100M provided the most sustained profile at a fixed polymer concentration (Phaechamud & Darunkaisorn, 2016). These findings support the concept that using a high-MW polymer allows for strong, prolonged mucosal attachment while creating a highly viscous environment that extends the drug's release over time (Park et al., 2022).

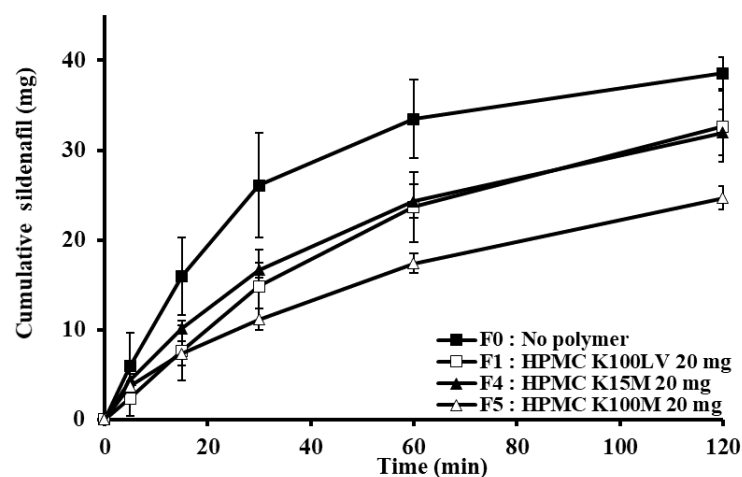


Figure 8. *In vitro* drug release profiles illustrating the effect of HPMC molecular weight (K100LV, K15M, and K100M at 20 mg)

This study has several limitations. The modified low-volume dissolution and falling liquid models were useful for characterizing the bilayer tablet, but the synthetic mucin-coated membrane used for mucoadhesion testing does not fully replicate living mucosal tissue. It lacks cellular epithelial layers, enzymatic activity, and continuous mucus turnover, so the adhesion results should be treated as screening data rather than a direct prediction of *in vivo* behavior. Permeation kinetics across a biological barrier were also not measured. The flux of sildenafil through excised porcine sublingual mucosa using Franz diffusion cells remains to be quantified. *In vivo* pharmacokinetic data are also absent, meaning the relationship between prolonged sublingual mucoadhesion and systemic bioavailability remains to be confirmed.

4. CONCLUSION

This study successfully developed a bilayer sublingual tablet for sildenafil, addressing a largely unexplored delivery route that bypasses first-pass metabolism and suits the on-demand nature of ED treatment. By combining a fast-dispersible upper layer with a mucoadhesive lower layer, this system provides both rapid disintegration and prolonged oromucosal retention in the sublingual space. The fast-dispersible upper layer disintegrated within an average of 3.30 min, while the lower mucoadhesive layer formed a gel matrix for sustained release at the sublingual mucosa. Systematic evaluation showed that the specific type, concentration, and molecular weight of the mucoadhesive polymer critically dictate the structural integrity and drug release of the system. HPMC K100LV exhibited superior performance in both adhesive durability and controlled drug diffusion compared to HPC-SL and Carbopol 940. Increasing HPMC concentration (up to 30 mg) and molecular weight (up to K100M) significantly enhanced mucoadhesive durability and progressively retarded drug release, confirming the tunability of the hydrated matrix for sustained delivery. This bilayer sublingual tablet showed good *in vitro* performance in both retention and controlled drug release and offers a promising formulation strategy for the sublingual route in erectile dysfunction management. However, this study is based on *in vitro* drug release and *ex vivo* mucoadhesion evaluations. While these results support the feasibility of the bilayer design, transmucosal permeation data and *in vivo* pharmacokinetic evidence need to be investigated. Further permeation assays and *in vivo* studies are needed to confirm the actual sublingual bioavailability, systemic absorption, and clinical efficacy of this system.

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AUTHOR CONTRIBUTIONS

Conceptualization, W.K. and S.S.; methodology, W.K., P.K., S.T. and S.S.; investigation, W.K., P.K. and S.T.; writing—original draft preparation, W.K. and S.S.; writing—review and editing, W.K. and S.S.; visualization, W.K. and S.S.; supervision, S.S.; project administration, W.K. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

- Abbasi, S., Yousefi, G., Ansari, A. A., & Mohammadi-Samani, S. (2016). Formulation and *in vitro* evaluation of a fast-disintegrating/sustained dual release bucoadhesive bilayer tablet of captopril for treatment of hypertension crises. *Research in Pharmaceutical Sciences*, 11(4), 274–283. <https://doi.org/10.4103/1735-5362.189284>
- Alamer, A. A., Alshehri, A. A., Aodah, A. H., Almughem, F. A., Alghmadi, H. A., Alali, A. S., Halwani, A. A., Ahmed, M. M., & Tawfik, E. A. (2024). Development and evaluation of sildenafil/glycyrrhizin-loaded nanofibers as a potential novel buccal delivery system for erectile dysfunction. *Saudi Pharmaceutical Journal*, 32(5), Article 102038. <https://doi.org/10.1016/j.jsps.2024.102038>
- Ambarish, S., Shirsand, S., Anandkumar, Y., & Shirsand, S. (2024). To study the effect of HPMC and Carbopol in mucoadhesive buccal tablets of meclizine hydrochloride using central composite design: *In-vitro* characterization. *German Journal of Pharmaceuticals and Biomaterials*, 3(1), 3–18. <https://doi.org/10.5530/gjpb.2024.1.2>
- Deveci, S., Peşkırcioğlu, L., Aygün, C., Tekin, M. I. L., Dirim, A., & Özkardes, H. (2004). Sublingual sildenafil in the treatment of erectile dysfunction: Faster onset of action with less dose. *International Journal of Urology*, 11(11), 989–992. <https://doi.org/10.1111/j.1442-2042.2004.00933.x>
- Dighe, P. P., & Tank, H. M. (2019). Formulation development and statistical optimization of a bilayer tablet of bosentan monohydrate and sildenafil citrate in management of pulmonary arterial hypertension. *International Journal of Applied Pharmaceutics*, 11(2), 239–246. <https://doi.org/10.22159/ijap.2019v11i2.30927>
- Goldstein, I., Lue, T. F., Padma-Nathan, H., Rosen, R. C., Steers, W. D., & Wicker, P. A. (1998). Oral sildenafil in the treatment of erectile dysfunction. *The New England Journal of Medicine*, 338(20), 1397–1404. <https://doi.org/10.1056/nejm199805143382001>
- Jung, S.-Y., Seo, Y.-G., Kim, G. K., Woo, J. S., Yong, C. S., & Choi, H.-G. (2011). Comparison of the solubility and pharmacokinetics of sildenafil salts. *Archives of Pharmacol Research*, 34(3), 451–454. <https://doi.org/10.1007/s12272-011-0313-y>

- Kavanagh, N., & Corrigan, O. I. (2004). Swelling and erosion properties of hydroxypropylmethylcellulose (hypromellose) matrices—influence of agitation rate and dissolution medium composition. *International Journal of Pharmaceutics*, 279(1–2), 141–152. <https://doi.org/10.1016/j.ijpharm.2004.04.016>
- Kriangkrai, W., Puttipipatkachorn, S., Sriamornsak, P., & Sungthongjeen, S. (2024). Design and evaluation of new gel-based floating matrix tablets utilizing the sublimation technique for gastroretentive drug delivery. *Gels*, 10(9), Article 581. <https://doi.org/10.3390/gels10090581>
- Luca, I., Albu Kaya, M. D. L. G., Titorencu, I., Dinu-Pîrvu, C.-E., Marin, M. M., Popa, L. C. M., Rosca, A.-M., Antoniac, A., Anuta, V., Prisada, R. Z. M., Kaya, D. A., & Ghica, M. V. (2025). Influence of mucoadhesive polymers on physicochemical features and biocompatibility of collagen wafers. *ACS Polymers Au*, 5(3), 282–297. <https://doi.org/10.1021/acspolymersau.5c00010>
- Mady, O. Y., Dewedar, O., Abdine, N., Zaytoon, H., & Haggag, Y. (2024). Bioadhesive behaviors of HPMC E5: Comparative analysis of various techniques, histological and human radiological evidence. *Scientific Reports*, 14(1), Article 1840. <https://doi.org/10.1038/s41598-024-52144-x>
- Mawla, N., Alshafiee, M., Gamble, J., Tobyn, M., Liu, L., Walton, K., Conway, B. R., Timmins, P., & Asare-Addo, K. (2023). Comparative evaluation of the powder and tableting properties of regular and direct compression hypromellose from different vendors. *Pharmaceutics*, 15(8), Article 2154. <https://doi.org/10.3390/pharmaceutics15082154>
- Park, C., Lee, J. H., Jin, G., Ngo, H. V., Park, J.-B., Tran, T. T. D., Tran, P. H. L., & Lee, B.-J. (2022). Release kinetics of hydroxypropyl methylcellulose governing drug release and hydrodynamic changes of matrix tablet. *Current Drug Delivery*, 19(5), 520–533. <https://doi.org/10.2174/1567201818666210820101549>
- Phaechamud, T., & Darunkaisorn, W. (2016). Drug release behavior of polymeric matrix filled in capsule. *Saudi Pharmaceutical Journal*, 24(6), 627–634. <https://doi.org/10.1016/j.jsps.2015.04.003>
- Phan, T. Q., Tran, P. H. L., & Tran, T. T. D. (2020). The relationship between mucoadhesive polymers and surface coating in tablets for the controlled colonic delivery of a poorly water-soluble drug. *DARU Journal of Pharmaceutical Sciences*, 28(2), 545–553. <https://doi.org/10.1007/s40199-020-00360-x>
- Radicioni, M., Castiglioni, C., Giori, A., Cupone, I., Frangione, V., & Rovati, S. (2017). Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers. *Drug Design, Development and Therapy*, 11, 1183–1192. <https://doi.org/10.2147/DDDT.S124034>
- Sarnoski, S., Machado, F., Rahal, A., Andreolli, A., Hayochi Choji, C., Hayochi Choji, C. T., Almeida, L., Rocha Junior, A., Abdul Wahab, A., Cunha, A., Martins, D., de Biasi Filho, F., Andreolli, J., Rios, M., Atwi, M., Ruas, R., Villegas, R., Stujui, R., & Dos Santos, T. (2026). Global prevalence of erectile dysfunction in adult men: A systematic review (2010–2024). *The Journal of Sexual Medicine*, 23(Suppl. 4), Article qdag118.270. <https://doi.org/10.1093/jsxmed/qdag118.270>
- Sarode, A., Wang, P., Cote, C., & Worthen, D. R. (2013). Low-viscosity hydroxypropylcellulose (HPC) grades SL and SSL: Versatile pharmaceutical polymers for dissolution enhancement, controlled release, and pharmaceutical processing. *AAPS PharmSciTech*, 14(1), 151–159. <https://doi.org/10.1208/s12249-012-9897-x>
- Sheu, M.-T., Hsieh, C.-M., Chen, R.-N., Chou, P.-Y., & Ho, H.-O. (2016). Rapid-onset sildenafil sublingual drug delivery systems: *In vitro* evaluation and *in vivo* pharmacokinetic studies in rabbits. *Journal of Pharmaceutical Sciences*, 105(9), 2774–2781. <https://doi.org/10.1016/j.xphs.2016.01.015>
- Shirsand, S. B., Suresh, S., Keshavshetti, G. G., Swamy, P. V., & Reddy, P. V. P. (2012). Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method. *International Journal of Pharmaceutical Investigation*, 2(1), 34–41. <https://doi.org/10.4103/2230-973X.96924>
- Soliman, G. M., Fetih, G., & Abbas, A. M. (2017). Thermosensitive bioadhesive gels for the vaginal delivery of sildenafil citrate: *In vitro* characterization and clinical evaluation in women using clomiphene citrate for induction of ovulation. *Drug Development and Industrial Pharmacy*, 43(3), 399–408. <https://doi.org/10.1080/03639045.2016.1254239>
- Sulaiman, H. T., Jabir, S. A., & Al-Kinani, K. K. (2018). Investigating the effect of different grades and concentrations of pH-sensitive polymer on preparation and characterization of lidocaine hydrochloride as *in situ* gel buccal spray. *Asian Journal of Pharmaceutical and Clinical Research*, 11(11), 401–407. <https://doi.org/10.22159/ajpcr.2018.v11i11.28492>
- Trirattanapintusorn, P., Leatpianpanit, S., Thanarangsarit, P., Sungthongjeen, S., & Kriangkrai, W. (2019). Development and evaluation of acetaminophen orodispersible disc with taste-masking property. *Key Engineering Materials*, 819, 233–239. <https://doi.org/10.4028/www.scientific.net/KEM.819.233>
- Wattanaphraya, N., Manchun, S., Taokaew, S., & Kriangkrai, W. (2021). Development of mucoadhesive film-forming systems containing black ginger extract for aphthous ulcers. *Key Engineering Materials*, 901, 104–110. <https://doi.org/10.4028/www.scientific.net/KEM.901.104>