

Folded Gastroretentive Bilayer Films Driven by Kollicoat SR 30-D for Sustained Release of Highly Water-Soluble Drugs

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Folded Gastroretentive Bilayer Films Driven by Kollicoat SR 30-D for Sustained Release of Highly Water-Soluble Drugs

Kollicoat SR 30-D ile Yönlendirilen Katlanmış Gastroretentif Bileşenli (Bilayer) Filmler: Yüksek Derecede Suda Çözünür İlaçlar için Sürekli Salım

SUMMARY

This study introduces a bilayer unfoldable oral film for propranolol hydrochloride that combines immediate and sustained release in a single dosage form. The system comprises an immediate-release (IR) layer formulated with HPMC K-100LV and a sustained-release (SR) layer of Kollicoat SR 30-D, a film-forming polymer. The novelty of this system lies in the use of Kollicoat SR 30-D, which is typically employed as a coating polymer, as a matrix-forming polymer to regulate the release of a highly soluble drug. The use of conventional hydrophilic and hydrophobic polymers for this purpose has shown limited success due to burst release and poor film-forming properties. Both the IR layer and the SR layer were statistically optimized using Design-Expert®. In the optimized formulation, the IR layer exhibited rapid drug release with a t_{90} value of 5.18 minutes, and the SR layer maintained sustained release for up to 12 hours (t_{90} = 688.71 minutes). The release followed Korsmeyer–Peppas kinetics (n = 0.483), confirming a diffusion-controlled mechanism through the Kollicoat matrix. Scanning electron microscopy revealed a uniform, dense film of Kollicoat SR 30-D with microchannels after dissolution, which supports the idea that the film acts as a diffusion barrier. The bilayer film showed good folding endurance, low moisture absorption, and minimal water vapour transmission rates, indicating mechanical and physicochemical stability. This study demonstrates that Kollicoat SR 30-D can be successfully used as a sustained-release film-forming polymer for highly water-soluble drugs, offering a scalable, commercially viable platform for gastroretentive formulations.

Keywords: Kollicoat SR 30-D, gastroretentive film, bilayer film, sustained release, design-Expert®, unfolding-type film, highly water-soluble drug.

ÖZ

Bu çalışma, propranolol hidroklorür için tek bir dozaj formunda hızlı ve uzatılmış salımı birleştiren çift katmanlı açılabilir bir oral film sistemi sunmaktadır. Sistem, HPMC K-100LV ile formüle edilmiş bir hızlı salım (IR) katmanı ve film oluşturu bir polimer olan Kollicoat SR 30-D'den oluşan bir uzatılmış salım (SR) katmanından meydana gelmektedir. Bu sistemin yeniliği, genellikle kaplama polimeri olarak kullanılan Kollicoat SR 30-D'nin, yüksek çözünürlüğe sahip bir ilacın salımını düzenlemek amacıyla matris oluşturu polimer olarak kullanılmasıdır. Bu amaçla geleneksel hidrofilik ve hidrofobik polimerlerin kullanımı, ani salım (burst release) ve yetersiz film oluşturma özellikleri nedeniyle sınırlı başarı göstermiştir. Hem IR hem de SR katmanları, Design-Expert® yazılımı kullanılarak istatistiksel olarak optimize edilmiştir. Optimize edilmiş formülasyonda, IR katmanı hızlı ilaç salımı göstermiş ve t_{90} değeri 5,18 dakika olarak belirlenirken, SR katmanı 12 saate kadar uzatılmış salımı sürdürmüştür (t_{90} = 688,71 dakika). Salım, Korsme-ye-PPeppas kinetiğini (n = 0,483) takip etmiş ve Kollicoat matrisi boyunca difüzyon kontrollü bir mekanizmayı doğru-lamıştır. Taramalı elektron mikroskopu analizleri, çözünme sonrası mikrokanaallar içeren homojen ve yoğun bir Kolli-coat SR 30-D filmi ortaya koymuş olup, bu durum filmin bir difüzyon bariyeri olarak işlev gördüğünü desteklemektedir. Çift katmanlı film, iyi katlanma dayanımı, düşük nem absorpsiyonu ve minimal su buharı geçirgenlik oranları göstermiş, bu da mekanik ve fizikokimyasal stabilitesini ortaya koymuştur. Bu çalışma, Kollicoat SR 30-D'nin yüksek suda çözünürlüğe sahip ilaçlar için uzatılmış salım sağlayan bir film oluşturu polimer olarak başarıyla kullanılabilir-leceğini ve gastroretentif formülasyonlar için ölçeklenebilir, ticari açıdan uygulanabilir bir platform sunduğunu göstermektedir.

Anahtar Kelimeler: Kollicoat SR 30-D, gastroretentif film, iki katmanlı film, sürekli salım, Design-Expert®, açılabilir tip film, yüksek derecede suda çözünür ilaç.

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INTRODUCTION

Various polymers have been used in recent times to develop gastroretentive sustained-release films for drugs that are highly soluble in water, such as metformin, atenolol, and ranitidine hydrochloride. These drugs diffuse rapidly in water, which makes it challenging to achieve sustained release and sometimes has serious side effects (Chauhan, Zehra, & Chauhan, 2024; Mora-Castaño, Millán-Jiménez, & Caraballo, 2023; Sharma & Awasthi, 2015). Many of these drugs exhibit limited absorption in the gastrointestinal tract. Further, they are characterized by poor bioavailability, poor stability, toxicity, and other issues (Murphy, Pillay, Choonara, & du Toit, 2009; Rahi, 2022).

Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), xanthan gum, guar gum, sodium alginate, chitosan, carbopol, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), hydroxypropyl cellulose (HPC), and sodium carboxymethyl cellulose are extensively used in gastroretentive drug delivery systems owing to their swelling, gel-forming, and in some cases, mucoadhesive properties. These properties allow for prolonged gastric residence and sustained drug release by forming hydrated gel matrices that control drug diffusion. Hydrophobic polymers like cellulose acetate, ethyl cellulose, and several grades of Eudragit® have also been used in gastroretentive sustained-release films, as they can delay drug release by creating diffusion-controlling polymeric barriers. The choice and combination of these polymers play a crucial role in attaining the desired balance of gastric retention, mechanical strength, and controlled drug-release characteristics (Adeleye, Femi-Oyewo, Mosuro, & Fakoya, 2019; Elsabee & Abdou, 2013; Iglesias et al., 2020; Waqar et al., 2024).

Dzouza Lenson employed a combination of three polymers—chitosan, hydroxypropyl methylcellulose (HPMC), and polyvinyl alcohol—as a film-forming polymer to create a bilayer unfolding drug delivery system for the simultaneous release of the H₂ receptor antagonist famotidine and the proton pump inhibi-

tor rabeprazole sodium (Koland, Lenson, & Marina, 2016). Due to the low mechanical strength, chitosan-based films may crack, deform, or fail during handling. Chitosan is strongly hydrophilic, which causes it to absorb water and swell, producing a gel-like matrix. This may retard drug release by forming barriers to diffusion (Elsabee & Abdou, 2013; Liu et al., 2019). However, chitosan has a drawback in that its mechanical resistance is poor, as a result of which the drug is released faster than desired. This negates the purpose of prolonged administration (Garg, Chauhan, Nagaich, & Jain, 2019).

Porwal, Dwivedi and Pathak (2020) used HPMC K3, Eudragit RSPO, and Carbopol 934P to develop a gastroretentive bilayer film that would release amlodipine besylate immediately and atorvastatin calcium over time. The hydrophilic nature of Carbopol 934P may cause the film to inflate rapidly and become unstable, which could alter drug-release characteristics of the polymers (Rania, Areej, & Ahlam, 2020). Further, the low tensile strength of Carbopol 934P may compromise the integrity of a film, which may cause difficulties during handling and storage (Garg et al., 2019; Renuka, Nishadh, Jigar, & Tejal, 2016) and reduce the effectiveness of sustained delivery.

Wagh, Ahirrao and Kshirsagar, (2019) prepared a film using Carbopol 934 and Eudragit L100 for gastroretentive administration of ranitidine hydrochloride (Wagh et al., 2019). However, exposure to the acidic gastric pH ($\approx 1-2$) may cause rapid erosion of Carbopol 934, resulting in premature drug release and reduced gastric retention, which may result in loss of gastric retention and premature transit from the target site (Rania et al., 2020). Further, the pH sensitivity of Eudragit L100 may influence its release behaviour in the fluctuating pH levels of the gastrointestinal tract (Ofriidam, Lebaz, Gagnière, Mangin, & Elaissari, 2020).

Kollicoat SR 30-D is an aqueous polyvinyl acetate dispersion that is non-sticky. It is used for controlled drug release because of its great capacity to withstand mechanical stress (Kolter, Dashevsky, Irfan, & Bod-

meier, 2013). Kollicoat SR 30-D serves as a stable matrix that keeps drugs effective for the duration of their shelf life. This polymer provides sustained release through the formation of a permeable polyvinyl acetate film that controls drug diffusion in a pH-independent manner (Dashevsky, Kolter, & Bodmeier, 2004; Dashevsky, Wagner, Kolter, & Bodmeier, 2005; Sawicki & Lunio, 2005).

The ionic strength and pH of the release medium have no effect on the drug release from Kollicoat SR 30-D coated pellets. Such pellets are insoluble in dilute acids and dilute alkalis. Thus, the limitations imposed by the properties of various polymers, such as high hydrophilicity, poor tensile strength, pH-dependent behaviour, and poor mechanical strength, can be minimized by using Kollicoat SR 30-D (Dashevsky et al., 2005; Kolter et al., 2013). Depending on the thickness and solubility of the Kollicoat SR 30-D, coatings of this material allow active ingredients to be released over an extended period of time, primarily through diffusion.

Several efforts have been made to produce unfolding-type gastroretentive film (UGF) for the prolonged-release administration of water-soluble drugs (Koland et al., 2016; Ullah et al., 2017; Porwal et al., 2020). In the current study, we attempted to use a single polymer, Kollicoat SR 30-D, to produce a UGF. The goal was to create a UGF of water-soluble propranolol hydrochloride (PPH) for sustained release. Following ingestion, the capsule dissolves and releases the film, which would unfold in the stomach and release the drug by diffusion. Thus, the key novelty of this research lies in the repurposing of Kollicoat SR 30-D as a sustained-release film-forming matrix for a highly soluble drug, achieving controlled diffusion through a stable, solvent-free polymeric network.

MATERIALS AND METHODS

Materials

A PPH sample was obtained from CTX Lifesciences Pvt. Ltd., Surat, India; BASF India Pvt. Ltd., Mumbai, India, provided Kollicoat SR 30-D; Colorcon Asia Pvt. Ltd., Mumbai, India supplied HPMC K-100LV;

and Loba Chemie Pvt. Ltd., Mumbai, India, provided polyvinyl pyrrolidone K-30 (PVPK-30), polyethylene glycol 400 (PEG), propylene glycol (PG), and ethanol.

Preparation of the IR layer

The IR layer was optimized using the Design-Expert® software package (version 13) based on a two-factor, three-level central composite design (CCD), CCD was selected because it efficiently evaluates both linear and quadratic effects of formulation variables, it enables optimization using fewer experimental runs compared with full factorial designs, it is particularly suitable for studying curvature effects and interaction terms, and it provides high predictive accuracy for formulation optimization. Since the formulation variables were expected to show non-linear influences on drug release behavior and film properties, CCD was considered the most appropriate experimental design for this study (Alaithan et al., 2022). The influence of two formulation variables, HPMC K-100LV concentration (X_1) and PVP K-30 concentration (X_2), on the time required for 90% of drug release (t_{90}) was assessed.

UGF were prepared using HPMC K-100LV and PVP K-30. The weighed amounts of HPMC K-100LV and PVPK-30 (Table 1 and 2.) were carefully dissolved in distilled water with continuous stirring until a polymeric aqueous solution was formed. The loading dose of PPH was dissolved in this solution, and PEG 400 (2 % w/w) was added as a plasticizer. After 5 minutes of sonication, the resultant dispersion was transferred to a Petri dish and allowed to dry for 6–7 hours at room temperature. The total volume of solution to be poured in a designated casting area and a loading dose of 14 mg per 6 cm² of film were used to determine the amount of drug incorporated into the polymeric aqueous solution (Porwal et al., 2020). The thickness, weight, and visual appeal of each film were noted.

Preparation of the SR layer

The SR layer was prepared using Kollicoat SR 30-D. The formulation was optimized using a cen-

tral composite design (CCD) in Design-Expert®. The independent variables were the concentration of Kollicoat SR 30-D (X_1) and plasticizer concentration (X_2), and the dependent variables included the time required for 90% of drug release. A polymeric dispersion was created by dissolving an appropriate quantity of PPH in Kollicoat SR 30-D (Tables 1 and 2.). PG was added as a plasticizer, after which the mixture was agitated vigorously to ensure uniform mix-

ing. The amount of drug added to the film-forming solution was calculated using the total volume of the solution to be poured in a predetermined casting area and a maintenance dose of 26 mg per 6 cm² of film. The resultant polymeric dispersion was poured into a Petri dish, which was then dried at room temperature for 6–7 hours (Porwal et al., 2020; Ullah et al., 2017). The thickness, weight, and visual appeal of each film were noted.

Table 1. Levels of variables with experimental values for IR and SR layers

Sr. no.	Independent variables of the IR layer	Level					Independent variables of the SR layer	Level				
		-α	-1	0	1	+α		-α	-1	0	1	+α
1	HPMC K-100LV (mg)	45.85	50	60	70	74.14	Kollicoat SR 30-D (g)	0.792	1.0	1.5	2.0	2.207
2	PVP K-30 (mg)	5.85	10	20	30	34.14	PG (mL)	0.21	0.3	0.5	0.7	0.78

The non-proportional value of the +1 level for PG was due to adjustment based on preliminary film-forming studies and practical processing limitations. Preliminary experiments showed that higher PG concentrations beyond 0.78 ml caused excessive softness and tackiness of the SR films, adversely affecting film integrity and handling. Therefore, the selected level represented the upper practical limit for obtaining mechanically stable films suitable for unfolding gastroretentive systems.

Evaluation of IR and SR layers of UGF

Several quality parameters, including percent drug content, *in vitro* drug release, and folding endurance of the IR and SR UGF, were determined so that various concentrations of the polymers could be identified for improving the dosage form.

Folding endurance of IR and SR layers

The folding durability of each film was assessed by folding it at the same place up to 300 times until breaking (Alaithan et al., 2022; Orgul, Yigit, Gultekin, & Arisoy, 2025; Saha, Atrneriya, Joshi, & Solanki, 2024).

Drug content

IR and SR films containing 14 mg and 26 mg of PPH, respectively, with an area of 6 cm², were cut and dissolved in 100 mL of ethanol in a 100 mL of volumetric flask and stored overnight with occasional

shaking. After that, the entire solution was sonicated. Following filtering and sonication, appropriate dilutions were made, and the solutions were examined at 289 nm using a UV-visible spectrophotometer.

In vitro release study and t_{90} determination

The *in vitro* release of PPH from the IR and SR layer was measured using a paddle-type USP dissolving device called the Modified Electro-lab Dissolving Tester. The apparatus was operated at a rotational speed of 50 rpm to prevent disruptions. 0.1 N HCl (pH 1.2) was used as a medium in which PPH is highly soluble. A dissolution volume of 500 mL was used for IR (14 mg drug load) and 900 mL for SR (26 mg drug load), which helps in the accurate quantification of drug release by UV spectrophotometry. An equal volume of fresh dissolution medium maintained at 37 ± 0.5 °C was replaced at each sampling interval. Due to the high solubility of propranolol hydrochloride in the selected medium and the relatively low drug loads used, the drug concentration was well below saturation throughout the dissolution studies. Following filtering using Whatman Filter Paper No. 42, the absorbance of the PPH in each sample was measured at 291 nm using a UV spectrophotometer (UV 2401 PC, Shimadzu, Japan). Each experiment was performed in triplicate (Chopade et al., 2023; Porwal et al., 2020; Ullah et al., 2017). t_{90} values were obtained from plots of cumulative percent release against time.

Treatment of *in vitro* release data of SR layer with different kinetic equations

The mechanisms and rate at which a drug is released from a pharmacological dosage form into the surrounding media or biological environment are examined in release kinetics research. Understanding the drug release kinetics is needed to optimize drug delivery systems and obtain the desired therapeutic result. Drug release kinetics have been explained using a variety of mathematical models. The Korsmeyer–Peppas, Higuchi, Hixson–Crowell, zero-order, and first-order models are among the commonly used models. These models provide important insights into the kinetics and mechanisms of drug release. They are built using a variety of mathematical equations and assumptions (Koester, Ortega, Mayorga, & Bassani, 2004).

Preparation of bilayer UGF

The optimized IR layer was gently laminated over the preformed SR film using a small amount of hydroalcoholic HPMC solution as an adhesive. The films were cut into rectangular pieces of size 3 cm by 2 cm (6 cm², 40 mg PPH). The rolling method was used to fold the films (Anandkumar et al., 2023). The folded films were then placed into hard gelatin capsules. The film obtained had an area of 31.15 cm². It was cut into 6 cm² rectangles. The bilayer UGFs were evaluated for their visual appeal, weight, thickness, folding durability, drug content, and *in vitro* drug release as described in the IR and SR layer section. Other parameters were evaluated as described in the following.

Percent moisture absorbed

The prepared films were weighed individually and stored for 72 hours at room temperature in a humidity chamber filled with calcium chloride. The relative humidity was maintained at 68%. The films were weighed again after a predetermined period, after which their weights stayed constant. Formula No. 1 was used to determine the percentage of moisture absorbed (Elsabee & Abdou, 2013).

$$\% \text{ Moisture absorbed} = (\text{Final weight} - \text{Initial weight}) / \text{Initial weight} \times 100 \quad (1)$$

Water vapour transmission

In a humidity room at several humidities, poly-

meric films were adhered to the brim of glass vials (5 mL) that had been previously weighed and contained fused calcium chloride (1 g). Four humidity values (32%, 75%, 80%, and 90%) were used to determine the water vapour transfer (Latif et al., 2022; Venkatesh & Durga Srinivasrao, 2022). Formula No. 2 was used to calculate the transmission of water vapour:

$$\text{Water vapour transmission} = \text{Amount of water vapour transmitted} / (\text{Area} \times \text{time}) \quad (2)$$

Drug content

A 6 cm² film containing 40 mg of PPH was sliced, diluted in 100 mL of ethanol in a 100 mL volumetric flask, and shaken often during the night. After that, the entire solution was sonicated. The proper dilutions were made following sonication and subsequent filtration, and the resulting solutions were examined using a UV-visible spectrophotometer set to 289 nm.

In vitro unfolding behavior study

Films were carefully inserted into size 00 hard gelatine capsules. The *in vitro* unfolding behaviour of the films was evaluated using the USP apparatus-I (basket) operated at 100 rpm; six capsules were used for the study. The dissolution medium consisted of 900 mL aqueous hydrochloric acid pH 1.2 at 37±0.5°C. At predetermined time intervals of 5, 10, 5, 20, 30, 60, 120, 240, 480, and 720 min, baskets were removed, and the film was examined for unfolding behaviour (Anandkumar et al., 2023; Ullah et al., 2017).

Scanning electron microscopy (SEM)

The morphology of the polymeric film was studied by SEM. The UGF was inspected with a JSM-6490LA electron microscope (JEOL, Tokyo, Japan) outfitted with an EM-ASID 11 Scanning Image Observation Device, which employs secondary electrons. SEM investigation of the polymeric bilayer film was carried out employing a 20 kV acceleration voltage at various magnification levels (Garg, Gupta, & Gupta, 2008; Koester et al., 2004).

RESULTS AND DISCUSSION

A bilayer UGF was designed to deliver PPH, which is absorbed mainly in the upper gastrointestinal tract.

Table 2. Folding endurance, % drug content, and t_{90} values of IR batches I1–I13 and SR batches S1–S13

Code	Factor1 A: HP- MCK-100LV (mg)	Factor2 B: PVPK-30 (mg)	Folding endurance (number of folds $\pm$ S.D.; n = 3)	Drug content (%w/w) (mean $\pm$ S.D.; n = 3)	t_{90} (min- utes)	Code	Factor1 A: Kollicoat SR 30-D (g)	Factor2 B: PG (mL)	Folding endur- ance (number of folds $\pm$ S.D.) (n=3)	Drug content (% w/w) (mean $\pm$ S.D.; (n = 3))	t_{90} (minutes)
I1	60	5.85	250 $\pm$ 3.12	92.55 $\pm$ 0.586	17.65 $\pm$ 0.5197	S1	2.207	0.5	276 $\pm$ 3.15	93.30 $\pm$ 0.587	1133.62 $\pm$ 0.523
I2	74.14	20	240 $\pm$ 3.10	93.21 $\pm$ 0.823	33.07 $\pm$ 0.521	S2	1.500	0.78	268 $\pm$ 3.14	92.80 $\pm$ 0.156	843.46 $\pm$ 1.137
I3	60	20	237 $\pm$ 2.19	93.94 $\pm$ 0.755	14.05 $\pm$ 0.543	S3	1.500	0.5	264 $\pm$ 2.29	93.20 $\pm$ 0.278	738.23 $\pm$ 1.571
I4	60	20	235 $\pm$ 1.09	97.04 $\pm$ 0.516	16.82 $\pm$ 0.550	S4	0.792	0.5	251 $\pm$ 1.14	98.70 $\pm$ 0.523	688.71 $\pm$ 0.926
I5	45.85	20	234 $\pm$ 4.08	98.10 $\pm$ 0.423	5.18 $\pm$ 0.506	S5	1.00	0.3	249 $\pm$ 4.25	95.49 $\pm$ 0.324	636.04 $\pm$ 1.800
I6	60	34.14	240 $\pm$ 3.53	92.41 $\pm$ 0.235	25.21 $\pm$ 0.620	S6	1.500	0.5	255 $\pm$ 3.60	93.58 $\pm$ 0.146	721.00 $\pm$ 1.075
I7	60	20	242 $\pm$ 3.62	94.25 $\pm$ 0.727	14.43 $\pm$ 0.536	S7	1.500	0.21	254 $\pm$ 3.71	96.78 $\pm$ 0.434	726.092 $\pm$ 0.999
I8	70	30	246 $\pm$ 1.29	95.05 $\pm$ 0.209	29.08 $\pm$ 0.550	S8	1.00	0.7	253 $\pm$ 1.66	98.00 $\pm$ 0.189	645.80 $\pm$ 1.075
I9	60	20	235 $\pm$ 2.39	96.56 $\pm$ 0.148	12.83 $\pm$ 0.504	S9	1.500	0.5	261 $\pm$ 2.45	97.60 $\pm$ 0.298	751.35 $\pm$ 1.050
I10	50	10	238 $\pm$ 3.44	94.47 $\pm$ 0.321	10.06 $\pm$ 0.515	S10	1.500	0.5	265 $\pm$ 3.34	95.80 $\pm$ 0.334	650.21 $\pm$ 1.336
I11	50	30	239 $\pm$ 2.67	95.80 $\pm$ 0.426	11.79 $\pm$ 0.446	S11	1.500	0.5	259 $\pm$ 2.17	94.48 $\pm$ 0.428	652.46 $\pm$ 0.962
I12	60	20	241 $\pm$ 4.23	97.40 $\pm$ 0.214	13.56 $\pm$ 0.564	S12	2.00	0.3	271 $\pm$ 4.11	97.10 $\pm$ 0.112	889.581 $\pm$ 0.920
I13	70	10	245 $\pm$ 2.81	97.80 $\pm$ 0.159	24.21 $\pm$ 0.536	S13	2.00	0.7	274 $\pm$ 2.35	95.30 $\pm$ 0.199	1006.546 $\pm$ 1.7932

Optimization and preparation of IR and SR layers

IR layer

The IR layer was optimized using a central composite design (CCD), with HPMC K-100LV (X_1) and PVP K-30 (X_2) as variables influencing the time required for 90% drug release (t_{90}). For the IR layer, the minimum t_{90} was targeted to achieve rapid drug release. As expected, the HPMC concentration exerted a strong positive influence on t_{90} . With higher HPMC K-100LV levels, the viscosity of the hydrated gel matrix increased, as a result of which drug diffusion was restricted and release delayed (Golddoozian, Mohylyuk, Dashevskiy, & Bodmeier, 2021; Tundisi, Mostaço, Carricondo, & Petri, 2021). This was reflected in the progressive increase in t_{90} from batch I1 (17.65 minutes), with a low HPMC K-100LV content (60 mg), to batch I2 (33.07 minutes), with the higher content (74.14 mg).

In contrast, a reduction in t_{90} was noted in formulations I3 to I5 as the HPMC K-100LV level decreased, confirming that matrix viscosity is a decisive release-modifying factor (Hirun & Kraissit, 2022; Park et al., 2022). PVP K-30 primarily functions as a hydrophilic binder, and it enhances amorphous dispersion and facilitates drug diffusion. However, with higher concentrations (formulations I6 and I7), PVP K-30 may have influenced matrix characteristics, resulting in a moderate increase in t_{90} (Franco & De Marco, 2020). The formulations containing higher concentrations of both HPMC K-100LV and PVP K-30 (I8 and I9) exhibited increased polymer thickening and formed a stronger gel barrier, thereby delaying drug release and increasing t_{90} due to the gel-forming effect of HPMC K-100LV (Golddoozian et al., 2021; Rania et al., 2020; Tundisi et al., 2021).

Batch I5 (45.85 mg of HPMC K-100LV, 20 mg of PVP K-30) had the lowest t_{90} value (5.18 minutes)

among all the formulations. This value is likely to support rapid disintegration and immediate onset of action, which makes I5 the optimal IR formulation.

SR layer

A targeted t_{90} range of approximately 660-720 minutes was selected to obtain sustained release over 12 hours for the SR layer. As for the SR layer, a CCD was used to evaluate the effect of polymer concentration (X_1) and plasticizer (PG) concentration (X_2) on t_{90} .

A clear trend emerged: higher concentrations of Kollicoat SR 30-D significantly prolonged drug release. At the highest polymer concentration (2.207 g), t_{90} was 1133.62 minutes, whereas a lower value of 688.71 minutes was observed at the lowest polymer concentration (0.792 g). It may be attributed to increased diffusional resistance at higher polymer concentration due to formation of a more continuous polymeric matrix, resulting in slower drug release (Shao, Morales, Díaz, & Muhammad, 2002; Dashevsky et al., 2005). An inverse relationship between plasticizer content and t_{90} was found. It can be inferred that PG increased polymer flexibility and reduced interpolymeric interactions, facilitating faster water ingress and drug mobility (Dashevsky et al., 2005). The release from batches S5, S8, S10, and S11 was excessively fast (<660 minutes), unsuitable for prolonged delivery. In contrast, the drug release from batches S1-S3, S6, S7, and S9-S13 was too slow (>720 minutes). Such prolonged release may delay the onset of the therapeutic effect (Table 2.).

Batch S4, with a t_{90} value of 688.71 minutes, fell within the target range (660-720 minutes), offering both adequate therapeutic coverage and controlled release. Therefore, S4 was selected as the optimized SR layer (Figure 1-3.).

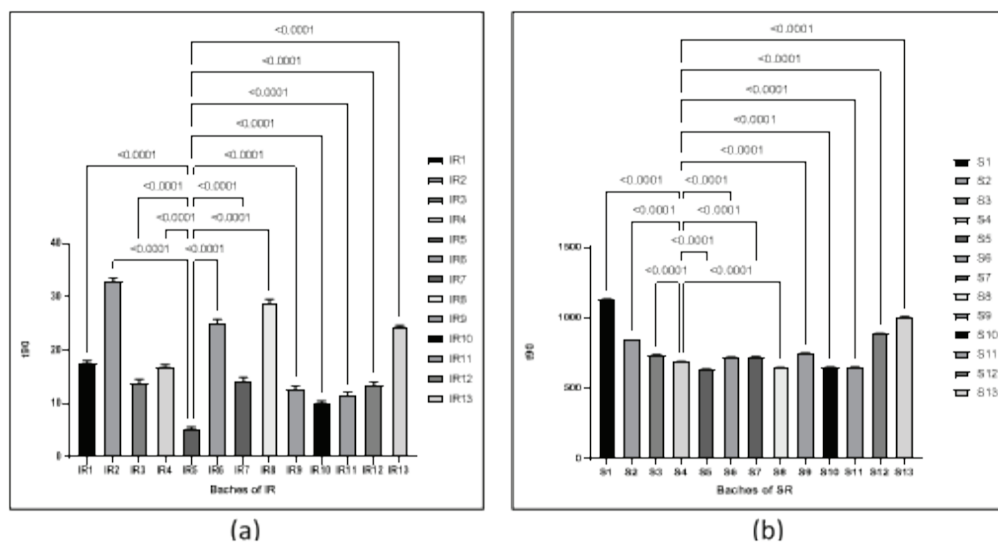


Figure 1. t_{90} values of the a) IR layer and (b) SR layer

The folding endurance of formulations containing higher concentrations of HPMC K-100LV, PVP K-30, and Kollicoat SR 30-D was improved as a result of increased film elasticity and enhanced polymer chain entanglement. Similarly, the function of PEG 400 and PG as plasticizers in enhancing flexibility and preventing brittleness has been thoroughly examined (Alaithan et al., 2022; Koland et al., 2016).

During film preparation, all formulations demonstrated minimal drug loss, efficient blending, and homogeneous casting, as evidenced by drug content within acceptable limits. The reproducibility and reliability of the solvent-casting process were confirmed by the minimal variations in drug content among formulations.

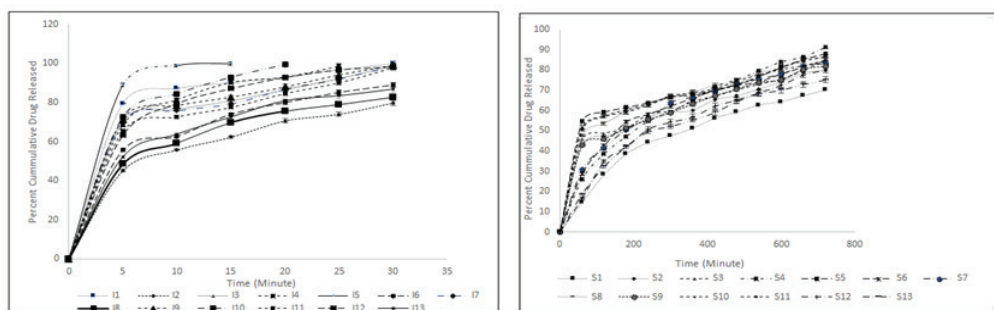


Figure 2. Percent cumulative drug released of (a) IR layer (b) SR layer

Statistical analysis (ANOVA)

ANOVA confirmed the robustness of the optimization models of the two layers. The p-values were extremely low (<0.0001), which indicated that the effects of the formulation variables on t_{90} were statistically significant.

The t_{90} of the IR layer is now methodically explained in relation to the concentrations of HPMC

K-100LV (X_1) and PVP K-30 (X_2). The positive coefficient of HPMC K-100LV suggested that the concentration of polymer increased the viscosity of the matrix and the strength of the gel, thereby extending the duration of drug release.

The central composite design (CCD) was employed to generate a quadratic model for the optimization of the sustained-release (SR) layer. The depen-

dent response (t_{90}) was substantially influenced by the selected independent variables, as evidenced by the statistical significance of the model (F-value of 91.69 and p -value < 0.0001). The model's predictive capability and robustness were demonstrated by the high coefficient of determination ($R^2 = 0.9850$), adjusted R^2 (0.9742), and predicted R^2 (0.9419), which confirmed outstanding agreement between experimental and predicted values. Furthermore, the quadratic model's ability to adequately describe the experimental data was demonstrated by the non-significant lack-of-fit value ($p = 0.4978$).

The SR layer's polynomial equation in terms of coded factors was as follows:

$$T_{90} = 686.60 + 211.84A - 95.38B + 56.25AB + 102.64A^2 + 16.64B^2 \quad (3)$$

in which location:

A represents the concentration of Kollicoat SR 30-D, while B represents the concentration of PG.

The positive coefficient of factor A (+211.84) suggested that the concentration of Kollicoat SR 30-D led to a substantial increase in t_{90} by forming a denser and thicker hydrophobic matrix. This matrix, in turn, restricted drug diffusion and water penetration. The ANOVA results also confirmed that factor A had the most significant impact on drug release behavior, as evidenced by its maximum F-value (317.87) and highly significant p -value (< 0.0001).

In contrast, factor B (propylene glycol) exhibited a negative impact on t_{90} , suggesting that the release of the drug was marginally accelerated as the PG concentration increased. PG's plasticizing effect may be responsible for this behaviour, as it enhances polymer flexibility, reduces interpolymeric interactions, and facilitates water ingress into the matrix system. The impact of PG was also statistically significant, with an F-value of 64.44 ($p < 0.0001$).

The release profile was synergistically influenced by the combined effect of Kollicoat SR 30-D and PG, as evidenced by the statistical significance of the inter-

action term AB ($p = 0.0123$). The positive interaction coefficient suggested that the impact of one variable on t_{90} was contingent upon the level of the second variable. Furthermore, the quadratic term A^2 was highly significant ($p < 0.0001$), which serves as confirmation of the non-linear impact of polymer concentration on sustained drug release. Nevertheless, the quadratic term B^2 was determined to be non-significant ($p = 0.2329$), suggesting that the curvature effect of PG concentration on t_{90} was relatively less pronounced.

The concentration of Kollicoat SR 30-D was the most critical factor governing sustained drug release, as these findings plainly demonstrated. Conversely, PG primarily modulated film flexibility and diffusional characteristics.

Figure 3 illustrates the contour plots and three-dimensional response surface plots generated from the central composite design for both the IR and SR layers. For the IR layer (Figures 3a and 3b.), increasing the concentration of HPMC K-100LV resulted in a pronounced increase in t_{90} due to the formation of a thicker hydrated gel barrier that restricted drug diffusion. PVP K-30 exerted a comparatively smaller effect, although higher concentrations slightly increased t_{90} because of enhanced swelling and matrix viscosity (Rania et al., 2020). The response surface indicates a synergistic interaction between HPMC K-100LV and PVP K-30, leading to slower drug release at higher concentrations of both polymers.

For the SR layer (Figures 3c and 3d), Kollicoat SR 30-D concentration significantly increased t_{90} by forming a dense hydrophobic matrix that prolonged the diffusional path of the drug (Kolter et al., 2013). Conversely, increasing PG concentration reduced t_{90} , likely because PG enhanced polymer-chain mobility and facilitated water penetration into the matrix. The contour plot identifies the design space where the desired release profile was achieved, while the 3D response surface demonstrates that polymer concentration had a greater influence on drug release than plasticizer concentration. These findings confirm that

careful adjustment of Kollicoat SR 30-D and PG concentrations is critical for obtaining the targeted sustained-release profile.

Drug release kinetic analysis demonstrated that the optimized formulation showed the best fit with the Korsmeyer–Peppas model, indicating diffusion-controlled drug release. The release exponent ($n = 0.483$) suggested a predominantly Fickian diffusion mechanism, where drug release occurred mainly through diffusion across the hydrated polymeric matrix. According to Korsmeyer–Peppas theory, n values below 0.5 indicate diffusion-controlled release from polymeric systems. Similar diffusion-mediated

release mechanisms have been reported for hydrophobic matrix systems containing Kollicoat SR 30-D and other sustained-release polymers (Asare-Addo, Levina, Rajabi-Siahboomi, & Nokhodchi, 2012; Dashkevsky et al., 2005; Koester et al., 2004).

The Higuchi model also showed good correlation, further supporting diffusion as the dominant release mechanism. In contrast, comparatively lower correlation with first-order and Hixson–Crowell models indicated that drug release was not primarily governed by matrix erosion or concentration-dependent dissolution.

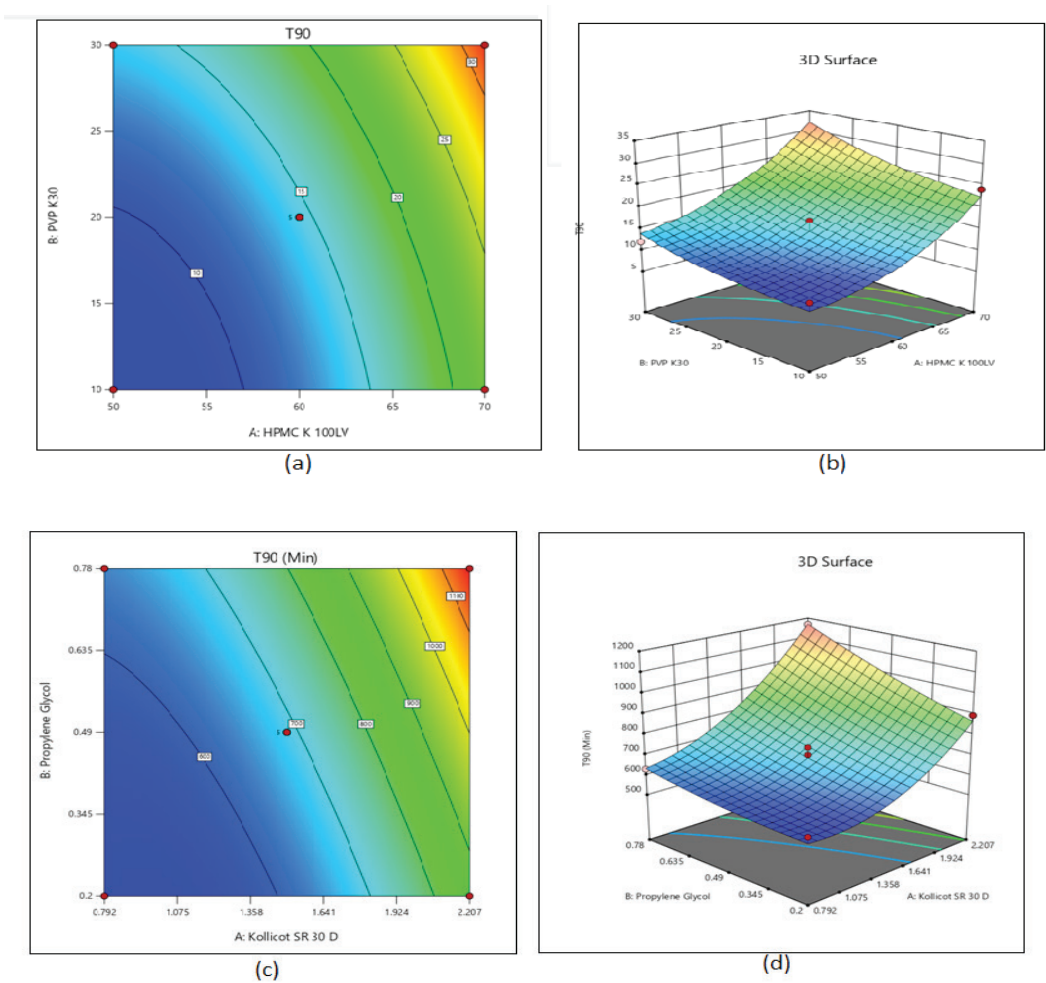


Figure 3. (a) (b) Contour plot and 3D surface plot of *in vitro* drug release from immediate release layers. (c) (d) from sustained release layers

Formulation and evaluation of the bilayer UGF

Film formation and folding technique

The optimized IR and SR films were laminated with a thin hydroalcoholic HPMC solution to form a cohesive bilayer structure using a rolling folding mechanism (Alaithan et al., 2022; Kolter et al., 2013; Ullah et al., 2017).

The bilayer UGF, measuring 3 cm × 2 cm (6 cm²), was appropriately sized for encapsulation in hard gelatine capsules, while maintaining structural foldability. The rolling folding technique created compact films that could be easily placed within firm gelatine capsules without cracking or delamination between IR and SR layers. The films, after capsule dissolution, could rapidly return to their original size due to the inherent elasticity of the polymeric matrix, permitting efficient stomach retention. The good mechanical performance obtained suggests that the improved formulation has adequate flexibility and structural stability for practical gastroretentive application.

Physical assessment

The optimized bilayer UGF formulation exhibited a uniform film thickness of 50.03 µm ± 0.65 µm, consistent with its polymer load and indicative of controlled solvent evaporation during casting. Variations in thickness across the batch were minimal, suggesting a stable and reproducible casting process.

Mechanical properties

Folding endurance

Mechanical integrity is critical for UGF, which must resist fragmentation during gastric motility. While ideal films withstand >300 folds, UGF demonstrated an endurance of 265 folds ± 2.11 folds (Table 3.), sufficient for capsule filling and gastric unfolding without breakage (Alaithan et al., 2022). When compared with previously reported gastroretentive and film-based drug delivery systems, the obtained value is higher than that reported for many formulations, such as Alaithan, S., who developed a novel unfolding film system of itopride hydrochloride, in which

the optimized film exhibited a folding endurance of 115.29, and the authors reported that a folding endurance value greater than 100 indicates high flexibility and integrity (Alaithan et al., 2022). Therefore, a folding endurance of 265 folds confirms that the developed bilayer UGF has sufficient mechanical integrity to withstand repeated folding and unfolding cycles (Alaithan et al., 2022; Koland et al., 2016) (Table 3.).

Table 3. Drug content and folding endurance of UGF

Code	Drug content percentage	Folding endurance (number of folds ± S.D.; n = 3)
UGF	98.90% ± 0.44%	265 ± 2.11

Moisture uptake and water vapour transmission

Moisture absorption

Moisture sensitivity can compromise film integrity, mechanical behaviour, and release performance. Bilayer film absorbed 6.11% ± 1.22% moisture over 72 hours at 68% relative humidity, indicating moderate hygroscopicity. Most conventional polymers used in gastroretentive films, such as HPMC, chitosan, and Carbopol, are highly hydrophilic and contain numerous hydroxyl and carboxyl groups, which are responsible for their high hydrophilic nature, so they increase the hydrophilicity of the film and exhibit higher moisture absorption due to extensive hydrogen bonding and swelling compared with Kollicoat SR 30-D (Elsabee & Abdou, 2013; Hadi, Nawab, Alam, & Naqvi, 2023; Rania et al., 2020). Kollicoat SR 30-D is a polyvinyl acetate-based polymer dispersion that exhibits lipophilic (hydrophobic) characteristics; the polyvinyl acetate backbone contains a non-polar acetate group and lacks hydrophilic functional groups (Kolter et al., 2013), resulting in low affinity for water and reduced moisture absorption compared to hydrophilic polymers.

Water vapour transmission rate (WVTR)

WVTR evaluations at 32 to 90% relative humidity revealed that bilayer films were generally impermeable to moisture penetration. At the highest humidity

level (90% RH), the bilayer UGF gained only $0.95 \text{ g} \pm 0.028 \text{ g}$, which indicates a low WVTR (Figure 4). This finding demonstrates the ability of Kollicoat SR 30-D to form dense hydrophobic films and supports the formation of a compact, defect-free polymer network, unlike highly hydrophilic polymers such as chitosan,

carbopol, and HPMC. A low WVTR is particularly desirable for maintaining the mechanical integrity and diffusional characteristics of the SR layer (Elsabee & Abdou, 2013; Hadi et al., 2023; Kolter et al., 2013; Rania et al., 2020).

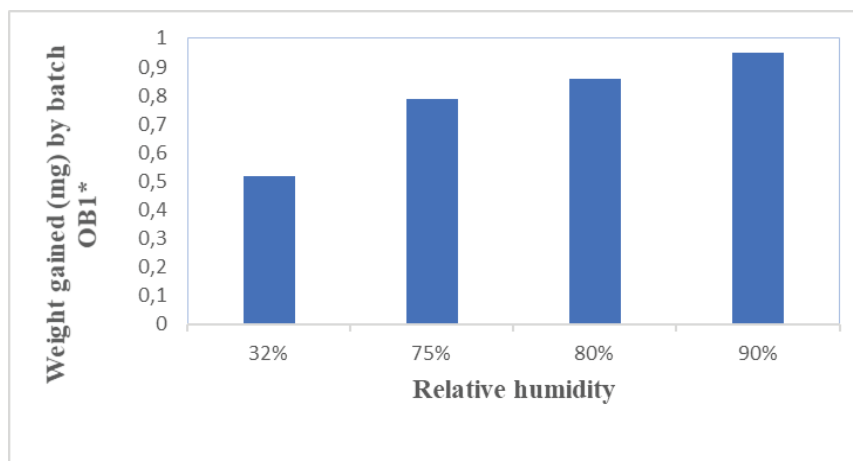


Figure 4. Water vapour transmission of bilayer UGF

Drug content uniformity

The drug content of bilayer film was found to be $98.90\% \pm 0.44\%$ (Table 3.), confirming that the uniformity across the film surface was excellent. The solvent-casting method facilitated a homogeneous drug distribution without crystalline drug deposition, as supported by SEM evidence shown in Figure 5. Kollicoat SR 30-D formed a compact matrix with uniform polymer distribution throughout the sustained-release layer. After dissolution, microchannels and pores were formed due to hydration-induced polymer relaxation and release of water-soluble drug. Over time, both the number and diameter of the microchannels increased, and drug release occurred through a gradual diffusion-controlled mechanism (Kolter et al., 2013; Sawicki & Łunio, 2005; Shao et al., 2002).

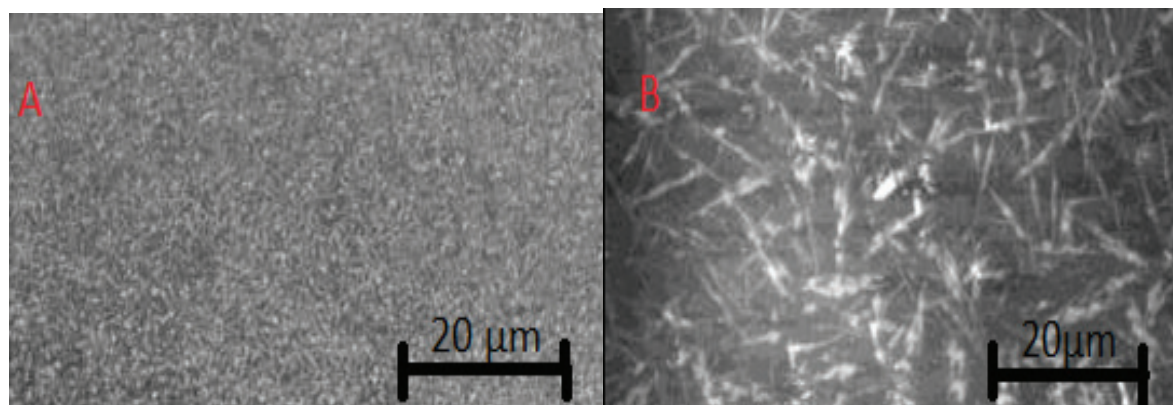


Figure 5. Scanning electron micrograph of UGF A) Before dissolution B) After dissolution

Unfolding behaviour

The UGF exhibited complete unfolding within 10-15 minutes (Anandkumar et al., 2023), after capsule disintegration, and maintained its structural integrity over the dissolution period. Rapid unfolding is necessary because it allows the dosage form to achieve dimensions bigger than the pyloric aperture and therefore reduce the chance of premature gastric emptying. The film also exhibited enough flexibility so that the stomach motility did not break the film, resulting in prolonged gastric residence and prolonged drug release.

In vitro drug release

The optimized bilayer UGF exhibited a unique biphasic release pattern. Formulation I5 exhibited a t_{90} value of 5.18 minutes, indicating efficient immediate drug availability, as the IR layer rapidly released the loading dose. The reduced polymer viscosity of these films facilitated the penetration of the dissolution medium and accelerated drug diffusion (Chopade et al., 2023; Porwal et al., 2020).

The successful incorporation of immediate-release and sustained-release functionalities within a

single dosage form is evidenced by the 99.33% release of PPH by the complete bilayer UGF over 12 hours (Figure 6.). The release profile exhibited an initial surge effect that corresponded to the IR layer, which was subsequently followed by a controlled-release phase that was regulated by the SR layer (Koland et al., 2016; Porwal et al., 2020).

The apparent plateau that is observed at approximately 100 minutes is simply the conclusion of the IR phase of the bilayer gastroretentive film and does not indicate the end of the overall drug release process. In order to achieve prompt therapeutic action, the formulation was intentionally designed to exhibit a biphasic release pattern. This pattern consists of a rapid initial release from the IR layer, followed by a protracted sustained-release phase from the Kollicoat SR 30-D matrix layer that can last up to 12 hours. The slope of the dissolution curve decreased as a result of the diffusion-controlled release phase, which was comparatively delayed (Dashevsky et al., 2005; Kolter et al., 2013). The formulation showed the desired biphasic release profile: quick release from the immediate release layer and sustained release from the Kollicoat SR 30 D sustained release matrix.

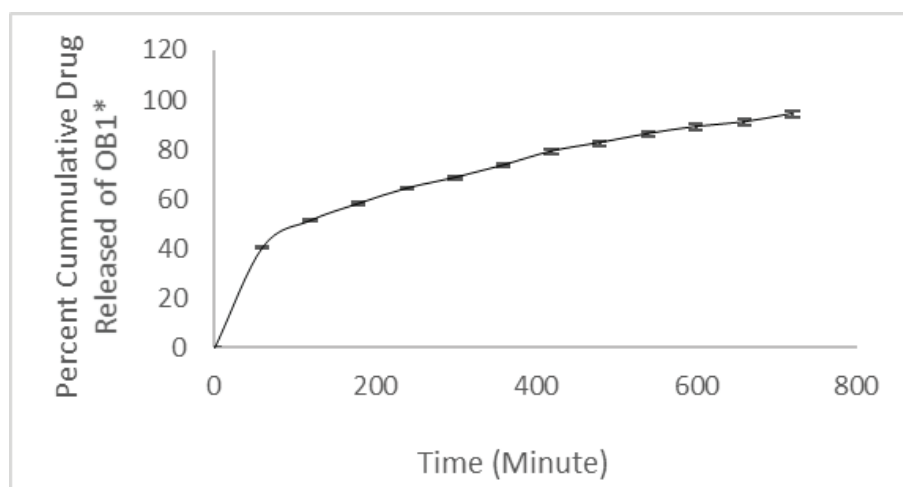


Figure 6. *In vitro* dissolution profile of PPH from UGF

CONCLUSION

In the present study, a bilayer unfoldable gastroretentive film of PPH was successfully prepared and

optimized to achieve immediate and sustained drug release from a single dosage form. The optimized system consisted of a fast-dissolving immediate-release

layer of HPMC K-100LV/PVP K-30 paired with a sustained-release layer based on Kollicoat SR 30-D, which provided rapid drug availability ($t_{90} = 5.18$ min) followed by controlled release for approximately 12 hours ($t_{90} = 688.71$ min). Remarkably, a coating polymer, Kollicoat SR 30-D, which is used conventionally, was successfully repurposed as a film-forming matrix for the controlled release of a highly water-soluble drug by a diffusion-dominated mechanism, as confirmed by Korsmeyer–Peppas kinetics ($n = 0.483$) and SEM analysis. The bilayer film showed good drug-content uniformity, acceptable mechanical strength, fast unfolding, low moisture uptake and low water vapour permeability, indicating its physicochemical stability and suitability for gastroretentive application. These results demonstrate the potential of unfoldable bilayer gastroretentive systems to improve the therapeutic performance of highly water-soluble drugs with a need for extended gastric residence time and controlled drug release, and establish Kollicoat SR 30-D as a promising platform for sustained-release film formulations.

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AUTHOR CONTRIBUTION STATEMENT

Resources, Materials, Data Collection and Processing, Literature Search, Writing – Original Draft (W.R.), Conceptualization, study Design, Supervision, Resources, Data Analysis and Interpretation, Literature Search, Writing, and Critical Reviews (S.D.), Analysis/ Interpretation, Writing (M.Y.), Analysis/ Interpretation, Critical Reviews (K.N.), Writing, Critical Reviews (G.R.).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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