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Formulation Development and Evaluation of a Bilayered Tablet Containing Dapagliflozin and Metformin

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Abstract:
The overall Bilayered tablets may offer an effective platform for combining the two drugs or formulations with distinct release characteristics within a single dosage form. The current study had been done to design and develop bilayered tablets based on the concept of loading dose to achieve quick attainment of peak plasma concentration and sustained therapeutic efficacy. Design and development of twenty bilayered tablet formulations, incorporating the concept of loading dose strategy for both dapagliflozin and metformin. The immediate-release layer containing dapagliflozin was formulated to provide a rapid pharmacological response, while the sustained-release layer containing metformin was designed to maintain prolonged drug release. Due to the interaction between dapagliflozin and magnesium stearate observed, excipients and superdisintegrants were tried in the developed formulations S1–S10 and include sodium starch glycolate, croscarmellose sodium, sodium citrate, sodium lauryl

sulphate, and potassium citrate (inclusive of BP grades). Metformin lactose monohydrate, lactose anhydrous, mascrogenol, and magnesium stearate were tested for interaction in the case of the metformin sustained-release layer. Based on this, formulations S11–S19 were prepared using hydrophilic polymers like HPMC K-15, HPMC E-50, and HPMC K-100 for controlled drug release. No major drug–excipient incompatibility was noted in optimized formulation. Optimized formulation S20 successfully ensured the loading dose through immediate release of dapagliflozin and sustained release of metformin. Optimization of immediate release layer and sustained-release layer was done separately.

Keywords: Dapagliflozin, Metformin, super disintegrants, hydrophilic polymers

INTRODUCTION

Bilayered tablets, also called double-layer tablets, are one of the latest innovative devices in controlled drug delivery systems. These particular tablets are designed mainly to overcome difficulties like the short life span of a drug and the incompatibility of drugs when co-administered. Such a drug delivery system has the advantage of combining two different drugs into one single tablet, which releases the drug immediately and then slowly, thereby providing optimal clinical results [1-5].

Dapagliflozin is an inhibitor of the sodium-glucose cotransporter 2 (SGLT2) and is used for the treatment of both type 1 and 2 diabetics. Another drug, metformin, a biguanide, finds widespread use as a medication for the treatment of patients suffering from type 2 diabetes, especially overweight individuals. Diabetes mellitus is a disease that requires prolonged treatment. Various side effects, like lactic acidosis, nephrotoxicity, and loss of vitamin B12 absorption followed by anemia, have been reported for metformin administered chronically. Moreover, polycystic ovary syndrome (PCOS), a frequent cause for infertility in women, is often associated with insulin resistance. Additionally, the inclusion of the loading dose of dapagliflozin in the immediate release layer may bring about a reduction in the dosage requirement for metformin, which could help reduce such adverse side effects. Moreover, the reduced frequency of administration also increases the patient compliance rates [6-9]. This study aims to develop a bilayer tablet form for the drugs metformin and dapagliflozin.

Methods

The materials used in this study were of an analytical grade. The preparation of the immediate-release component of dapagliflozin used the direct compression method. The materials were weighed precisely as shown in Table 1, and sieving through sieve numbers 12 and 16 followed. The formulation F10 used the superdisintegrates croscarmellose sodium and crospovidone [10-17].

The sustained release part of metformin was formulated by using the wet granulation method. All the ingredients were mixed uniformly in a mortar and granulated by a 5% wv solution of polyvinylpyrrolidone K30. The wet mass was passed through sieve number 18, and the obtained granules were dried at 40 + 5°C for 10 minutes [18-21]. Then, the dried granules were lubricated and pressed by a 16 Station Rotary Tablet Compression Machine. The composition of sustained release formulations is given in table 2.

Ingredients	**S1 mg**	**S2 mg**	**S3 mg**	**S4 mg**	**S5 mg**	**S6 mg**	**S7 mg**	**S8 mg**	**S9 mg**	**S10 mg**
Concentrations of Super disintegrants	**3%**	**5%**	**7%**	**3%**	**5%**	**7%**	**3%**	**5%**	**7%**	
Dapagliflozin	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**
Crosspovidone	**0.35**	**0.65**	**0.91**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Cross carmellose	**-**	**-**	**-**	**0.35**	**0.65**	**0.91**	**-**	**-**	**-**	**0.65**
Sodium starch glycol ate	**-**	**-**	**-**	**-**	**-**	**-**	**0.35**	**0.65**	**0.91**	**0.65**
Magnesium stearate (2%)	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.65**
Micro crystalline										

cellulose (25%)	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Lactose	102	102	102	102	102	102	102	102	102	102
Total Weight	120	120	120	120	120	120	120	120	120	120

.Table 1: Formulation of Dapagliflozin by Direct compression method

Ingredients	S11 (mg)	S12 (mg)	S13 (mg)	S14 (mg)	S15 (mg)	S16 (mg)	S17 (mg)	S18 (mg)	S19 (mg)
Metformin	500	500	500	500	500	500	500	500	500
HPMC K 15 (drug:polymer)	250 (1:0.5)	125 (1:0.25)	75 (1:0.125)	-	-	-	-	-	-
HPMC K 50	-	-	-	250 (1:0.5)	125 (1:0.25)	75 (1:0.125)	-	-	-
HPMC K 100	-	-	-	-	-	-	250 (1:0.5)	125 (1:0.25)	75 (1:0.1.25)
PVP K 30	10	30	40	10	30	40	10	30	40
MCC	5	40	40	5	40	40	5	40	40
Magnesium stearate	5	20	20	5	20	20	5	20	20
Isopropyl	qs	qs	qs	Qs	qs	Qs	qs	qs	qs

alcohol									
Lactose	**5**	**60**	**100**	**5**	**60**	**100**	**5**	**60**	**100**
Total weight	**775**	**775**	**775**	**775**	**775**	**775**	**775**	**775**	**775**

Table 2: Formulation of Metformin Sustained Release tablets by wet granulation method

Preformulation Studies

All dried granules of dapagliflozin and metformin were subjected to preformulation studies to evaluate their flow and compressibility characteristics. Parameters such as bulk density and tapped density (g/mL) were determined, along with other relevant precompression evaluations [22].

Post-Compression Studies

The prepared tablets were evaluated for the following post-compression parameters:

Weight Variation

Twenty tablets were randomly selected and individually weighed. The average weight was calculated, and percentage weight variation was determined using the following formula:

$$\%Weight\ variation = \frac{Average\ weight - Individual\ weight}{Individual\ weight} \times 100$$

Thickness

Tablet thickness was measured using a Vernier caliper. Ten tablets were randomly selected, and thickness was expressed as mean ± standard deviation (SD).

Hardness

Tablet hardness was evaluated using a Monsanto hardness tester. Five tablets were randomly selected, and hardness was expressed in kg/cm².

Friability

Ten tablets were dedusted and accurately weighed (W_0) and placed in the drum of an Electrolab Friabilator (EF-2, USP). The drum was rotated at 25 rpm for 100 revolutions. After testing, the tablets were removed, dedusted, and reweighed (W_1). Percentage friability was calculated using the formula:

$$\%Friability = (1 - \frac{W1}{W0}) \times 100$$

Swelling Index

Pre-weighed tablets (W_1) were immersed in 900 mL of 0.1 N HCl and maintained at 37 °C using a USP Type-I dissolution apparatus. At predetermined intervals, tablets were removed, surface liquid was blotted, and tablets were reweighed (W_2). The test was performed in triplicate [23].

$$Swelling\ Index = \frac{W2 - W1}{W1} \times 100$$

Content Uniformity

Twenty tablets were powdered, and a quantity equivalent to the labeled dose was accurately weighed and transferred to a 100 mL volumetric flask. Initially, 5 mL of phosphate buffer was added and shaken for 10 minutes, followed by volume adjustment with phosphate buffer. The solution was filtered, suitably diluted, and analyzed spectrophotometrically at 237 nm and 233 nm.

$$\%Drug\ content = \frac{Measured\ drug\ content}{Label\ claim} \times 100$$

Disintegration Time

The disintegration time of each tablet was determined using a USP disintegration test apparatus in 0.1N HCl at a temperature of 37 ± 0.5°C [3, 4].

In-Vitro Dissolution

The in-vitro dissolution test was performed using 0.1 N hydrochloric acid as the dissolution medium for the IR component, while the SR component was tested using phosphate buffer (pH 6.8). The test was conducted using a dissolution

apparatus of the USP type-II (paddle type), with a volume of 900mL of 0.1 N HCl maintained at a temperature of 37 °C ± 0.5 °C, with a paddle speed of 50 rpm for a period of 2 hours [24]. Following this, the dissolution medium was changed to pH 6.8 phosphate buffer, and the test was continued for another 12 hours. At regular time intervals, 5mL aliquots were removed, filtered, and replenished with the same volume of fresh medium. The samples were then appropriately diluted, whenever necessary, and analyzed by spectrophotometry at 233nm with a UV vis spectrophotometer [25]. Preparation of Bilayered Tablets Bilayered tablets containing dapagliflozin as IR component, and metformin as SR component, utilizing appropriate super-disintegrants, polymers, and other materials as given in Table 3.

Table 3: Formulation of bilayered tablet of Dapagliflozin and Metformin

S. No.	Ingredients	F 20 (Formulation code)
1	Dapagliflozin (mg)	13.76
2	Cros Carmel lose (6%)	0.69
3	Sodium starch glycol ate (7%)	0.67
4	Magnesium stearate (3%)	0.36
5	Micro Crystalline cellulose (4%)	0.67
6	Lactose (mg)	60.98
7	Metformin (mg)	500
8	HPMC K 100 (1: 0.7)	350
9	Micro crystalline cellulose (mg)	5.5
10	Poly vinyl pyrolidone k 40 (mg)	10.9
11	Isopropyl alocohol	Qs

1 **2**	**Lactose (mg)**	**5.3**

Bilayered Tablet Compression

Dapagliflozin bilayer tablets were compressed using 14 mm round concave punches in a tablet compression machine. First, the dapagliflozin granules were placed in the die cavity, and compression was carried out to produce tablets with a hardness of about 4-5KP to form the immediate release component. Then, the metformin granules were placed over the compressed dapagliflozin component and compressed to produce bilayered tablets of hardness 12-14KP [16-21].

Evaluation of Pre-Compression and Post- Compression Parameters

The prepared bilayered tablets were tested for both pre-compression and post-compression parameters. This will help analyze the compressibility properties and flowability of the prepared bilayered tablets.

Conclusion

FT-IR Compatibility Test

The FT-IR spectrum of the pure drug and the physical mixture (1:1 ratio) of Dapagliflozin and Metformin were recorded on the potassium bromide pellet method at a resolution of 2 cm^{-1} within the spectral range of 3200-3600 cm^{-1}. The lack of appearance and shifts indicated the lack of interaction.

Pre-Compression Evaluation

The pre-compression parameters, which included angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio, were also found to be within acceptable limits, which confirmed the optimum flow and compression properties of granules**.**

Evaluation after Compression - Immediate Release Layers and Sustained Release Layers

Results emerging from post-compression testing showed uniform weight, appropriate hardness, and adequate mechanical strength of all the formulated preparations, ensuring successful compression and flow characteristics. The friability values and height evaluation further confirmed that the tablets were non-breakable under handling and transportation factors while maintaining uniformity of size. The uniformity of content was between 96.12% +/− 0.04% w/v and 99.91% +/− 0.04% w/v, which was an excellent verification of uniformity (Tables 4 & 7).

Disintegration Time of Dapagliflozin

Disintegration time of dapagliflozin preparations was found to be in the range of 53 ± 0.03 to 75 ± 0.03 seconds (Table 5). Among all preparations, the shortest disintegration time was found in formulation S10, that is, a mixture of 5% croscarmellose sodium and 5% sodium starch glycolate, with a disintegration time of 53 ± 0.03 seconds. This can be ascribed to the combined effects of swelling and wicking properties of superdisintegrants [17].

In-Vitro Drug Release of Dapagliflo

In-vitro dissolution studies revealed that higher drug release was found in formulations S6 and S9 at 60 minutes. Further improvement in dissolution was achieved with formulation S10, which is prepared combining superdisintegrants. This formulation disintegrated completely in 30 minutes, making it ideal for an optimized IR formulation. The fast release of the drug can be attributed to the formation of a porous tablet structure and rapid water penetration due to superdisintegrants. A positive correlation coefficient was found between disintersion time and dissolution rate, validating that formulation S10 is an optimized IR layer.

Swelling Index Values for Metformin Formulations

Swelling index value ranges for sustained release formulation (S11-S19) varied from 32.45 to 47.53 (Table 7). The maximum swelling index was recorded for formulation S17 (47.53) which showed successful hydration and formation of polymer matrix. Evaluation post-Compression de comprimés libérateurs de The post-compression parameters for metformin sustained-release tablets were found to be well within the pharmacopoeial specifications, indicating the satisfactory length, thickness, and weight (Table 7). In-Vitro Drug Release of Metformin Tablets Dissolution studies were performed in pH 1.2 HCl for the initial 2 hours, followed by pH 6.8 phosphate buffer. It was observed that an increase in the concentration of the polymers resulted in decreased drug release because of the increased viscosity of the gel phase, hence increased diffusion paths. Of the tested polymers, HPMC K100 showed higher drug release compared with HPMC K15 and HPMC E50. This was due to the higher viscosity that increased chain entanglement, hence higher energy required for the disentanglement of the chains and diffusion of the drug molecules [18,19]. The formulation S17 with HPMC K100 in ratio 1:0.5 released 97.36% w/v drug in 12 hours, thereby classifying it as the best formulation among the sustained release formulations (Table 8).

Preparation and Evaluation of Bilayered Tablet

The optimized bilayered tablet (S20) was formulated with S10 as IR, and S17 as SR. The pre-compression and post-compression characteristics of bilayered tablets were within acceptable limits, showing a well-developed flow, compressibility, weight, and strength of the tablet (Tables 9 and 10). Bilayered Tablet Release of Drug in-vitro The dissolution profiles of bilayered tablets were done using 0.1 N HCl in the first 2 hours, followed by pH 6.8 phosphate buffer in the next 12 hours using a dissolution apparatus of Type II, as per USP standards. The IR component achieved the release of 90.62% w/v in 30 minutes, while the SR component achieved the release of 96.63% w/v in 12 hours. The release of metformin in the first 30 minutes was restricted to 10.49% w/v, which makes clear its negligible release in an acidic medium (Tables 11 & 12) [10]. Drug Release Kinetics and Stability Analysis Kinetics of drug release of optimized bilayered tablets (S20) were evaluated using mathematical models such as zero-order, Hixson Crowell models, etc. The drug release kinetics followed zero-order kinetics, which indicates that drug release is independent of concentration (Table 13). Stability studies were carried out at 40 ± 2°C and 75 ± 5% RH, which showed that there were no significant changes in drug content and cumulative drug release of S20 up to 3 months (Tables 13 **& 14).**

Table 4: Post Compression parameters of Dapagliflozin Immediate release Tablets

Formulation Code	**Weight variation[a] % (m g)**	**Hardness[b] kg/cm^2**	**Friability c %**	**Thickness (mm)**	**Drug content[d]**
S1	**125±0.07**	**3.0±0.10**	**0.56±0.03**	**3.38**	**97.25±0.03**
S2	**129±0.08**	**3.6±0.05**	**0.72±0.04**	**3.37**	**96.12±0.04**
S3	**129±.009**	**4.0±0.04**	**0.52±0.02**	**3.43**	**97.43±0.03**

S4	**131±0.09**	**4.0±0.02**	**0.52±0.01**	**3.29**	**97.05±0.03**
S5	**122±0.08**	**3.5±0.03**	**0.47±0.02**	**3.27**	**99.65±0.04**
S6	**134±0.09**	**3.0±0.21**	**0.42±0.03**	**3.40**	**98.31±0.05**
S7	**122±0.08**	**3.0±0.04**	**0.67±0.04**	**3.27**	**96.23±0.03**
S8	**125±0.09**	**3.0±0.2**	**0.49±0.05**	**3.30**	**98.41±0.03**
S9	**132±0.09**	**3.5±0.4**	**0.73±0.02**	**3.25**	**99.05±0.03**
S10	**126±0.08**	**4.0±0.10**	**0.75±0.03**	**3.44**	**99.91±0.04**

a: mean±%S.D n=10;b:mean ,n=3;c:mean,n=10,d:mean±S.D,n=3 Table 5:

Table 5: Disintegration time for Dapagliflozin Immediate Release tablets

S. No.	Formulation	Disintegration time (sec) ± SD(n=3)
1	S1	75±0.031
2	S2	55±0.041
3	S3	54±0.041
4	S4	53±0.031

5	**S5**	**54±0.031**
6	**S6**	**53±0.031**
7	**S7**	**56±0.031**
8	**S8**	**55±0.041**
9	**S9**	**53±0.041**
10	**S10**	**53±0.031**

values expressed in n ± SD (mean ± standard deviation)

Table 6: *In vitro* Drug release of Dapagliflozin Immediate release Tablets

Time in Mins	**% CDR (X ± S.D)**									
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**
15.01	**40.38 ±0.14**	**37.30 ±0.04**	**63.87 ±0.05**	**41.53 ±0.04**	**52.30 ±0.03**	**64.07 ±0.04**	**39.23 ±0.02**	**53.61 ±0.04**	**70.98 ±0.04**	**90.62± 0.05**
30.01	**43.53 ±0.31**	**43.53 ±0.3**	**70.21 ±0.3**	**43.84 ±0.31**	**62.69 ±0.04**	**83.56 ±0.04**	**46.23 ±0.03**	**66.30 ±0.21**	**85.67 ±0.03**	**99.97± 0.05**
45.01	**46.3**	**58.11**	**78.92**	**44.90**	**70.46**	**88.95**	**48.15**	**76.92**	**89.98**	**-**

	2 ±0.05	**±0.2**	**±0.02**	**±0.04**	**±0.03**	**±0.03**	**±0.04**	**±0.01**	**±0.05**	
60.01	**49.22 ±0.12**	**61.05 ±0.3**	**85.67 ±0.03**	**48.30 ±0.03**	**80.84 ±0.02**	**92.09 ±0.05**	**50.12 ±0.02**	**81.69 ±0.02**	**94.39 ±0.04**	**-**

Values expressed in n ± SD (mean ± standard deviation)

Table 7: Post Compression parameters of Metformin Sustained release Tablets

Formulation code	**% Weight variation[a] (mg)**	**Hardness [b]kg/cm²**	**Friability c%**	**Thickness (nm)**	**Swelling index(%)**	**Drug content[d]**
S11	**857±0.01**	**5.6±0.04**	**0.18±0.03**	**6.14±0.03**	**45.42**	**96.13±0.04**
S12	**854±0.02**	**5.3±0.05**	**0.16±0.04**	**6.12±0.03**	**42.51**	**95.34±0.03**
S13	**849±0.03**	**4.8±0.034**	**0.13±0.02**	**6.10±0.02**	**41.73**	**97.23±0.03**
S14	**859±0.04**	**5.7±0.030**	**0.16±0.035**	**6.14±0.03**	**46.31**	**97.56±0.02**
S15	**858±0.03**	**5.2±0.026**	**0.15±0.03**	**6.13±0.04**	**42.14**	**99.65±0.04**
S16	**856±0.02**	**4.6±0.045**	**0.13±0.04**	**6.10±0.04**	**39.31**	**98.09±0.02**

S17	847±0.02	5.8±0.036	0.18±0.02	6.14±0.04	47.53	99.78±0.03
S18	860±0.01	5.7±0.03	0.16±0.01	6.12±0.03	42.71	99.67±0.03
S19	849±0.04	5.5±0.05	0.13±0.03	6.10±0.03	32.45	99.45±0.04

a: mean±%S.D,n=10;b:mean ,n=3;c:mean,n=10,d:mean±S.D,n=3

Table 8: *In vitro* drug release of Metformin Sustained release Tablet

Time in hrs	% CDR (X ± SD)								
	S11	S12	S13	S14	S15	S16	S17	S18	S19
1.1hr	14.11 ±0.02	15.67 ±0.043	13.98 ±0.05	15.48 ±0.05	12.96 ±0.03	26.55 ±0.03	14.09 ±0.05	8.20 ±0.032	13.71 ±0.045
2.1hr	17.29 ±0.03	15.98 ±0.034	18.21 ±0.043	18.30 ±0.36	16.66 ±0.02	28.15 ±0.5	17.51 ±0.03	11.77 ±0.4	16.29 ±0.04
3.1hr	21.83 ±0.11	20.86 ±0.01	20.86 ±0.023	21.76 ±0.03	19.44 ±0.02	29.88 ±0.16	19.31 ±0.023	14.11 ±0.03	23.14 ±0.03
4.1hr	23.25 ±0.02	23.52 ±0.02	21.4 ±0.043	42.62 ±0.023	-	-	23.65 ±0.034	21.45 ±0.04	28.90 ±0.05
5.1hr	27.81 ±0.03	24.19 ±0.05	23.24 ±0.04	56.88 ±0.03	-	-	31.21 ±0.04	24.62 ±0.04	37.27 ±0.026
6.1hr	31.61 ±0.05	28.62 ±0.045	25.61 ±0.02	73.47 ±0.04	-	-	44.32 ±0.05	28.76 ±0.02	51.24 ±0.034

7.1hr	**34.75 ±0.04**	**32.34 ±0.034**	**31.05 ±0.03**	**74.10 ±0.05**	**-**	**-**	**55.14 ±0.02**	**31.03 ±0.03**	**52.00 ±0.042**
8.1hr	**39.73 ±0.01**	**35.37 ±0.023**	**31.84 ±0.02**	**79.16 ±0.035**	**-**	**-**	**69.14 ±0.03**	**-**	**60.66 ±0.045**
9.1hr	**42.30 ±0.03**	**35.49 ±0.012**	**38.48 ±0.03**	**81.46 ±0.040**	**-**	**-**	**76.58 ±0.03**	**-**	**63.9 ±0.0 5**
10.1hr	**44.14 ±0.04**	**45.73 ±0.032**	**-**	**-**	**-**	**-**	**80.79 ±0.040**	**-**	**69.91 ±0.049**
11.1hr	**46.11 ±0.05**	**47.57 ±0.030**	**-**	**-**	**-**	**-**	**89.23 ±0.036**	**-**	**76.17 ±0.05**
12.1hr	**49.91 ±0.03**	**50.90 ±0.045**	**-**	**-**	**-**	**-**	**97.36 ±0.041**	**-**	**86.63 ±0.05**

Values expressed in n ± SD (mean ± standard deviation)

Table 9: Evaluation of Pre compression parameters of bilayered tablet

Formulation code	Angle of repose[a] (°)	Bulk density[b] (g/cc)	Tapped density [c](g/cc)	Carr's index[d] (%)	Hausner's Ratio [e]
S20	**29.06±0.031**	**0.87±0.031**	**0.95±0.041**	**17.56±0.021**	**1.30±0.041**

a:equivalent weight to 2g, mean±S.D,n=3;b:equivalent weight to 5g, mean±S.D,n=3, c:eqivalent weight to 5g,mean±S.D,n=3; d:mean±S.D,n=3; e:mean±S.D,n=3

Table 10: Evaluation of post compression parameters of bilayered tablet

Formulation code	Weight variation[a](mg)	Hardness[b]kg/cm²	Friability c%	Thickness (nm)	Swelling index(%)	Drug content[d]
S20	868 ±0.031	6.1 ±0.031	0.17 ±0.041	6.13 ±0.041	40.131	99.81 ±0.021

Table 11: *In vitro* drug release of Dapagliflozin (in bilayered)

% CDR (X ± SD)		
		S20 (Dapagliflozin)
1	0.5	90.62 ±0.031
2	1	94.94 ±0.041
3	1.5	99.97 ±0.031

Table 12: *In vitro* drug release of metformin (in bilayered)

		% CDR (X ± SD)
S. No.	Time	F20 (Metformin)
1	0.5	10.49 ± 0.041
2	1.1hr	13.8 ±0.031

3	**2.1hr**	**19.35±0.041**
4	**3.1hr**	**25.92 ±0.041**
5	**4.1hr**	**31.12±0.041**
6	**5.1hr**	**41.1±0.031**
7	**6.1hr**	**44.86±0.051**
8	**7.1hr**	**52.33±0.031**
9	**8.1hr**	**59.68±0.031**
10	**9.1hr**	**68.47±0.041**
11	**10hr**	**79.55±0.041**
12	**11hr**	**88.76±0.031**
13	**12hr**	**96.63±0.041**

Values expressed in n±SD (mean± Standard deviation

Table 13: Kinetic modelling of optimized formulation F20

Formulation code	Zero ord	First ord	Higuchi (r^2)	Koresmeyers Pappas	n value

	er (r^2)	er (r^2)		(r^2)	
S20	**0.991**	**0.781**	**0.9101**	**0.971**	**0.8081**

Table 14: Stability studies for Optimized Formulation (Bilayered Tablet)

Test	Initial	Storage at 40°±°C and 75±5%RH		
		1 Month	2 Month	3Month
Drug Content	99.7	99.1	99.7	99.8
% Cumulative drug release	99.6	99.4	96.3	96.3
Hardness	6.1±0.01	6.1±0.01	6.1±0.01	6.1±0.01

Conclusion

The formulation and evaluation of a bilayered tablet containing dapagliflozin and metformin using suitable superdisintegrants and hydrophilic polymers were successfully done in the present study. Among all the immediate-release formulations, F10, formulated using a combination of croscarmellose sodium and sodium starch glycolate, emerged as an optimized immediate release layer due to its quick disintegration and improved in-vitro dissolution performance. Likewise, formulation S17 was screened as the optimized sustained-release layer due to its excellent swelling behavior and % drug release pattern within control. The optimized bilayered tablet, S20, which had been prepared by combining formulations S10 and S17, showed satisfactory precompression and post-compression parameters and was

within official pharmacopeial limits. In-vitro dissolution studies of S20 showed an initial burst release of dapagliflozin, thus providing a loading dose, followed by sustained release of metformin for a period of up to 12 hours, with 96.4% w/v drug release that could assure maintenance therapy. Drug release from the optimized bilayered formulation was found to follow zero-order kinetics with a regression coefficient (r^2) of 0.9921, indicating release independent of concentration. The mechanism of release was found to be non-Fickian diffusion. Stability studies conducted on the optimized formulation confirmed that it remained stable for a period of three months, hence having the potential for long-term suitability in therapeutic use.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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