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FORMULATION DEVELOPMENT AND EVALUATION OF DAPAGLIFLOZIN AND METFORMIN BILAYERED TABLET

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ABSTRACT

Background: Bilayered tablets are formulations containing two different drugs or single drugs which are of different characteristic features. **Objectives:** The goal of this research was to develop bilayered tablets with a loading dose. of Dapagliflozin and maintenance dose of Metformin to achieve and maintain peak plasma concentrations rapidly. **Materials and Methods:** Twenty formulations were prepared, out of which F1- F10 comprises of optimizing Dapagliflozin immediate layer and F11 to F19 comprised sustained release layer of Metformin The loading dose was provided by an immediate release layer attempting several super disintegrants, while the maintenance dose was delivered through sustained release layer optimized using HPMC K-15, HPMC E-50, and HPMC K-100 polymers. **Results:** No drug-excipient interactions discovered. Both the immediate and sustained release layers were optimized separately before being merged to create the Bilayered tablets. The F10 formulation featured complete drug release within 30 minutes, whereas the F17 formulation had extended drug release of 97.36% w/v within 12 hours. F20 formulation, which was developed by mixing formulations F10 and F17, had a drug release of 96.63 percent w/v in 12hrs. The optimized formulation (F20) was found to have a Zero order release rate with a regression coefficient of 0.992, and the drug diffusion from the system was found to be Non-Fickian Diffusion. After three months, the optimized formulation (F20) was determined to be stable, with no changes in physical properties. **Conclusions:** The optimized formulation (F20) provided the loading dose of Dapagliflozin giving the immediate pharmacological effect, thus maintained the effect with sustained action of metformin.

Keywords: Dapagliflozin, Metformin, super disintegrants, hydrophilic polymers

INTRODUCTION

Bilayered tablets, often known as double-layer tablets, are a more recent breakthrough in the field of controlled release formulation. Bilayered tablets were developed to overcome a drug's half-life or a drug's conflicting activity when taken together. To create a new bilayered tablet with one drug acting as an instant release layer and the other acting as a sustained release layer **[1]**. Dapagliflozin is an SGLT2 inhibitor that treats both type 2 and type 1 diabetes. Metformin is a Biguanide that is employed in the treatment of type 2 diabetes, particularly in overweight people. Diabetes is a chronic disease which requires long term treatment, prolonged use of Metformin is associated with lactic acidosis which includes renal impairment, PCOS (polycystic ovarian syndrome) is a major cause of infertility in women and also interferes with the absorption of vitamin B12 leading to anemia. Dose reduction by giving loading dose of Dapagliflozin (immediate release) will eventually reduce the above effects; whereas reduction in dosing frequency will lead to patient compliance **[2]**. The goal of this study is to design and develop Dapagliflozin and Metformin Bilayered Tablets.

METHODS

All of the substances used in the investigation are analytical grade. Direct Compression Method was used to create the dapagliflozin immediate release layer. All the ingredients were weighed as per **Table 1** sieved, using sieve number 12 and 16. Formulation F10 was prepared using combination of super disintegrants (crosscarmellose and crospovidone).

Preparation of metformin sustained release tablets

Wet granulation method is employed for preparing metformin in which all the contents were mixed in mortar, wet granulated with 5% solution of PVP K30, passed via sieve number 18. The granules obtained were dried for 10min at 40ºC ±5 for a period of 10min. The resultant dried granules were lubricated, compressed using 16 station rotary tableting machine. The composition of formulation was given in the **Table 2**.

Table 1: Formulation of Dapagliflozin by Direct compression method

Ingredients	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 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 2: Formulation of Metformin Sustained Release tablets by wet granulation method

Ingredients	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)	F16 (mg)	F17 (mg)	F18 (mg)	F19 (mg)
Metformin	500	500	500	500	500	500	500	500	500
HPMC K 15 (drug:polyme r)	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 alcohol	qs	qs	qs	Qs	qs	Qs	qs	qs	qs
Lactose	5	60	100	5	60	100	5	60	100
Total weight	775	775	775	775	775	775	775	775	775

Preformulation studies

All the dried granules of dapagliflozin and metformin were subject to preformulation Studies like Bulk and Tapped density (g/ml) and remaining studies.

Tablets were subjected for following post compression studies

Weight variation

At random, the average and individual weights of twenty tablets were calculated.

Percentage Average weight-individual weight/individual weight *100 = Weight variance

Thickness

To measure the thickness of tablets, vernier callipers are routinely employed. There were a total of ten tablets. selected at random for measuring the thickness, which was expressed in mean SD using nm as the unit.

Hardness

The hardness of tablets was determined by sampling five tablets at random and evaluating the hardness of each using a Monsanto hardness tester. The hardness was

measured in kilograms per square metre.

Percentage Friability

Prior to testing, ten tablets were meticulously dedusted and precisely weighed (Wo) fed into the Electrolab Friabilator's EF-2 drum (USP). At a speed of 25rpm, the drum was turned 100 times. The tablets were collected, dusted, and weighed precisely (W1). The following formula is used to compute it:

% Friability= 1-W1/Wo * 100

Swelling index determination

The weighed (W1) tablets were immersed in 900ml of 0.1N HCl and stored at 37^{o}C in a USP apparatus type-I. At regular intervals, the tablets were selected out of the basket and any extra liquid was swept away. The tablets were weighed once again (W2). The tests were performed three times.

Swelling Index = W2-W1/W1 * 100

Content Uniformity

After powdering 20 tablets, the dose equivalent weight of the powder blend was correctly weighed and placed in a 100mL volumetric flask. Phosphate buffer (5 mL) was introduced first, followed by 10 minutes of agitation. The volume was then increased to 100mL using the phosphate buffer. The filtrate was diluted to the appropriate concentration and spectrophotometrically detected at 237 and 233 nanometers in the volumetric flask.

Percentage Drug content = Drug content label claim × 100

Disintegration Time

Using a disintegration test apparatus in 0.1N HCl, 37±0.5ºC the disintegration time was calculated **[3, 4]**.

Invitro Dissolution study

The study was conducted in 0.1N Hydrochloric acid for immediate release layer and buffer for sustained release layer. Briefly, the USP-II apparatus (Paddle method) with 900mL of 0.1 N HCl was setup which was allowed to reach a temperature of 37ºC after equilibration. A tablet was placed in the vessel and equipment was run at 50 rpm for up to 2 hours. 0.1 N HCL was removed after 2 hours, replaced it with 6.8 phosphate buffer, and then continued for another 12 hours. 5ml of dissolution medium was taken at regular intervals, filtered, and replaced with 5ml of fresh medium. (If necessary, appropriate dilutions with dissolving medium were made and examined) spectrophotometrically at max 233 nm using a UV – spectrophotometer **[5]**.

Preparation of bilayered tablets

Bilayered tablet was prepared by the Dapagliflozin as immediate layer and Metformin as sustained layer with suitable super disintegrants, polymers and excipients **(Table 3)**.

Table 3: Formulation of bilayered tablet of Dapagliflozin and Metformin

S. No.	Ingredients	F 20 (Formulation code)
1	Dapagliflozin (mg)	13
2	Cros Carmel lose (5%)	0.65
3	Sodium starch glycol ate (5%)	0.65
4	Magnesium stearate (2%)	0.26
5	Micro Crystalline cellulose (5%)	0.65
6	Lactose (mg)	60
7	Metformin (mg)	500
8	HPMC K 100 (1: 0.5)	250
9	Micro crystalline cellulose (mg)	5
10	Poly vinyl pyrolidone k 30 (mg)	10
11	Isopropyl alocohol	qs
12	Lactose (mg)	5

Compression of Bilayer Tablet

The contents were punched using 14 mm round concave punches utilising tablet compression machine. Dapagliflozin granules were introduced first , compressed to a hardness of about 4-5KP. Then the granules of Metformin were added and compressed to a good pressure of 12- 14 KP **[6]**.

Evaluation of Precompression and post compression parameters

The prepared Bilayered tablets were tested for pre and post Compression tests.

RESULTS

By using potassium bromide pellet method, FT-IR spectra of pure drug and drug: polymer (1:1) for dapagliflozin and metformin physical mixtures were in the range of 3200-3600 cm-1 at a spectral resolution of 2cm-1, with no additional peak observed. Pre- compression results for angle of repose, bulk density, tapped density, Compressibility index and Hausner's ratio exhibited the required attributes following the limits.

Post compression studies of Immediate release and sustained release layers

Weight variation, hardness values among all the blends indicates good flow property, mechanical strength and compressibility properties. The percentage friability and thickness figures show that the product can withstand wear and tear during handling and shipping, and consistency in depth fill. The percentage drug content were in the range of 96.12%w/v ±0.04 to 99.91%w/v ±0.04 indicating a high level of uniformity in the drug's content **(Table 4 &7)**.

Determination of Disintegration time

Disintegration time for all the formulation blend of Dapagliflozin was conducted, the results in the table 5 ranged from 53 ± 0.03 to 75 ±0.03 sec. F10, formulated using the combination of excipients i.e., 5% crosscarmellose and 5% sodium starch glycollate exhibited disintegration time of

53±0.03sec, the combination of swelling and/or wicking of crosscarmellose and sodium starch glycollate could be the source **[7]**.

In vitro drug release of Dapagliflozin tablets

The formulations of Dapagliflozin were studied for vitro drug release studies **(Table 6)**. Of all formulations, F6 and F9 showed the highest release at 60 mins. An attempt was made formulating F10 using combination of superdisintegrants namely 5% of crosscarmellose and 5% of sodium starch glycollate in order to increase the dissolution rate. Thus, formulation F10 exhibited complete drug release within 30min time indicating to be an optimized formulation. Formation of porous structure on the tablet surface due to sublimation and the presence of superdisintegrants enhancing water permeation into the tablet, leading to faster wetting action, disintegration time, and ultimately causes the fast dissolution rate might be the reason behind it . A positive correlation was observed between disintegration time and dissolution rate which indicates that the F10 formulation is the optimized formulation for Bilayered tablet.

Swelling Index: Swelling index revealed that all the formulation (F11 – F19) developed in the formulation‘s development phase are in the range of 32.45 to 47.53 **(Table 7)**. Formulation F17 exhibited maximum swelling index of 47.53.

Post Compression parameters of Metformin Sustained release Tablets

Post compression parameters of metformin sustained release tablets were found to be within the limits satisfying the physical attributes of a tablet **(Table 7)**.

In vitro drug – release of metformin tablets

Formulations of Metformin were endured to in vitro release studies in 900 ml of pH 1.2 HCL during the initial 2 hours, then phosphate buffer pH 6.8 for the remainder of the time. The results indicate that increase in polymer ratio resulted in the decrease in the drug release. The reason is that when the polymer proportion increased, the viscosity of the matrix gel layer expanded, leading to a longer diffusion path. As a result of this phenomenon, the drug's effective diffusion decreased, lowering the drug's release rate. Among the polymers used, HPMC K100 found to have extended drug release compared to HPMC K15 and HPMC E50. The polymer chain disentanglement is influenced by the viscosity of the polymer. A polymer with a higher viscosity causes more chain entanglement than a polymer with a lower viscosity at the same polymer

concentration. As a result of the considerable energy required to pull longer chains off the matrix, it is more difficult for them to dissolve **[8, 9]**. F17 formulated with HPMC K 100 (1:0.5) was found to have extended drug release of 97.36 %w/v within 12 hrs of time than compared to HPMC K 15 and HPMC E 50. Thus, it can be stated that F17 formulation can be an optimized formulation. Hence it is considered to be a best formulation for sustained release layer **(Table 8)**.

Formulation of Bilayered tablet

Bilayered tablet was formulated taking F10 formulation as an immediate release layer and F17 formulation as a sustained release layer.

Evaluation of pre compression and post compression parameters of bilayered tablet

For bilayered tablets, pre and post-compression parameters were investigated and the results were determined to be within acceptable bounds **(Table 9)**. Results indicate all the granules were observed to have good flow and good compressibility properties.

Post compression results indicate that all the tablets in the batch (F20) were observed to have uniform weight variation and mechanical strength **(Table 10)**.

In vitro drug release of bilayered Tablets

In vitro drug release experiments of bilayered tablets were conducted in 900mL of 0.1N HCl for the first 2 hours and then in phosphate buffer pH6.8 of 900mL for the remaining 12 hours, using the USP dissolving apparatus type II. From the results, drug release of immediate release layer was found to be 90.62%w/v in 30 min and that of Metformin sustained release layer was observed to be 96.63%w/v at the end of 12hrs and %drug release of Metformin in first half an hour found to be 10.49%w/v **(Table 11 & 12)**. It means that the release of sustained release medication in the preferred medium for immediate release layer was determined to be insignificant, indicating that there were no anomalies in bilayered tablet drug release **[10]**.

Kinetics drug release and Stability studies

To understand the release mechanism kinetics of Bilayered Tablet an attempt is made to fit into mathematical models and n, (r^2) values for zero order, Hixson Crowell was calculated. F20 formulation fits good into the Zero - order kinetics which describes that the systems is independent of concentration **(Table 13)**. Stability studies were performed for optimized formulation F 20 at 40º±ºC and 75±5%RH. The drug content, Percentage Cumulative drug release values indicates that the formulation was highly stable up to 3 months time **(Table no 13 & 14)**.

Table 4: Post Compression parameters of Dapagliflozin Immediate release Tablets

Formulation Code	Weight variation[a] % (m g)	Hardness[b] kg/cm²	Friability c %	Thickness (mm)	Drug content[d]
F1	125±0.07	3.0±0.10	0.56±0.03	3.38	97.25±0.03
F2	129±0.08	3.6±0.05	0.72±0.04	3.37	96.12±0.04
F3	129±.009	4.0±0.04	0.52±0.02	3.43	97.43±0.03
F4	131±0.09	4.0±0.02	0.52±0.01	3.29	97.05±0.03
F5	122±0.08	3.5±0.03	0.47±0.02	3.27	99.65±0.04
F6	134±0.09	3.0±0.21	0.42±0.03	3.40	98.31±0.05
F7	122±0.08	3.0±0.04	0.67±0.04	3.27	96.23±0.03
F8	125±0.09	3.0±0.2	0.49±0.05	3.30	98.41±0.03
F9	132±0.09	3.5±0.4	0.73±0.02	3.25	99.05±0.03
F10	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: Disintegration time for Dapagliflozin Immediate Release tablets

S. No.	Formulation	Disintegration time (sec) ± SD(n=3)
1	F1	75±0.03
2	F2	55±0.04
3	F3	54±0.04
4	F4	53±0.03
5	F5	54±0.03
6	F6	53±0.03
7	F7	56±0.03
8	F8	55±0.04
9	F9	53±0.04
10	F10	53±0.03

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)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
15	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	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	46.32 ±0.05	58.11 ±0.2	78.92 ±0.02	44.90 ±0.04	70.46 ±0.03	88.95 ±0.03	48.15 ±0.04	76.92 ±0.01	89.98 ±0.05	-
60	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]
F11	857±0.02	5.6±0.04	0.18±0.03	6.14±0.03	45.42	96.13±0.04
F12	854±0.04	5.3±0.05	0.16±0.04	6.12±0.03	42.51	95.34±0.03
F13	849±0.05	4.8±0.034	0.13±0.02	6.10±0.02	41.73	97.23±0.03
F14	859±0.04	5.7±0.030	0.16±0.035	6.14±0.03	46.31	97.56±0.02
F15	858±0.04	5.2±0.026	0.15±0.03	6.13±0.04	42.14	99.65±0.04
F16	856±0.04	4.6±0.045	0.13±0.04	6.10±0.04	39.31	98.09±0.02
F17	847±0.05	5.8±0.036	0.18±0.02	6.14±0.04	47.53	99.78±0.03
F18	860±0.02	5.7±0.03	0.16±0.01	6.12±0.03	42.71	99.67±0.03
F19	849±0.03	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)								
	F11	F12	F13	F14	F15	F16	F17	F18	F19
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
2hr	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
3hr	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
4hr	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
5hr	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
6hr	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
7hr	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
8hr	39.73 ±0.01	35.37 ±0.023	31.84 ±0.02	79.16 ±0.035	-	-	69.14 ±0.03	-	60.66 ±0.045
9hr	42.30 ±0.03	35.49 ±0.012	38.48 ±0.03	81.46 ±0.040	-	-	76.58 ±0.03	-	63.9 ±0.05
10hr	44.14 ±0.04	45.73 ±0.032	-	-	-	-	80.79 ±0.040	-	69.91 ±0.049
11hr	46.11 ±0.05	47.57 ±0.030	-	-	-	-	89.23 ±0.036	-	76.17 ±0.05
12hr	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] (º)	Bulk density[b] (g/cc)	Tapped density [c](g/cc)	Carr's index[d] (%)	Hausne r's Ratio [e]
F20	29.06±0.03	0.87±0.03	0.95±0.04	17.56±0.02	1.30±0.04

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

Formula tion code	Weight variation[a](mg)	Hardnes s[b]kg/cm²	Friability $c_{\%}$	Thickness (nm)	Swelling index(%)	Drug content[d]
F20	868 ±0.03	6.1 ±0.03	0.17 ±0.04	6.13 ±0.04	40.13	99.81 ±0.02

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

% CDR (X ± SD)		
		F20 (Dapagliflozin)
1	0.5	90.62 ±0.03
2	1	94.94 ±0.04
3	1.5	99.97 ±0.03

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

% CDR (X ± SD)		
S. No.	Time	F20 (Metformin)
1	0.5	10.49 ± 0.04
2	1hr	13.8 ±0.03
3	2hr	19.35±0.04
4	3hr	25.92 ±0.04
5	4hr	31.12±0.04
6	5hr	41.1±0.03
7	6hr	44.86±0.05
8	7hr	52.33±0.03

9	**8hr**	**59.68±0.03**
10	**9hr**	**68.47±0.04**
11	**10hr**	**79.55±0.04**
12	**11hr**	**88.76±0.03**
13	**12hr**	**96.63±0.04**

Values expressed in n±SD (mean± Standard deviation

Table 13: Kinetic modelling of optimized formulation F20

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Koresmeyers Pappas (r^2)	n value
F20	**0.992**	**0.785**	**0.910**	**0.976**	**0.808**

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	**99.79**	**99.77**	**99.75**	**99.71**
% Cumulative drug release	**99.63**	**99.60**	**96.58**	**96.55**
Hardness	**6.1±0.03**	**6.1±0.02**	**6.1±0.02**	**6.1±0.02**

CONCLUSION

The present study demonstrated successful formulation of Dapagliflozin and Metformin bilayered tablet prepared using super disintegrants and hydrophilic polymers. Formulation F10 prepared using combination of crosscarmellose and sodium starch glycolate was observed to be an optimized formulation based on disintegration time and in vitro dissolution studies. Similarly on the basis of in vitro drug release and swelling index, F17 formulation was considered to be an optimized formulation.

F20 was prepared using the combination of above optimized formulation (F10 and F17).The pre and post compression results was found to be within limits of official compendia. In vitro dissolution studies of F20 indicate that there was a burst release effect observed due to immediate release of Dapagliflozin studies providing loading dose and later sustaining the release of drug up to 12hrs with release rate of 96.63%w/v sustaining the release of maintenance dose.

Drug release of Optimized formulation followed Zero order kinetics with regression coeffient of r^2 0.992 and the diffusion of drug from the system was observed to be Non- fickian diffusion and stable for 3months.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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