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Original article

Response Surface Methodology (RSM) approach to formulate and optimize the bilayer combination tablet of Tamsulosin and Finasteride

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ABSTRACT

An orally administered bilayer tablet with Tamsulosin (TAM) as the sustained release (SR) and Finasteride (FIN) as immediate release (IR) was manufactured. A response surface methodology was employed to formulate bilayer tablets with individual release layers, i.e., sustained and immediate release (SR and IR). Independent variables selected in both cases comprise hydroxypropyl methylcellulose (HPMC) as SR polymer, and avicel PH102 in the inner layer while Triacetin and talc in the outer layer, respectively. Tablets were prepared by direct compression, a total of 11 formulations were prepared for inner layer TAM, and 9 formulations for outer layer FIN were designed; these formulations were evaluated for hardness, friability, thickness, %drug content, and %drug release. A central composite design was employed in response surface methodology to design and optimize the formulation. The percentage of drug released was evaluated by *in-vitro* USP dissolution method of optimized formulation for 0.5, 2, and 6 hrs, and results were 24.63, 52.96, and 97.68 %, respectively. Drug release data was plotted in various kinetic models using a D.D solver, where drug release was first order that is concentration dependent and was best explained by Korsmeyer–Peppa kinetics, as the highest linearity was observed (R^2 = 0.9693). However, a very close relationship was also noted with Higuchi kinetics (R^2 = 0.9358). The mechanism of drug release was determined through the Korsmeyer model, and exponent "n" was found to be 0.4, indicative of an anomalous diffusion mechanism or diffusion coupled with erosion.

1. Introduction

Bilayer tablets are medicines that consist of two same or different drugs combined in a single dose to effectively treat the disease (Akhtar et al., 2020). Bilayer tablet has patient compliance and is beneficial for either the sequential release of two drugs in combination or sustained and immediate release of the same drug, one as an initial and the other as a maintenance dose (Arun et al., 2012; Bhuiyan & Dewan, 2014; Din et al., 2014). Bilayer tablets are appropriate for the sequential release of two drugs to be given combined. It separates the two mismatching drugs.

Benign prostatic hyperplasia (BPH) is a common disease in older men that can result in bothersome lower urinary tract symptoms that decrease quality of life by interrupting sleep and daily activities (Kaplan, 2006; Welch et al., 2002). The available data suggest that combination therapy can be beneficial in treating BPH and associated lower urinary tract symptoms (Greco & McVary, 2008). combination therapy with tamsulosin and finasteride was significantly more effective than either

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component alone in reducing symptoms (Shrestha & Karmacharya, 2015).

Finasteride *N-(I,* l-Dimethylethyl)-3-oxo-4-aza-5iX-androst-l-ene-17 ~ carboxamide having molecular formula $C_{23}H_{36}N_2O_2$, molecular weight 372.6, melting point 252–254 °C. White or almost white, crystalline powder, practically insoluble in water, freely soluble in ethanol, and methylene chloride (Commission et al., 2020; Convention, 2019). Finasteride is the first 5 alpha-reductase inhibitor that has gotten clinical endorsement for treating human benign prostatic hyperplasia and androgenetic alopecia (Finn et al., 2006). Oral finasteride (FNS), a synthetic 4-aza-3-oxosteroid compound with poor water solubility, blocks the peripheral conversion of testosterone to dihydrotestosterone (DHT), causing a marked decrease in DHT concentration, accomplishing adequate results in treating alopecia (Roque et al., 2017). Finasteride is promptly absorbed from the gastrointestinal tract. The bioavailability of orally administered finasteride in humans was reported in one study to be 80 %; Finasteride crosses the blood–brain barrier and is distributed into semen. It is metabolized in the liver. The mean terminal half-life is about 6 h in patients under 60 years of age but may be prolonged to about 8 h in those 70 years of age or older (Carlin et al., 1992).

Tamsulosin is a selective alpha-1A and alpha-1B adrenoceptor antagonist that has a major effect on the prostate and bladder (Dunn et al., 2002; O'Neil, 2006), It has therapeutic significance in treating symptomatic BPH (Caine et al., 1975). Tamsulosin is available as a controlled release (modified release) 0.4 mg and 0.8 mg once-daily oral formulation with almost 100 % bioavailability (Wilde & McTavish, 1996). Tamsulosin is approximately 99 % protein-bound (Franco-Salinas et al., 2010); its metabolism takes place in the liver via the cytochrome P450 (CYP) enzyme system, primarily CYP3A4 and CYP2D6 (Dunn et al., 2002). The pharmacokinetics of Tamsulosin are not affected to a major extent by age; the half-life of Tamsulosin is 9–13 h (Tolou Ghamari & Mazdak, 2017). American Urological Association guidelines advise that combination therapy with an alpha-blocker and a 5-alpha-reductase inhibitor can be appropriate and effective for patients with lower urinary tract symptoms with enlarged prostates (Kaplan, 2006). Sabbagh *et al. designed a study to compare the effect of tamsulosin (a selective α1- blocker)* on BPH with the effect of combination therapy with tamsulosin and finasteride. The study's results suggested that tamsulosin and finasteride are effective drugs for BPH treatment (Sabbagh & Khalighinezhad, 2018). Combination therapy with finasteride and tamsulosin was significantly more effective in our study compared to tamsulosin alone.

2. Material and method

Active Pharmaceutical Ingredients (APIs) used in this research project, tamsulosin and finasteride, were taken from Lee Pharma India and Hubei Gedian Humanwell Pharmaceutical Co Ltd. China, respectively, while excipients, Avicel PH-102 (JRS Pharma Germany), HPMC K100M (Hangzhou Zhongbao, China), HPMC E5 (Hangzhou Zhongbao, China), lactose anhydrous (DMV-Fonterra Germany), Aerosil (Evonik Germany), magnesium stearate (Peter Geven Malaysia), triacetin (Hangzhou Zhongbao, China), talc (Merck Germany), Tween 80 (Croda Singapore), titanium dioxide (Precheza Czech Republic), iron oxide yellow (Univar Color the UK) procured through local vendors.

2.1. Preformulation studies

Two percentages of HPMC were chosen to generate a range for a central composite design using RSM modeling by a design expert. 10 % (TF1) and 90 % (TF2) concentration of sustained-release polymer HPMC K100 were used along with other excipients and API. The drug content and dissolution results are tabulated in Table 1, which helped form the range to be given in RSM modeling. The technique used was direct compression.

2.2. Levels of coded factors

The levels of coded factors and their values were tabulated in Table 2 for the inner layer and Table 3 for the outer layer.

2.3. Formulation of the sustain release layer

The TAM SR layer was prepared by direct compression to reduce time and cost. TAM 0.4 mg is the recommended amount corresponding to 0.436 mg of TAM hydrochloride.

2.3.1. Formulation design

The RSM is used in modeling and optimizing the formulation Field (Chelladurai et al., 2021). Both inner and outer layers were designed by using a design expert. Later the optimization of both layers was done, followed by the preparation of bilayer tablets, enclosing TAM as the inner layer and FIN as a coated outer layer, to be released immediately. During pilot studies, the hit and trial method was employed using various concentrations of the polymers. Amongst different trials, TF1 and TF2 were processed and evaluated, containing HPMC 10 % and avicel PH102 85 % and HPMC 60 % along with 35 %. Although the hit and trial method were quite laborious and costly, it was still concluded that an HPMC K100M, in the range of 20–40 %, and an avicel pH 102 in the range of 15 to 55 % could be used to develop a reasonable formulation. Hence, making the best use of the efforts during pilot studies, the said ranges of the excipients were considered as minimum and maximum levels to be used by design experts to generate different trials following Central Composite Rotatable Design (CCRD).

Table 1
Drug Content Inner and outer layer.

Tamsulosin					**Finisteride**		
Formulation (inner layer)	% Drug content	% Drug Dissolved in buffer pH 7.2			Formulation (Outer layer)	% Drug content	% Drug dissolved in water (at 45 min)
		30 min (<40 %)	2 Hours (20 to 60 %)	6 Hours (NLT 75 %)			
TF1	98.9	5.23	18.62	26.39	FF1	98.43	99
TF2	100.7	89.46	90.51	92.01	FF2	100.25	70
TF3	99.4	80.99	91.27	99.65	FF3	98.67	68
TF4	101.3	27.45	36.86	67.28	FF4	98.43	87.59
TF5	100.9	12	25.59	34.18	FF5	92.21	18.76
TF6	98.4	68.77	71.89	72.62	FF6	99.08	99
TF7	99.7	22.08	32.63	58.98	FF7	100.64	98.98
TF8	100.3	75.98	84.03	85.71	FF8	98.47	86.87
TF9	100.9	22.19	53.79	101.37	FF9	101.78	77.24
TF10	102.1	14.17	33.89	43.3	FF10	100.96	98.36
TF12	101.8	24.63	52.96	97.68			
TF12 at pH 1.2		16.85	43.69	82.05	FF10 at pH 1.2		98.01

Table 2
Numerical optimized results inner layer.

Formulation	HPMC K100M (%)	Avicel pH 102 (%)	Dissolution 6hrs (predicted)	Dissolution 6hrs (actual)	Desirability
TF12	28.90	38.70	85	97.68	1

Table 3
Numerical optimized results outer layer.

Formulation	Plasticizer (%)	Lubricant (%)	Dissolution 6hrs (predicted)	Dissolution 6hrs (actual)	Desirability
FF10	1.4	0.75	95.8836	98.36	0.9987

2.3.1.1. Inner layer manufacturing technique. A total of nine (9) numbers of trials were generated using HPMC K100M as variable 1 (X_1) and Avicel PH102 as variable 2 (X_2) **(**Table 4**).** Two drug release responses at different time intervals and assay were studied and used to optimize the formulation.

An accurate weight of 0.218 g of TAM was taken on butter paper, and 2 g of HPMCK100 was added. The contents were then transferred to a polythene bag and 10 g of HPMCK100 was added and mixed for 100 cycles. The remaining HPMCK100, Avicel PH102 plus lactose anhydrous were added to the polythene bag and mixed for 50 cycles. Aerosil 200 (sieved through 20 mesh sieve) was added to the polythene bag, unified for 50 cycles. Magnesium stearate was added to a polythene bag and mixed for 50 cycles.

The responses of the design were added to the design software and only TF9 passed all the tests. Optimization was carried out, and TF12 was determined as the optimized drug design and was manufactured according to the procedure written above **(**Table 4**).**

2.4. Formulation design of outer layer IR

A total of nine (9) numbers of trials were generated using triacetin as variable 1 (X_1) and Talc as variable 2 (X_2) **(**Table 4**).** Two drug release and assay responses were studied and used to optimize the formulation.

2.4.1. Drug coating of outer layer IR

Purified water 50.192 g was accurately weighed, and FIN 10 g was dispersed in it; triacetin and talc in the concentration as per the designed formulation were added. HPMC E5, titanium dioxide, and iron oxide yellow were added in suspension and mixed for 45 min, then tween 80 was added and combined for a minute. The mean is noted, and a 13 % coating is calculated to bring about the desired results, increasing the tablet weight to 132 mg. The coating was carried out through the spray coating technique while the coating pan was rotating, the weight of five tablets are checked every 5 min, and the coating was stopped when the solution was finished. Further, 10 tablets were weighed to verify weight, and the process was completed.

2.5. Numerical optimization

Numerical optimization responses were evaluated and optimized formulation and their predicted outcomes were observed. The constraint parameters for numerical optimization of the inner layer were HPMC and Avicel pH 102 and both were targeted as 28.90 and 38.70, respectively. The outer layers were plasticizer and lubricant and both were targeted as 1.4 and 0.75, respectively as given in Tables 2 & 3.

2.6. Mathematical modeling

A quadratic model was selected and mathematical modeling was done by a design expert for calculated response and variables for both layers are

$$Y = X_0 + X_1 + X_2 + X_1X_2 + X_1^2 + X_2^2 \quad (4.1)$$

2.7. Evaluation of tablets

Physical tests of tablet thickness, weight variations, hardness, and friability were carried out on the sustained released tablet (inner layer), and weight variation of complete formulation (both inner and outer layer) was also performed, tabulated in Table 5 **&** Table 6.

2.7.1. Assay of tablet

Assay of prepared sustained release layer tablet (inner formulation) and complete formulation (both inner and outer layer) was conducted through a developed and validated method on HPLC (Table 1).

2.7.2. In vitro release studies of sustained-release tamsulosin tablet (inner layer)

Drug dissolution of prepared tamsulosin sustained-release tablet (inner layer) was evaluated, Test was performed in USP Apparatus Type-II. For the test method and chromatographic conditions, a USP monograph of tamsulosin pallets was used (Convention, 2019**).** Tablets were put in a dissolution vessel. 500 mL phosphate buffer pH 7.2 was transferred and the temperature was maintained at 37 °C. Test started rotating paddle at 100 rpm speed. After completion of 30 min of the

Table 4
Formulation design of TAM and FIN by DOE.

S. No.	TAM inner layer			FIN outer layer (drug coat)		
	Formulation	HPMC K100M (%)	Avicel pH 102 (%)	Formulation	Triacetin %	Talc%
1	TF03	15.86	35.00	FF1	1.05	0.29
2	TF04	30.00	63.28	FF2	0.70	0.50
3	TF05	40.00	55.00	FF3	0.70	1.50
4	TF06	20.00	55.00	FF4	1.05	1.00
5	TF07	40.00	15.00	FF5	0.56	1.00
6	TF08	20.00	15.00	FF6	1.40	0.50
7	TF09	30.00	35.00	FF7	1.40	1.50
8	TF10	44.14	35.00	FF8	1.54	1.00
9	TF11	30.00	6.72	FF9	1.05	1.71
10	TF12	28.9	38.7	FF10	1.4	0.75

Table 5
Weight Variation of the inner layer and complete tablet with both layer.

Formulation (inner layer)	Weight Variations in mg				Formulation (After drug coat)	Weight Variations in mg			
	Avg of 20 tab	Min weight	Max weight	RSD		Avg of 20 tab	Min weight	Max weight	RSD
TF3	125.2	121	132	2.56	FF1	130.2	127.6	135.4	1.77
TF4	125.32	121	132	2.51	FF2	130.5	126.7	134.8	1.68
TF5	125.31	121	131.7	2.5	FF3	130.2	127.1	136.7	1.85
TF6	125.21	121	131.7	2.45	FF4	128.5	126.8	132.2	1.19
TF7	125.19	121	132	2.36	FF5	129.5	122.4	138.7	2.92
TF8	125.2	121	131	2.06	FF6	130.5	127.0	136.6	2.15
TF9	125.3	122	131	1.97	FF7	130.1	125.5	133.6	1.8
TF10	125.33	121	131.5	2.14	FF8	129.6	125.3	134.1	1.95
TF11					FF9	131.6	127.5	137	2.25
TF12	125.21	121	129	1.82	FF10	132.8	127.8	137.6	2.5

Table 6
Thickness and Hardness.

Formulation (inner layer)	Thickness in mm				Hardness in KP			
	Avg of 20 tab	Min Thickness	Max Thickness	RSD	Avg of 20 tab	Min Hardness	Max Hardness	Std. Dev
TF3	3.27	3.22	3.34	1.47	9.8	8.8	10.4	0.55
TF4	3.27	3.21	3.34	1.43	9.9	8.5	11.3	0.89
TF5	3.27	3.25	3.34	0.93	9.6	9	11	0.7
TF6	3.29	3.23	3.35	1.22	9.8	9.1	10.4	0.48
TF7	3.23	3.2	3.3	1.5	9.3	8.3	10.3	0.56
TF8	3.23	3.1	3.3	2.09	9.7	8.8	10.9	0.7
TF9	3.21	3.1	3.3	2.3	10.6	9.3	12.1	0.83
TF10	3.21	3.1	3.3	2.3	9.4	8.9	9.9	0.32
TF12	3.19	3.1	3.4	3.12	10.7	9.6	11.7	0.72

tablet being immersed 10 mL of aliquot was withdrawn and stored in a test tube after filtration. The volume was replaced with 10 mL of the drug-release medium (phosphate buffer). The samples of 10 mL solution were withdrawn at specified time intervals of 2 and 6 h of tablet immersed and replaced the volume with 10 mL of drug release medium each time when the sample is withdrawn. 1 mL of 0.5 N HCl and 2 mL of internal standard solution (8 ppm propylparaben) were added to the test tube with a 10 mL withdrawn sample. This sample was used for the testing on HPLC. These time points were taken by a patent of tamsulosin formulation of sustained-release tablet (Lemmens and Maria, 2003).

For the final formulation (TF12) dissolution was also performed at pH 1.2 buffer. The test proceeded, and the time intervals and solution preparation performed were the same as for buffer pH 7.2. HPLC with an ultraviolet (UV) detector was used to quantify tamsulosin in both dissolution mediums, and analysis was performed using a C18 (4.00-mm x 15 cm) 5 μm column, temperature 40 °C. The wavelength of 225 nm and the flow rate was 1.3 mL per minute while the injection volume was 250 μL. Results are tabulated in Table 1 and Figs. 1–3.

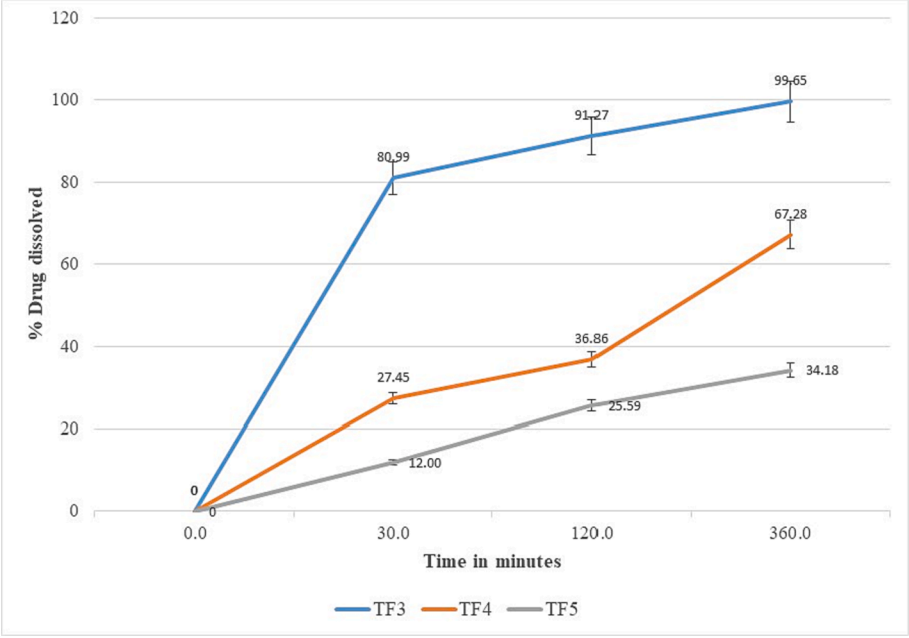

Fig. 1. Graph showing release pattern of TAM (inner layer) formulation No. TF3, TF4 & TF5 at different time point.

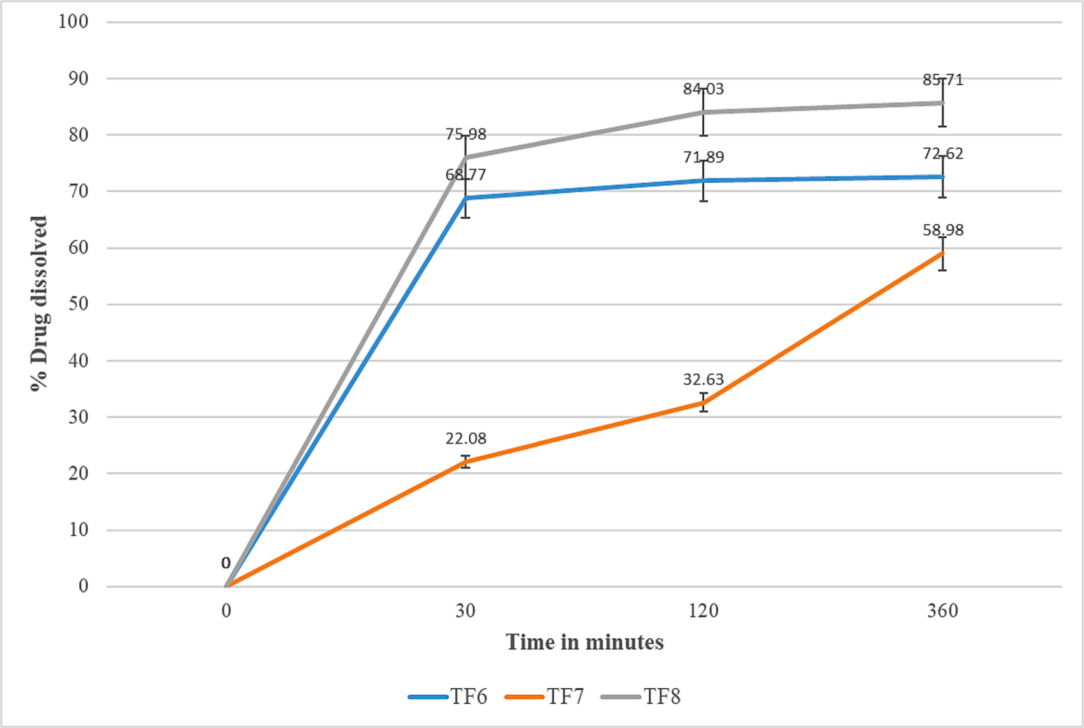

Fig. 2. Graph showing release pattern of TAM (inner layer) formulation No. TF6, TF7 & TF8 at different time point.

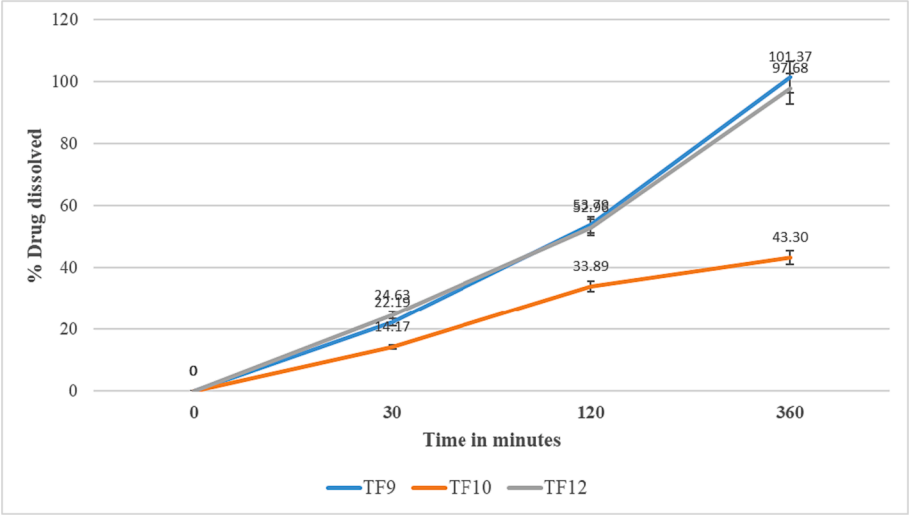

Fig. 3. Graph showing release pattern of TAM (inner layer) formulation No. TF9, TF10 & TF12 at different time point.

2.7.3. In vitro release studies of immediate-release finasteride (outer layer)

In-vitro drug release of the outer drug coat of FIN in a bilayer tablet was evaluated according to the USP monograph of FIN (Convention, 2019). Test performed in USP Apparatus Type-II, where tablets were put in dissolution vessel. 900 mL water as dissolution medium was added to the vessel and the temperature was adjusted to 37 °C. The test started rotating the paddle at 50 rpm speed. After the completion of 45 min of tablet immersion, 10 mL of aliquot was withdrawn and stored in a test tube after filtration. For final formulation (TF12)/ FF10 dissolution was also performed at pH 1.2 buffer. The test proceeded, time intervals, and solution preparation performed were the same as mentioned above. Results are tabulated in Table 1.

2.7.4. Drug release Kinetics

Release kinetics were studied for developed formulation using D.D solver software confirming release patterns and are elucidated in Table 7.

3. Result

3.1. Formulation and in-vitro drug release studies of bilayer

Nine (9) trials were formed with different concentrations of HPMC K100 (X_1), and avicel PH102 (X_2) were generated. All the formulations were tested on different physical and chemical parameters and all those formulations were excluded that didn't meet the specifications. In TF3 the HPMC K100 was 15.86 %, (X_1) avicel was 35 % (X_2) and the

Table 7
Release kinetics of TAM formulations by D. D solver.

Models		TF4	TF5	TF7	TF9	TF10	TF12	Mean
Zero order	R^2	0.2545	−0.0332	0.4002	0.8319	0.0017	0.7684	0.3706
	K_o	12.201	6.516	10.688	18.060	8.315	17.499	12.213
First order	R^2	0.6219	0.2244	0.6774	0.9684	0.3408	0.9714	0.6340
	K_1	0.219	0.085	0.172	0.446	0.120	0.435	0.246
Higuchi Model	R^2	0.9223	0.8896	0.9622	0.9822	0.8654	0.9933	0.9358
	KH	27.804	15.106	24.263	40.007	19.296	39.009	27.581
Korsmeyer-Peppas Model	R^2	0.9522	0.9613	0.9753	0.9994	0.9276	1.0000	0.9693
	KKP	31.406	17.881	26.430	34.968	22.689	36.087	28.243
	N	0.411	0.376	0.438	0.596	0.381	0.556	0.459
Hixson-Crowell Model	R^2	0.5181	0.1390	0.5951	0.9859	0.2292	0.9746	0.5737
	KHC	0.060	0.026	0.049	0.122	0.035	0.119	0.069

maximum drug was released in the first 30 min. However, with avicel 47 % and lactose anhydrous was also used which helped in quicker disintegration of tablets. TF4 was then formulated with 30 % HPMC K100 (X_1) and 63.28 % avicel PH102 (X_2) and failed to meet the sustained release effect on the 6th hour. TF5 was then formulated with 40 % HPMC K100 (X_1) plus 55 % avicel PH102 (X_2) and failed as only a small amount of the drug was released in the last time interval as HPMC K100 in higher concentrations decreases the release of the drug. TF6 was formulated with 20 % HPMC (X_1), 55 % avicel PH102 (X_2), and 22 % lactose anhydrous, and a large amount of drug was released initially in 30 min. TF7 was formulated with 40 % HPMC K100 (X_1), 15 % avicel (X_2), and adjusted with 23 % lactose and showed a more pronounced sustained effect, and approximately half of the quantity of the drug was released by 6 h.TF8 has 20 % HPMC K100 (X_1), 15 % avicel PH102 (X_2), and 62.8 % lactose anhydrous, and drug release followed the release kinetics of lactose with the maximum drug being released in the first 30 min. TF9 met all the specifications and was considered and used as an inner layer for coating nine different compositions of the outer layer that contained FIN. TF10 has increased % of HPMC that caused failure in drug release whereas TF11 has increased % of lactose decreased its flow and sticking problem and batch could not be compressed.

3.2. Formulation of outer layer

These nine formulations were also generated by the design expert having triacetin (X_1) and talc (X_2) as variables. The other ingredients along with the active FIN were used in a fixed quantity. In FF1 where the amount of triacetin was 0.303 (X_1) mixing time was enhanced to make a homogenous coating solution which resulted in difficulty in the coating. Although results of dissolution were found satisfactory but this formulation was rejected as extra time was given for mixing, in FF2 the concentration of triacetin (X_1 0.202) that is reduced, and talc (X_2 0.144) was increased that caused the formation of a heterogeneous mixture and drug was not incorporated properly causing lower dissolution rate. FF3 also failed on dissolution, and FF5 (X_1 0.162 and X_2 0.288) and FF6 (X_1 0.404 and X_2 0.144) had inadequate film and spray gun choking, respectively while in FF9 (X_1 0.444 and X_2 0.493) there was lower dissolution. FF4, FF7, FF8, and FF9 were found to be physically fine and showed dissolution specifications well within limits.

3.3. Physico chemical evaluation

3.3.1. FTIR

FTIR analysis of TAM and FIN API with their developed formulation was conducted. The pure drug TAM shows a characteristic absorption peak at 3394.59 cm^{-1} due to N—H bend, 1538 cm-1due to C═C stretching, and 1296.35 cm^{-1} due to S═O stretching 1257.21 cm-1 due to C═O stretching, 1166.72 cm-1 due to C—C stretching, 667.30 cm-1 due to C-S stretching. All these peaks remained unchanged in the IR of the physical mixture of drug and excipients which can be observed in the IR spectra of active in comparison with the inner layer. (Fig. 4) showed no physical or chemical reaction between TAM hydrochloride and other inactive inner layer (Fig. 5).

3.3.2. Hardness

The hardness of the inner layer was performed on 20 tablets; the rest were tabulated in Table 6.

3.3.3. Friability

The friability of all formulations was performed and elucidated in

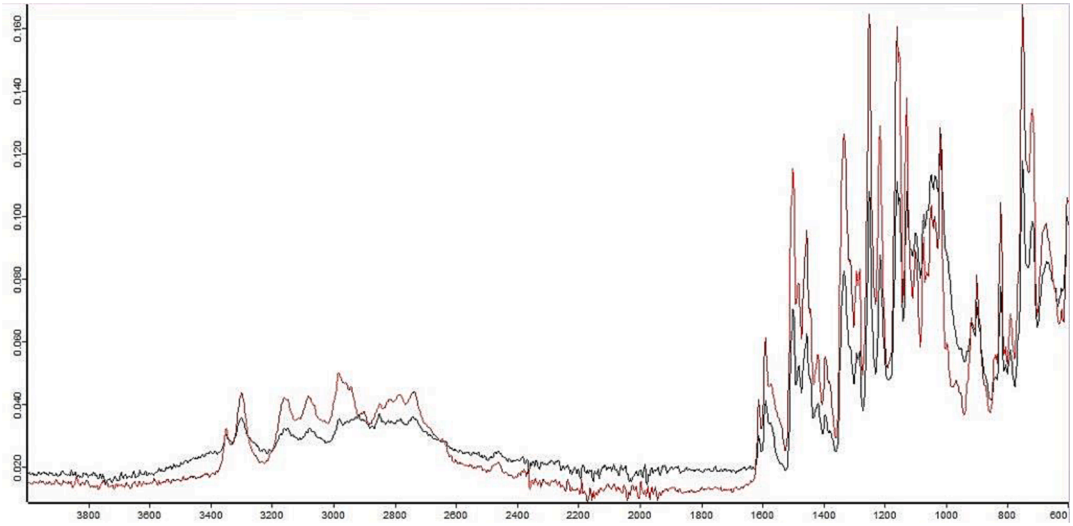

Fig. 4. IR Spectra of TAM API and the inner layer (Comparison).

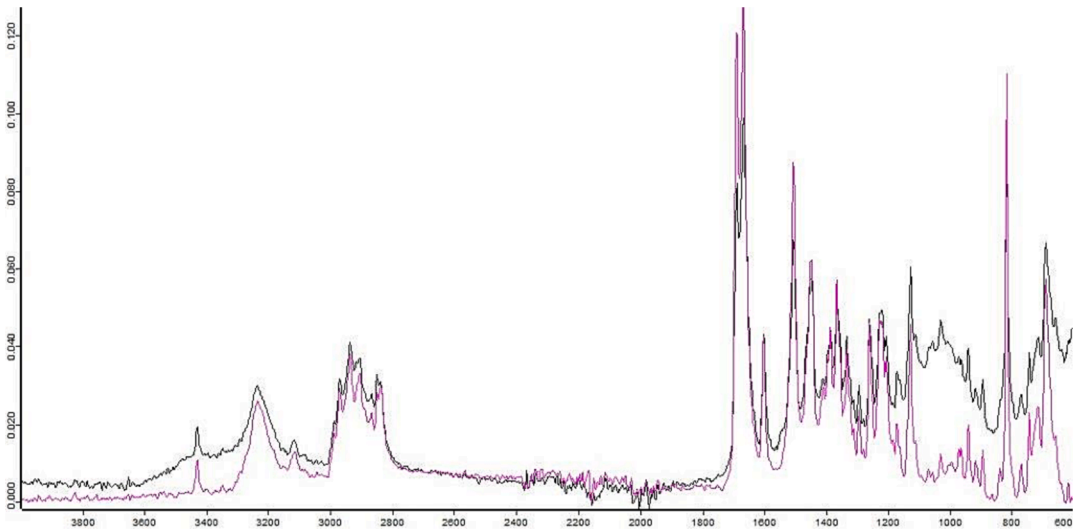

Fig. 5. IR Spectra of FIN API and optimized formulation (Comparison).

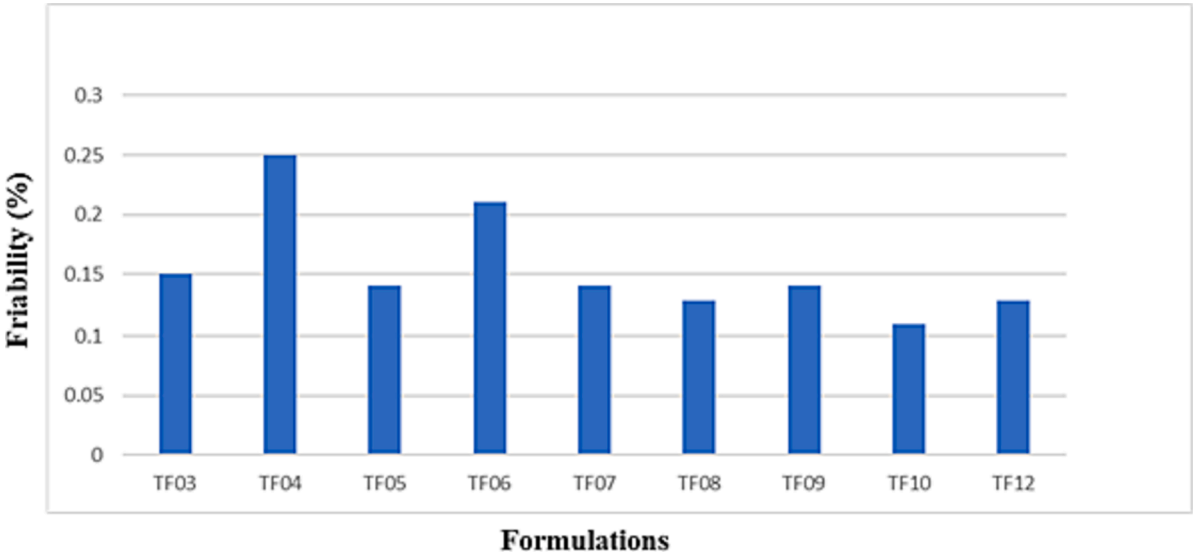

Fig. 6. Graphical representation of friability outcomes, confirming the values with in the prescribed range (<1%).

Fig. 6 showing all results are within the specified limit.

3.3.4. Weight variation

The weight variations of all compressed tablets (TF3 to TF12) came within the specified limit owing to the presence of a higher concentration of avicel PH102 (Table 5).

3.4. Assay

Simple, rapid, precise, and accurate HPLC method developed and validated for the concurrent determination of TAM and FIN in dosage forms. An assay of every developed formulation for both active ingredients was carried out and the content of all the formulations met the specifications mentioned in the individual monograph of USP as a separate drug product.

3.5. Drug release kinetics

Release kinetics tabulated in Table 7 was studied on formulations having a substantial change (TF4, TF5, TF7, TF9, TF10, and TF12). It followed Korsmeyer Peppawith n = 0.459 indicating non fickian diffusion. Delivery constants were determined from the slant of the fitting plots and regression coefficient (r^2) was determined (Table 7). It was found that *in-vitro* drug release of TF12 best explained by Korsmeyer-Peppas equation as plots showed highest linearity (r^2 = 0.9678) then Zero order (r^2 = 0.6269), First order (r^2 = 0.9441), Higuchi (r^2 = 0.9677), Hixon Crowell (r^2 = 0.9369). Followed non fickian diffusion (n = 0.459).

3.6. Mathematical modeling

3.6.1. Responses for the inner layer

All the 3D and contour graphs were generated from the results of responses in DOE were presented in Figs. 7–10 and ANOVA was applied on all the results to check the significance in Table 8**.** Variance studies by using ANOVA following the quadratic model were found significant for all time points of dissolution and the positive values of the equations define that the overall response is constructive. The assay was found insignificant but was very close to 0.1000 i.e. 0.1828. The equation a was positive shoeing beneficial response. The overall polynomial

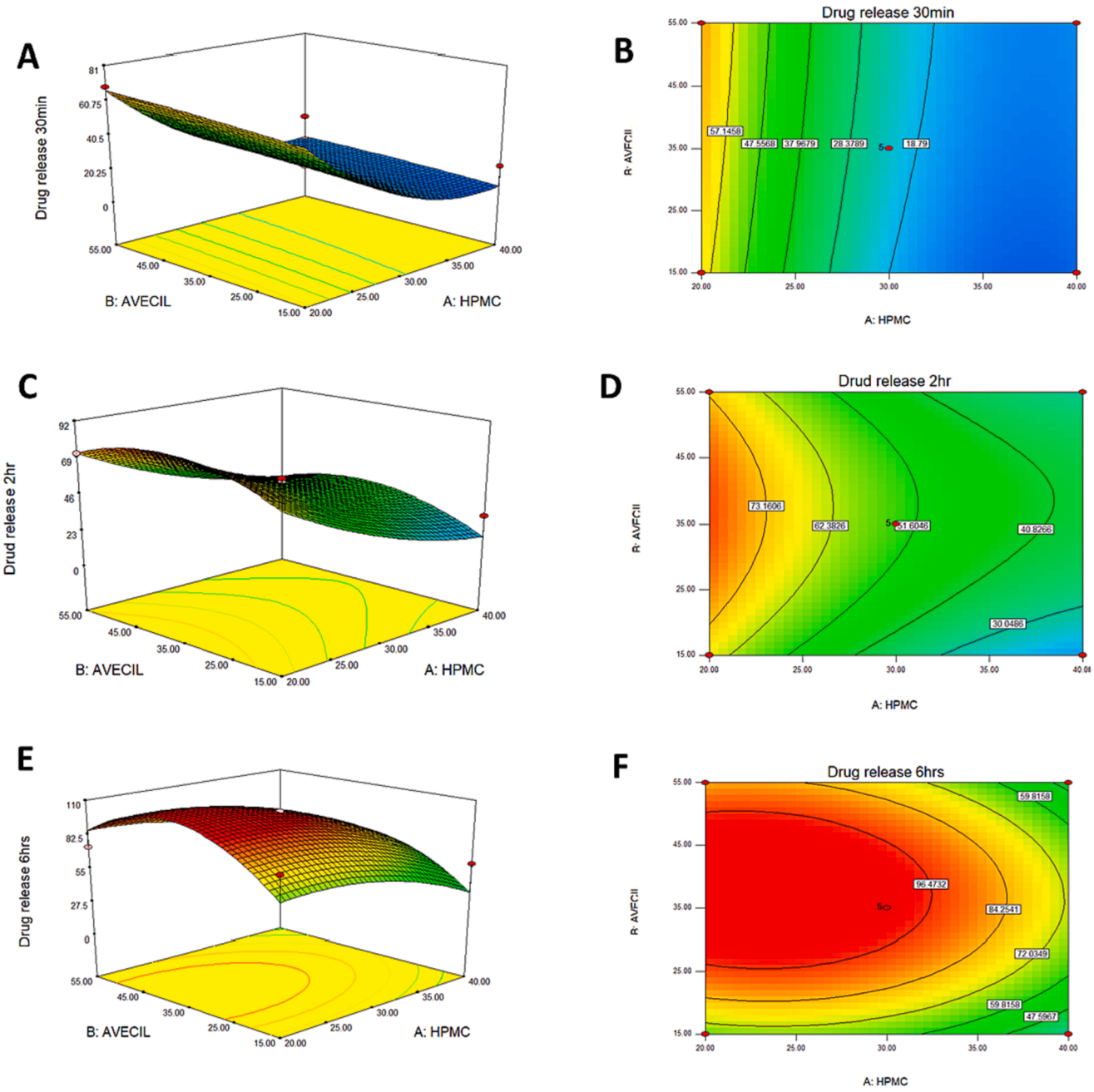

Fig. 7. 3D and Countor plots, describing the impact of HPMC K100M, and Avecil pH 102, on drug release (A & B) at 30 min, (C&D) at 2 hrs,(E&F) at 6hrs.

equation on the quadratic model was insignificant but the value was very close to the probability value. For assay both the factors were + ve and the complete equation was also positive depicting it being helpful. The product X_1X_2 correlates with positivity and thus will enhance drug content when their concentration increase.

Response 1 (Drug Release)

$$\text{TAM Diss. 30 min} : +22.19 - 25.65 + 2.69 - 0.72 + 16.21 - 0.72 \quad (7.1)$$

$$\text{TAM Diss. 2 hrs} : +53.79 - 22.36 + 4.12 + 1.28 + 7.65 - 14.42 \quad (7.2)$$

$$\text{TAM Diss. 6 hrs} : +101.37 - 18.11 + 7.16 - 2.93 - 12.37 - 31.29 \quad (7.3)$$

Response 2 (Assay)

$$\text{TAM Assay} : +100.90 + 0.95 + 35.81 + 0.78 + 5.96 - 19.09 - 35.99 - 0.48 \quad (7.5)$$

3.6.2. *Responses for the outer layer*

Response 1 (Drug Content)

$$\text{FIN Assay} : +98.43 + 1.22 + 0.56 + 0.84 - 1.06 + 1.32 \quad (7.6)$$

Response 2 (Drug Release)

$$\text{FIN Dissolution} : +87.59 + 19.54 - 4.10 + 0.50 - 14.01 + 3.65 \quad (7.7)$$

4. Discussion

A pilot scale study was conducted to determine excipients' suitability and their specific concentration range without applying design Expert (DOE). Different trials were attempted using varying concentrations of

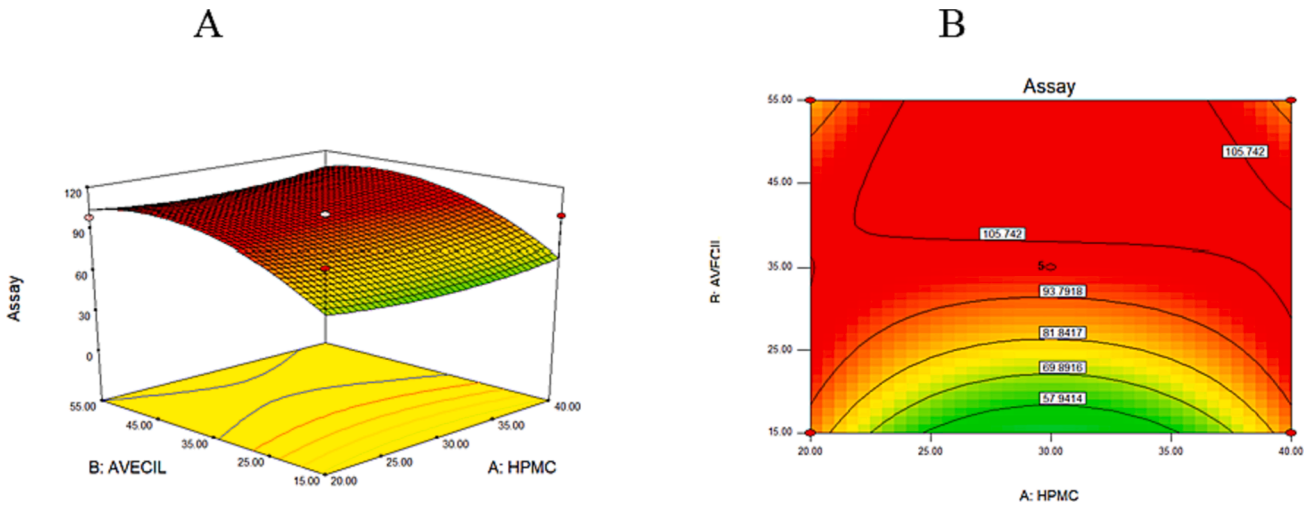

Fig. 8. 3D and Countor plots, describing the impact of HPMC K100M, and Avecil pH 102, on drug content (A & B).

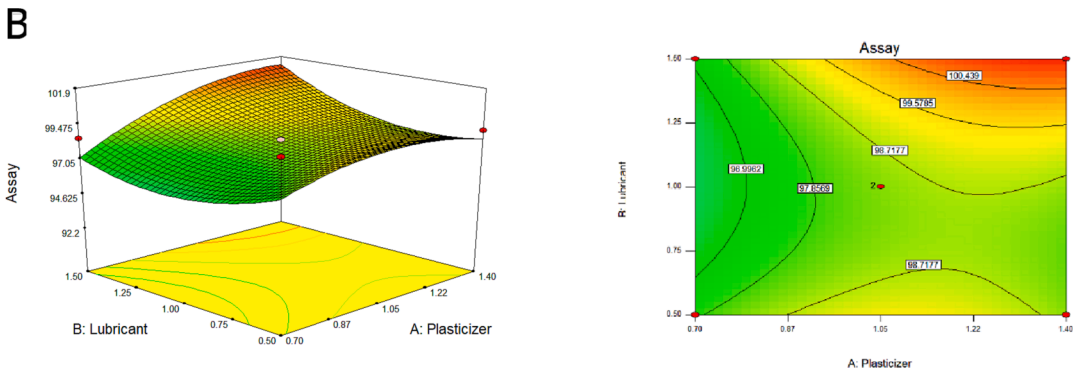

Fig. 9. 3D and Countor plots, describng the impact of Triacetin, and Talc, on drug content (A & B).

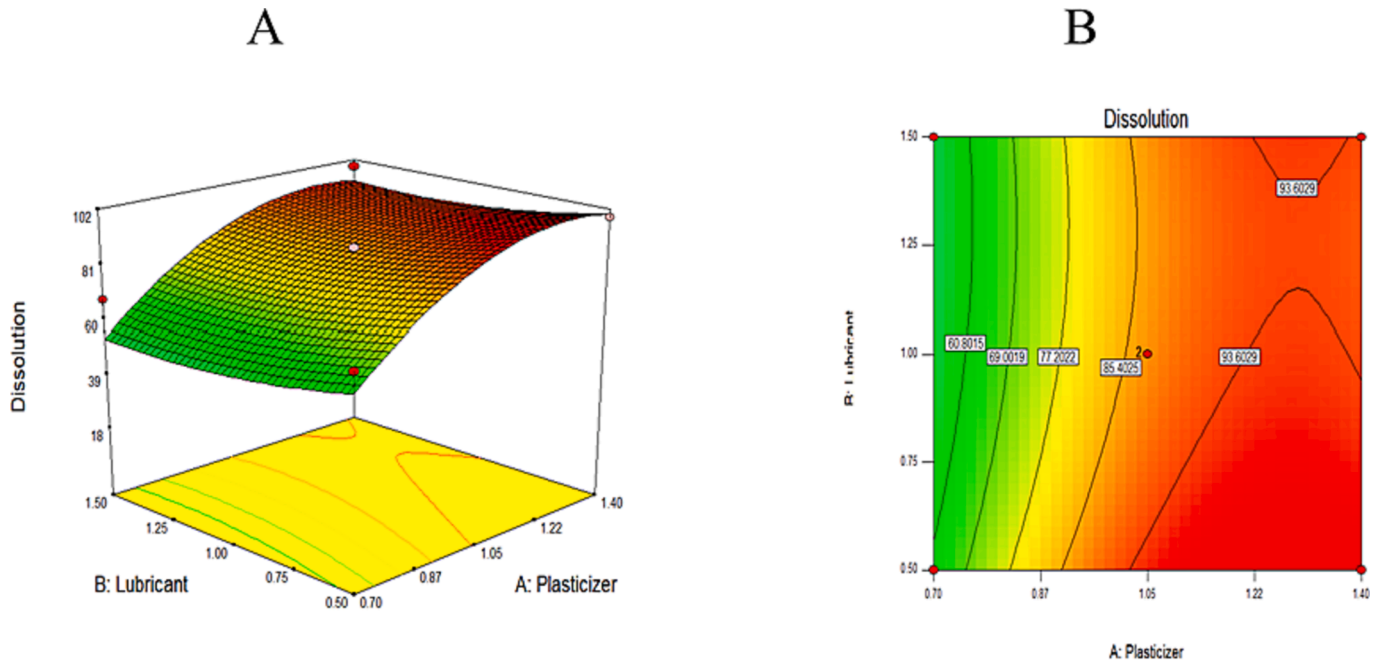

Fig. 10. 3D and Countor plots, describing the impact of Triacetin, and Talc, on drug Release (A & B).

Table 8
Analysis of variance for TAM dissolution 30 min.

Terms	Degree of Freedom	F-Value	P-Value	Significance
Model	7206.17	12.28	0.0023	Yes
X_1	5261.73	44.84	0.0003	Yes
X_2	57.94	0.49	0.5049	No
X_1X_2	2.06	0.018	0.8983	No
X_1^2	1827.64	15.58	0.0056	No
X_2^2	3.59	0.031	0.866	No

The applied model was found significant.

HPMC K100 along with other excipients. HPMC is used not only in oral tablets for a sustained release effect but also in tropical gels for the same purpose. Vaz *et al.*, formulated Hesperetin-loaded proposomal gel for topical antioxidant activity, suggesting that the gel can be an effective formulation with a controlled release profile and could be used to treat topical oxidative conditions (Vaz et al., 2021). The results demonstrated that TF1 showed very less release of the drug due to the high percentage of HPMC K100.

Saravanan *et al.,* reported the extended release pattern of cephalexin tablet in which 21 different trials were conducted with HPMC as polymer and dissolution consequences elucidates that higher quantity (Saravanan et al., 2003). HPMC in formulation resulted in minimized drug release whereas adding micro crystalline cellulose (MCC), commonly known as avicel caused faster drug release. In the second trial TF2, HPMC K100 was 10 %, avicel pH 102 was 85 % and lactose was 2.8 % and showed fast drug release within the first 30 min owing to the presence of a high percentage of avicel pH 102 made quick dispersible aceclofenac tablets and the impact of avicel PH102 was inspected on compressional, mechanical, and discharge properties of quick dispersible aceclofenac pills, and observed that formulation having avicel PH102 (20 %) displayed outstanding compactional strength with fast disintegration and speedy medication discharge (Yasmin et al., 2020).

In order to save time, to avoid wastage of excipients and to make the formulations optimized a statistical approach central composite rotatable design (CCRT) was applied using design expert version 12 with two variables (HPMC and Avicel pH 102 for inner layer and triacetin and talc for outer layer) and 5 level of factors. Singh *et al.,* used this technique resulting in developing atorvastation trihydrate porous tablet exhibiting improved dissolution rate of atorvastatin trihydrate (Singh et al., 2020). Bhaskaran, Jitta, *et al.,* also used DOE for the successful formulation of Irinotecan-loaded solid lipid nanoparticles (IRI-SLNs) which may benefit in delivering IRI to the tumour cells, therefore decreasing the dose and dose-associated toxicities (Bhaskaran et al., 2022a). DOE for response surface can be used in combination with other designs to effectively formulate optimize and study drug dependent variables. Praveen *et al.,* developed lamotrigine nanoliposomes (LTG-NLs) for the treatment in seizures. The nanoliposomes were optimized by plucket burman design (PBD) and response surface methodology (RSM) optimization techniques.the drug showed high entrapment in lipid bilayer and high release rate (Praveen et al., 2019). Kumari *et al.,* develop, optimize, and evaluate the naringin-loaded proposomal gel (PPG) for quick wound healing using central composite design optimized and naringin-loaded proposomes showed extended drug release that can be an alternative strategic approach to deliver the naringin for quick wound healing (Kumari et al., 2022). Similarly *Zaman et al.,* has also applied CCRD for the optimization and evaluation of different formulations (Zaman & Hanif, 2018; Zaman et al., 2018).

The generated variations of HPMC K100 (X_1), and avicel PH102 (X_2) were tested and results found that formulation TF5 having 40 % HPMC K100 (X_1) and 55 % avicel PH102 (X_2) failed in drug release studies as very less amount of the drug was released because of the different phenomenon and one is the high concentration of HPMC K100 as higher concentrations of HPMC K100 decreases the drug release. The results were similar with a previous study where authors developed different formulations of ketoprofen with natural and synthetic polymers and concluded that upon increasing the polymer ratio there is a decreased rate of drug release (Kaleemullah et al., 2017). In formulation TF6, having 20 % HPMC, a large amount of drug was released initially in 30 min as well and formulation TF7, having 40 % HPMC K100, showed more than half of the drug was released in the first 6 h. TF7, TF8, and TF10 were also unable to give the desired result, and TF11 showed increased stickiness, probably due to increased lactose content, and couldn't be compressed. TF9 and met all the specifications and the results were incorporated in DOE. An optimized formulation of TF12 was suggested with the desirability of 1(Table 2), met all the desired results and was considered and used as inner core for coating nine different compositions of outer layer that contained FIN where triacetin and talc were kept as variables A study reported that MCC of two different particle sizes from two manufacturers at two concentration levels showed different results (Patel et al., 1994). In grouping with anhydrous lactose or Fast-Flo lactose on several properties of hydrochlorothiazide tablets. Anhydrous lactose is more compressible than Fast-Flo lactose however Fast-Flo is more flowable and can be used in extra quick API release at increased MCC levels. In formulation of outer layer nine formulations were used to analyze the variables using CCD and an optimized formulation was also designed with the desirability as 0.9987 (Table 3) The results depicted that mixing time was increased in formulation FF1 to make a homogenous coating solution which resulted in difficulty in the coating. The results support the dissolution rate but rejected because of extra time. In contrary the formulation FF2 having less concentration of triacetin makes the heterogeneous mixture and drug was not incorporated properly causing lower dissolution rate. A study reported that HPMC due to its high tensile strength needs a plasticizer such as PEG or triacetin for optimal film formation (Kestur et al., 2021). While another study reported the impact of different plasticizers on some physical, and mechanical characteristics of HPMC concluded that plasticizers not only improve flexibility and decrease the fragility of the film but also may regulate the drug diffusion into the polymeric film (Rowe, 1984).

A study report the adsorption of bromhexine hydrochloride (BXH) on talc furthermore, announced that by expanding the concentration of talc the rigidity of the powder blend improved and prolonged the release of the drug (Jadhav et al., 2013). FF4, FF7, FF8 and FF9 were found to be physically fine and showed dissolution specification well within limits. An optimized formulation was tabulated and tested on TF12 forming both optimized layers showing desired results of dissolution of inner sustained layer and immediate drug release of outer layer The drug release kinetics was found to be anomalous diffusion with a value of $n = 0.459$ following Korsmeyer Peppa model indicating non fickian diffusion i.e diffusion coupled with erosion and it is time dependant. Kumar *et al.,* also formulated vaginal films using HPMC and the release kinetics followed korsmeyer Peppa model indicating a non fickian diffusion for sustained release of drug (Kumar et al., 2013). Bhaskaran *et al.,* studied the drug release kinetics on its different formulations of fluconazole cream showing anomalous diffusion following korsmeyer peppa model. The drug showed increased drug delivery, antifungal study and animal studies confirmed that the prepared formulation is non-irritant and has an enhanced antifungal activity that reduces the side effects of fluconazole (Bhaskaran et al., 2022b).

5. Conclusion

The present work deals with the formation of bilayer tablets with Tamsulosin as the sustained release and Finasteride as immediate release by utilizing a response surface methodology with individual release layers. It is observed that the percentage of drug released was evaluated the by *in-vitro* USP dissolution method of optimized formulation. Drug release was found first order that is concentration dependent and was best explained by Korsmeyer–Peppa kinetics. However, a very close relationship was also noted with Higuchi kinetics. The mechanism of drug releases an indicative of an anomalous diffusion mechanism.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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