Biological Forum – An International Journal **15(2): 794-803(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Design and Optimize a Bilayer Tablet of Antihypertensive Drugs using a 3^2 Factorial Design

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(Received: 04 January 2023; Revised: 12 February 2023; Accepted: 16 February 2023; Published: 20 February 2023)
(Published by Research Trend)

ABSTRACT: This research aimed to develop a bilayer tablet of telmisartan and Cilnidipine using a 3^2 factorial design approach. Telmisartan is an angiotensin II receptor antagonist, while Cilnidipine is a calcium channel blocker. By combining these drugs in a bilayer tablet, the physicochemical differences between them could be overcome, reducing the need for frequent dosing. The compatibility of the active ingredients and excipients in each layer is critical to the success of a bilayer tablet. One of the major challenges of bilayer tablet formulation is ensuring that the two layers remain separate and do not mix during manufacturing, storage, or handling. The tablet was formulated using Croscarmellose sodium and sodium starch glycolate as super disintegrants for the telmisartan layer, and HPMC K-100M, methylcellulose, and dicalcium phosphate for the Cilnidipine layer. The optimized batch of immediate-release F7 showed 95.51% drug release, while the sustained-release F5 batch showed 96.46% drug release. Compatibility studies using FTIR and different scanning calorimetry analyses confirmed compatibility between drug and excipients. Evaluation tests, including tablet dimension, hardness, friability, weight uniformity, drug content, and in-vitro dissolution, yielded satisfactory results, indicating the potential effectiveness of the optimized bilayer tablet for treating hypertension.

Keywords: Bilayer tablet, HPMC K100m, Telmisartan, Cilnidipine, Factorial design.

INTRODUCTION

The oral drug delivery system has its inherent advantage of patient-centric compliance as drug acceptance is decided by the patient. This patient autonomy suffers from less patient compliance with multiple drugs. One bilayer tablet can deliver two APIs, the same API with separate release profiles. Bilayer tablets can be designed to produce tablets with the same or different Active pharmaceutical ingredient (API) with an immediate release layer and a sustained release layer (Abebe *et al,* 2014). Different active excipients are used for tablet compression, such as lubricant, disintegrate, and binding agent (Tuyen *et al*., 2021). Croscarmellose sodium and sodium starch glycolate are used as super disintegrants in the layer of instant release (Ryakala *et al.,* 2015). HPMC was used as a hydrophilic matrix for sustained release layer (Khaled *et al.,* 2014). The bilayer tablet needs to pass mechanical strength parameter tests. The mechanical strength of the tablet includes the tablet's elastic stiffness (Young's modulus), which is essential for joining two tablet layers, tablet hardness and friability. The tablet's mechanical strength is necessary for tablet processing, handling, shipping, storage, and good pharmacokinetics of drug (Abebe *et al*, 2014). The factorial design shows the relation between a variable and one or more independent variables. It may determine the multiple variables in a response. Study the different simultaneous factors. The factorial design shows the actual relative value and numerical value. Factorial design helps to combine multiple independent studies and can explore the interaction effects of different variables. The factorial design can be denoted by number and superscript, such as 3^2. In this case, 3 represents levels, whereas 2 represents factors. With 3^2 designs, a total of 3×3 = 9 different combinations of experiments can be designed (Trochim *et al.,* 2022; Banker *et al.,* 2002; Aguilar Yerenas, 2018). In a previous study, Telmisartan was employed with meglumine as a solubilizing agent, exhibiting favorable solubility properties. Furthermore, PVP k25 was utilized as a binding agent in the tablet formulation. The analysis of variance yielded a p-value of less than 0.005, indicating a significant effect (Lee *et al.,* 2017). Telmisartan is a drug with poor aqueous solubility. However, its solubility has been enhanced through the utilization of a ternary solid dispersion method. This method has also been found to improve the dissolution rate of the drug in intestinal fluid (Luo *et al.,* 2017). A complex of 2-hydroxypropyl-beta-cyclodextrin (2-HP-beta CD) and telmisartan was synthesized and evaluated for its potential to enhance the stability of telmisartan. The interaction between telmisartan and 2-HP-beta CD was investigated by nuclear magnetic resonance (NMR) spectroscopy (Kaur *et al*., 2014). A conventional drug release layer containing telmisartan was formulated using crosscarmellose sodium as the disintegrant. To evaluate any potential interaction between the drug and

excipients, Fourier transform infrared (FTIR) spectroscopy was employed. However, no significant interaction between telmisartan and the excipients was observed in the FTIR spectra, indicating the compatibility of the drug with the selected excipients (Dhiman and Awasthi 2016).

Telmisartan belongs to the angiotensin – II receptor antagonist (Bakheit *et al.,* 2015). In response to hypotension, sympathetic stimulation or decreased renal perfusion, the renin is secreted from distal convoluted tubules in the kidney. Telmisartan 40 to 80mg/day dose give maximum effect to reduce blood pressure (Sharpe *et al*., 2001). The renin breakdown angiotensinogen into angiotensin (10 amino acid peptide), which furthers the action of the angiotensin-converting enzyme and gets converted to angiotensin II. The angiotensin II attaches to the AT1 receptor causing vasoconstriction, hypertrophy and increased aldosterone secretion. Telmisartan acts on the AT1 receptor, inhibiting vasoconstriction and hypertrophy of vascular smooth muscle (Rao *et al*., 2011). The elimination half-life is 24hrs. Telmisartan is a BCS class II drug. It has poor water solubility drugs (Yang *et al.,* 2014). Different techniques have been used to improve the dissolution rate of telmisartan. Beta-cyclodextrin is a good solubility enhancer. The beta-cyclodextrin was a carrier for complexation, and the ratio of drug to beta-cyclodextrin was kept at a 1:2 ratio (Borba *et al.,* 2015).

A calcium channel blocker called cilnidipine is used to treat cardiovascular disease. It blocks calcium channel L-type and N-type activity (Hu *et al.,* 2012; Kai and Kuzumoto 2009). The bioavailability of Cilnidipine is low (13%) due to low water solubility and high permeability. The metabolism of Cilnidipine occurs both in the kidneys and liver. The prepared tablet with desired release pattern and optimized formulation by Using Factorial Design. Bilayer tablets improve physiological and pharmacological responses. Telmisartan and Cilnidipine are used in combination, giving a synergistic effect. Telmisartan gives an immediate release effect, and Cilnidipine gives a sustained release effect in the systemic circulation.

MATERIALS AND METHOD

Materials. Telmisartan (purity 99.9%) was purchased from Manvicare Trade and co. The Cilnidipine (purity 98%) was purchased from Dhamtec Pharma and a consultant. Beta cyclodextrin and HPMC K100m were purchased from R.P. chemicals suppliers. MCC, Dicalcium Phosphate, and Magnesium Stearate gifted by Adora Product Pvt.Ltd, Aurangabad.PVPk30, Methanol, Cross carmellose sodium, Sodium Starch Glycolate and Methylcellulose was purchased from S.B. fine chemicals Mumbai.

Method

Preformulation study. Organoleptic characteristics, solubility, melting point, I.R. spectra, and differential scanning calorimetry were examined in Preformulation studies of the medication.

Melting point. The open capillary method with melting point equipment was used to ascertain the drug's melting point. The sample was placed in the melting point device after being filled in a capillary tube and sealed at one end.

Solubility. Telmisartan is poorly insoluble in water. It was soluble in methanol, Ethanol, and 0.1N HCL. The telmisartan solubility was enhanced using a beta-cyclodextrin complex. Telmisartan was added to the solvent, which was then left to stand for 24 hours at room temperature (37°C) while being frequently shaken.

Cilnidipine is poorly insoluble in water but soluble in methanol and Ethanol.

FTIR. A Fourier-transform infrared spectroscopy (FTIR) analysis was conducted to evaluate the compatibility of Telmisartan and Cilnidipine with the excipients used in their formulation. The samples were prepared using potassium bromide (KBr) disks for analysis. The study identified the drug peaks of both Telmisartan and Cilnidipine in the presence of the excipients, confirming their compatibility (Hu *et al.,* 2012; Zhang *et al*., 2012).

DSC. Differential Scanning Calorimetry (DSC) analysis is a thermal analytical technique used to determine the compatibility of drugs and excipients. In this analysis, a small amount of the sample was accurately weighed and placed in an aluminium pan. The pan was then heated at a rate of 10°C/min to observe the thermal behaviour of the sample. The DSC results were used to evaluate the interaction between the drug and excipients and to identify any potential incompatibilities between them. The DSC technique is commonly used to assess the physical and chemical stability of pharmaceutical formulations and to optimize the manufacturing process (Hu *et al*., 2012; Zhang *et al*., 2012; Lin, 2021).

Preparation of drug and beta-cyclodextrin complex(kneading method). The drug and carrier were mixed in a 1:1 ratio and triturated using water and a small amount of ethanol to create a thick paste. The mixture was then kneaded for up to 60 minutes and left to dry by air. The resulting solid material was pounded and scraped, and then passed through a 100-mesh sieve (Kausalya *et al*., 2011).

Preparation of Granules

Preparation of Immediate release granules. The ingredients were accurately weighed, and then sieved through sieve number 60. Dry mixing was carried out to ensure proper mixing of all ingredients. The starch paste was added to the I.R. layer to form a dump mask. The mixture was passed through an 8-mesh sieve and subsequently dried at 600 C for 2 hours in a hot air oven. The dried material was then passed through a sieve number 18 mesh. Lubricant, consisting of magnesium stearate and talc, was blended with the granules. The blend was shaken in a polyethylene bag for 5 minutes. The IR granules were prepared according to the above procedure (He *et al.,* 2014).

Preparation of sustained release granules. The ingredients were accurately weighed and sieved through a sieve number 60. Dry mixing of all ingredients was performed. To create a dump mask, a binder (PVP k30) and a colouring agent (Ferric oxide) were added to the S.R. layer. It was then passed through a sieve with meshes of number 8 and dried at 60°C for two hours in a hot air oven. Afterwards, it was passed through a sieve

number 18 mesh. The dried granules were then mixed with lubricant and shaken for 5 minutes in a polyethene bag. Both SR Granules were prepared with reference to number (He *et al.,* 2014).

Table 1: Composition of formulation of telmisartan immediate release layer (400mg).

Formulation (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	20	20	20	20	20	20	20	20	20
Beta cyclodextrin	20	20	20	20	20	20	20	20	20
CCS	30	40	50	30	40	50	30	40	50
Sodium starch glycolate	60	60	60	80	80	80	100	100	100
MCC	198	188	178	178	168	158	158	148	138
Starch past	60	60	60	60	60	60	60	60	60
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8
Total	400	400	400	400	400	400	400	400	400

Table 2: Composition of formulation of Cilnidipine sustained release layer(300mg).

Formulation (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	10	10	10	10	10	10	10	10	10
HPMC k100m	45	60	75	45	60	75	45	60	75
Methylcellulose	45	45	45	60	60	60	75	75	75
PVP k30	45	45	45	45	45	45	45	45	45
Dicalcium phosphate	147	131	116	131	116	101	116	101	86
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6
Colour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	300	300	300	300	300	300	300	300	300

Evaluation parameters of granules. Various parameters were assessed to evaluate the granules, including bulk density, tap density, compressibility index, Hausner's ratio, and angle of repose. The analysis was conducted as per standard procedures and guidelines. Reference number for this information is Dholariya *et al*. (2014).

Formulation of tablet. To prepare granules for bilayer tablet formulation, a wet granulation technique was used. The bilayer tablet was created by employing double compression methods.

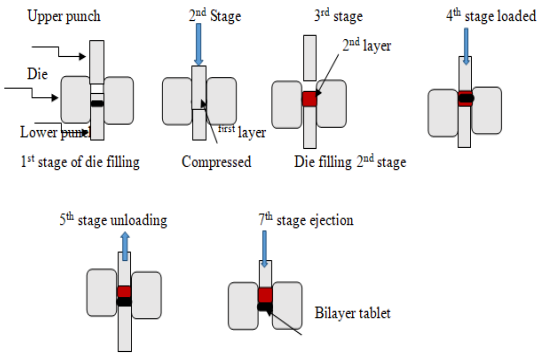

Fig. 1. Steps of bilayer tablet.

The compression was carried out using a 6mm standard round flat punch set in a laboratory press compression machine. The first layer of the bilayer tablet was formed by introducing a precisely weighed quantity of sustained layer blend into the die cavity, which was subsequently slightly compressed to produce a consistent layer. The second layer of the bilayer tablet was prepared by introducing a precisely weighed quantity of immediate layer blend into the die cavity (Verma *et al*., 2014).

Physical characterization of tablets (Dholariya *et al.,* 2014; Tuyen *et al.,* 2021). Weight Variation. A weight variation test was performed to ensure uniform weight among tablet batches. Twenty tablets were randomly selected and assessed for their average weight, weight variation, and individual weights.

Thickness. Ten tablets were randomly selected, and their thickness was measured using a Digital Vernier calliper scale.

Friability and Hardness. To determine the mechanical strength of tablets by using friability and hardness. Strength was related to the dissolution profile.

Friability (%F). To assess the mechanical strength of tablets, friability and hardness tests were conducted, and their relation to the dissolution profile was examined. For the friability test, twenty tablets were randomly chosen from each batch and weighed. These tablets were then subjected to 100 rotations in a Roche Friabilator. Subsequently, the tablets were removed, cleaned, and weighed again. The percentage friability (%F) was calculated as the weight difference between the pre- and post-test tablets divided by the pre-test weight, expressed as a percentage.

Hardness. The Monsanto hardness tester was employed to measure the hardness of ten tablets from each batch, and the average tablet hardness was determined.

Drug Content. Five tablets were individually weighed and powdered. To prepare a 100-ppm solution in phosphate buffer at pH 7.5 or another appropriate

solvent, 5 mg of telmisartan was accurately weighed and added to a 100 ml volumetric flask to make a stock solution. A 10-ppm solution was prepared by adding 1 ml of the stock solution to a 10 ml volumetric flask. Telmisartan concentrations were determined from the standard curve created by measuring the samples at λmax 294 nm using a Shimadzu UV spectrophotometer.

Disintegration test (Ryakala *et al.,* 2015). The disintegration test was performed using the USP disintegration apparatus, which consists of a six-glass tube basket rack assembly with ten-mesh screen bottoms, and a one-liter beaker filled with simulated gastric fluid heated to 37°C ± 2°C. One tablet was placed in each of the six-glass tubes, and the basket rack assembly was lowered into the beaker. The basket oscillated up and down at a frequency of 28-32 cycles per minute for 5-10 minutes.

In vitro dissolution study (Dholariya *et al.,* 2014; Tuyen *et al.,* 2021). The release rate studies of bilayer tablets were determined up to 12 hours using a USP-type II dissolution testing apparatus (paddle type). The dissolution test was performed in a dissolution medium (900 mL) containing 0.1N hydrochloric acid for the first 2 hours, followed by phosphate buffer at pH 7.5 for the remaining 3 to 12 hours. The paddle rotated at a speed of 75 rpm, and the temperature was maintained at 37°C throughout the experiment. At predetermined intervals, a sample of 5 mL was withdrawn from the dissolution apparatus and replaced with fresh dissolution medium to maintain the sink condition. The 5 mL sample was diluted with phosphate buffer at pH 7.5 and filtered using Whatman Filter Paper. Telmisartan was analysed at 294 nm and cilnidipine at 270 nm using a Shimadzu UV-1800 UV/Visible double-beam spectrophotometer. Using PCP Disso Software and an equation derived from a standard curve, cumulative percentage drug release (% CDR) was calculated.

Data analysis. For data analysis, a software for experimental design was utilized. A factorial design approach was adopted to investigate the combined effects of multiple independent variables and their interactions. The factorial design was denoted by a number with a superscript, such as 3^2. The coefficients were analysed using regression analysis, and the significance of the coefficients was evaluated using ANOVA based on Yates or the student t-test, as appropriate (Trochim *et al.,* 2022; Banker *et al.,* 2002; Aguilar Yerenas, 2018)

Statistical analysis (Khaled *et al.,* 2014). Statistical analysis was performed to determine significant differences between the nine formulations. A p-value of less than 0.05 was considered significant.

Stability study (Ryakala *et al.,* 2015). The optimized batch of the current work underwent a stability assessment to evaluate the active drug content under the conditions of 40°C and 75% relative humidity for a period of three months.

RESULT AND DISCUSSION

Preformulation Study

Characterization of Telmisartan. The melting point, colour, odour, and appearance of telmisartan and cilnidipine were evaluated to confirm compliance with official standard references. Telmisartan was found to be poorly soluble in water but soluble in methanol and ethanol. Similarly, cilnidipine was observed to be poorly soluble in water but soluble in methanol.

FTIR. The study of interactions between drugs and excipients was conducted using FTIR and DSC analysis, which revealed compatibility between the two. FTIR spectroscopy was used to investigate molecular interactions, with functional groups of particular ranges identified in the spectra. Absorption bands were observed in the FTIR spectra of telmisartan and cilnidipine, corresponding to their functional groups in their molecular structure. The FTIR spectrum of telmisartan and cilnidipine with excipients exhibited characteristic signals, as shown in (Table 3). The FTIR spectra were presented in Figs. 2-5.

Table 3: FTIR observed ranges.

Functional Group	Wave Number (cm^{-1}) of telmisartan	Wave Number (cm^{-1}) of telmisartan and excipients	Functional Group of Cilnidipine	Wave Number (cm^{-1}) of Cilnidipine	Cilnidipine and Excipient
C=C	2250.52	1455.99	N-H(stretching)	3383.5	3422.06
C=N	1620.88	1695.12	C=C (Alkenes)	1625.7	1695.12
C-N	1014.38	-	N=O	1270.86	1294
C-O	1270.86	1008.59	N-O(Nitro)	1357	-
C-H	-	2912.95	C=O	-	1000.87
	-	-	C-H (str.)	-	2920.66

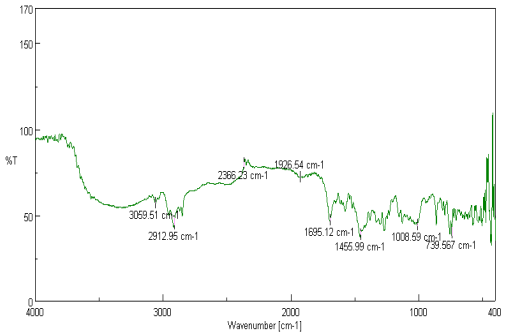

Fig. 2. FTIR Spectrum of Pure drug telmisartan.

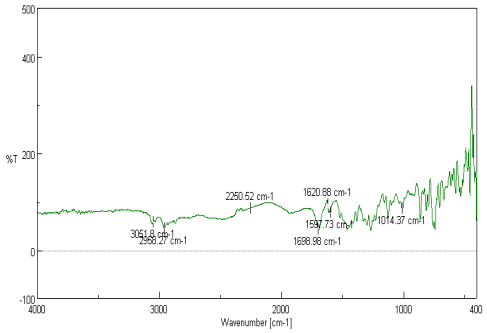

Fig. 3. FTIR spectrum of Drug+ Excipients.

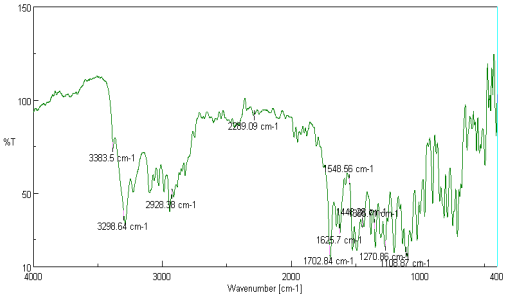

Fig. 4. FTIR spectrum of Cilnidipine.

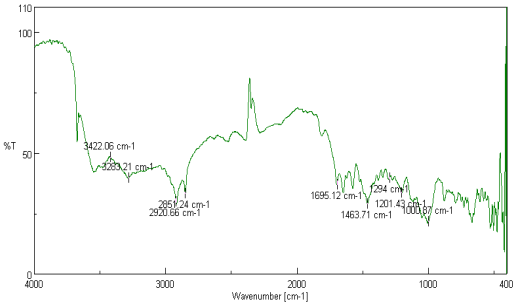

Fig. 5. FTIR spectrum of drug+ Excipients.

Difference scanning calorimetry (DSC). Differential scanning calorimetry (DSC) analysis was employed to determine the amorphous and crystalline nature of the compounds and study other characteristics, such as melting point, oxidative stability, and heat capacity. The DSC analysis was also utilized to investigate the interaction or compatibility between the drug and excipient. The compatibility study involved evaluating the drug peaks of telmisartan and cilnidipine with excipients through DSC analysis. The telmisartan endothermic peak was observed at 270.52°C (Fig. 6), while the cilnidipine peak was found at 112.62°C (Fig. 8). In the presence of the excipient mixture, the peak for telmisartan was observed at 269.32°C (Fig. 7), and that for cilnidipine was observed at 189.07°C (Fig. 9).

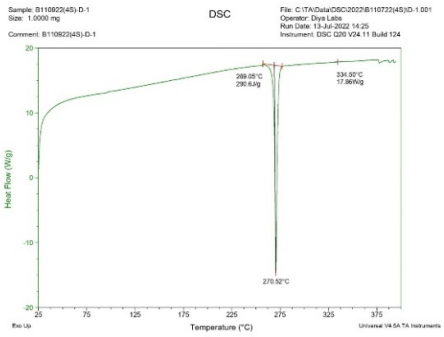

Fig. 6. DSC thermogram of Telmisartan.

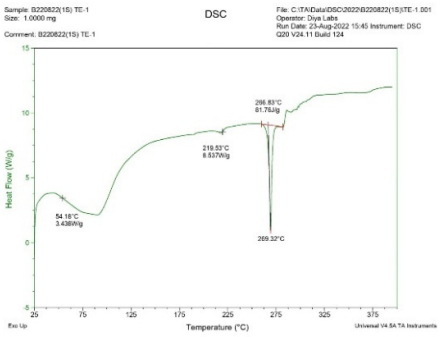

Fig. 7. DSC thermogram of telmisartan + Excipient.

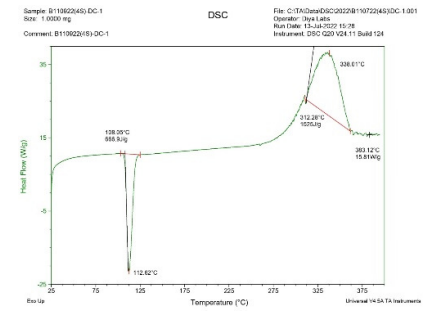

Fig. 8. DSC thermogram of cilnidipine.

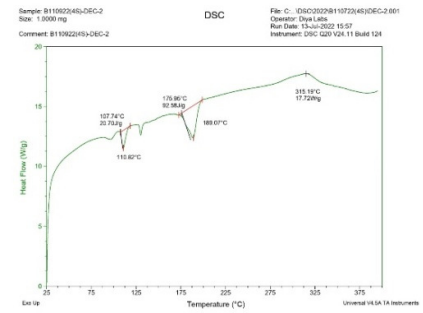

Fig. 9. DSC thermogram of cilnidipine+ Excipients.

Pre-Compressional Evaluation Parameters for Granules

Telmisartan. All batches exhibited a Hausner ratio below 1.5, and Carr's Index values ranged from 12 to 20%, indicating good flow properties. Additionally, the formulations had a repose angle less than 30 degrees, indicating excellent flow properties. The disintegration time (D.T.) was less than 10 minutes, and formulations containing sodium starch glycolate and Croscarmellose sodium in varying concentrations demonstrated greater D.T.

Cilnidipine. All batches of the formulation demonstrated a Hausner ratio of less than 1.06. Additionally, the Carr's Index was observed to range from 5-20%, indicating good flow properties. Furthermore, the formulations displayed excellent flow properties, as evidenced by repose angles less than 30 degrees.

Evaluation parameter of Bilayer tablet. The measured data indicate that all formulations displayed uniform levels of hardness and thickness. The medication content remained largely consistent across all formulation batches. Furthermore, all batches of formulations successfully met the prescribed limit of 1% friability and weight variation, as evidenced by the results presented in Table 4.

Table 4: Evaluation parameter.

Batch	Weight variation [n=20mg]	Thickness (mm) (n=10)	Diameter (mm) (n=10)	Hardness (kp) (n=10)	Friability (%) (n=20)
F1	700 ± 0.5	7.01 ± 0.2	9.01 ± 0. 2	5-6	0.77
F2	700 ± 1.00	7.00 ± 0.1	8.01 ± 0.3	5-6	0.79
F3	700± 1.00	6.02 ± 0.3	8.00 ± 0.1	5-6	0.53
F4	700 ± 0.5	7.01 ± 0.2	9.01 ± 0.2	5-6	0.68
F5	700 ± 0.5	6.01 ± 0.3	9.01 ± 0.2	5-6	0.62
F6	700 ± 1.0	6.00 ± 0.2	9.02 ± 0.2	5-6	0.67
F7	690 ± 1.0	6.00 ± 0.2	9.01 ± 0.2	5-6	0.61
F8	700 ± 0.5	7.01 ± 0.2	9.02 ± 0.2	5-6	0.70
F9	700 ± 0.5	6.01 ± 0.3	9.01 ± 0.2	5-6	0.58

In vitro dissolution study. In this study, a bilayer tablet of telmisartan and cilnidipine was formulated using CCS and SSG as super-disintegrants for the immediate release layer and HPMC k100m for the sustained release layer. Dissolution studies were conducted using the USP type II apparatus, and drug release was plotted against time using Microsoft Excel. The optimized batch of immediate-release F7 showed a 95.51% (Fig.10) drug release, while the sustained-release F5 batch showed a 96.46% (Fig. 11) drug release. The dissolution study indicated that there were no issues with capping or lamination. To enhance solubility, a 1:1 ratio of beta-cyclodextrin was used, based on a literature survey. The bilayer tablet demonstrated excellent flow properties, with a Hausner ratio below 1.5 and a Carr's index ranging from 12 to 20%. The disintegration time was less than 10 minutes, with the use of different concentrations of sodium starch glycolate and Croscarmellose sodium. The bilayer tablet's sustained release effect was observed for 12 hours, which is desirable considering that cilnidipine has a half-life of 2 hours and telmisartan has a half-life of 24 hours. For optimization, design expert software version 13 can be used.

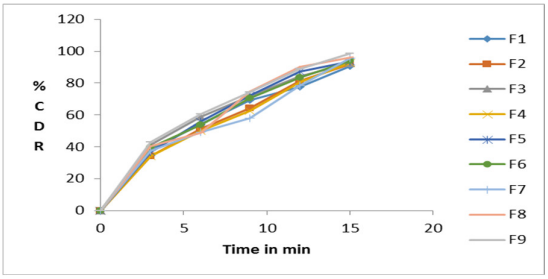

Fig. 10. %CDR of Immediate release layer.

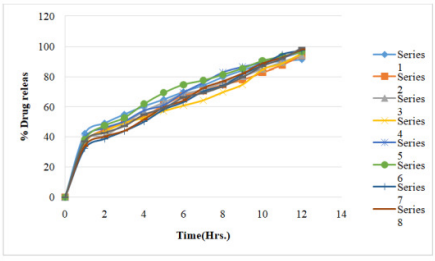

Fig. 11. % drug release of Cilnidipine sustained layer (F1-F9).

Fig. 12. Bilayer table formulation.

The bilayer tablet exhibited a smooth surface and round shape, with the two distinct layers readily discernible by their pink and white colour (as depicted in Fig. 12). No evidence of chipping or mottling was observed in any of the tablet formulations, and weight variation was found to be consistent across the bilayer tablets. Friability testing indicated a percentage of 0.70, which was deemed acceptable for tablet strength. Hardness testing yielded values of 5-6 kp. Drug release kinetics for telmisartan demonstrated a release rate of 95.51% within 15 minutes, while cilnidipine exhibited a sustained-release profile, achieving 96.46% release within 12 hours, indicating an effective release pattern.

RSM optimization result

ANOVA(Optimized F7 batch of Immediate release). The model is suggested to be significant by the model's F-value of 47.73 (Table 5). An F-value this large might happen owing to noise only 0.02% of the time. Model terms are considered significant when the P-value is less than 0.05 (Table 5). The R^2 value is observed0.9409 (Table 6). The optimized batch of immediate release shown in (Fig. 13).

Table 5: RSM optimize result.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	42.72	2	21.36	47.73	0.0002	significant
A-CCS	5.66	1	5.66	12.66	0.0120	
B-SSG	37.05	1	37.05	82.81	< 0.0001	
Residual	2.68	6	0.4474			
Cor Total	45.40	8				

Table 6: Fit Statistics.

Std. Dev.	0.6689		**R^2**	0.9409
Mean	93.94		**Adjusted R^2**	0.9212
CV %	0.7121		**Predicted R^2**	0.8523
			Adeq Precision	17.9012

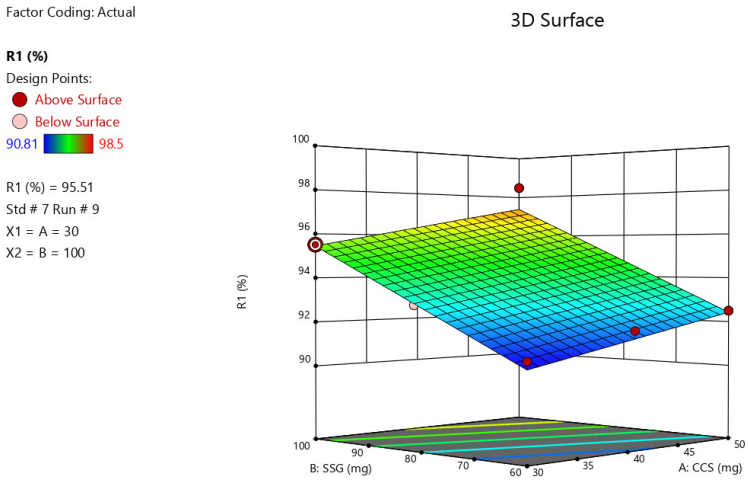

Fig. 13. Response Surface Plot for showing the effect of CCS and SSG on % CDR at 15min.

Sustained release(Optimized F5 batch of sustained release). The model is shown to be significant by the Model F-value of 55.17 (Table 7). Model terms are considered significant when the P-value is less than 0.05(Table 7). The R^2 value was observed 0.9484(Table 8). The F5 optimized batch was observed (Fig. 14).

Table 7: RSM optimized result

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	41.20	2	20.60	55.17	0.0001	Significant
A-HPMC	5.63	1	5.63	15.07	0.0082	
B-MC	35.58	1	35.58	95.28	< 0.0001	
Residual	2.24	6	0.3734			
Cor Total	43.44	8				

Table 8: Fit statistics.

Std. Dev.	0.6111		**R^2**	0.9484
Mean	95.72		**Adjusted R^2**	0.9312
CV %	0.6384		**Predicted R^2**	0.8769
			Adeq Precision	19.2937

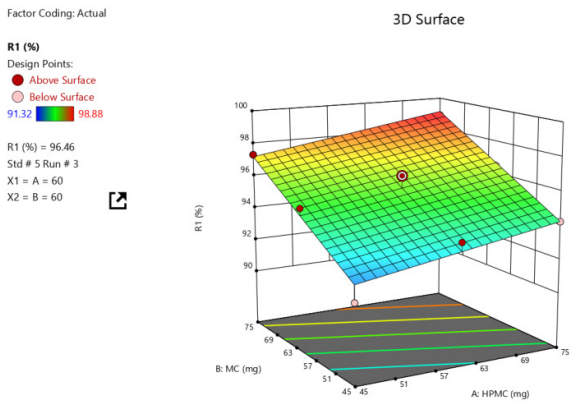

Fig. 14. Response Surface Plot for showing the effect of HPMC and MCon %CDR at 12 hrs.

Response surface analysis. The utilization of the expert application version 13 for analysis design allowed for the generation of three-dimensional response surface plots and two-dimensional contour plots. These plots provided a clearer understanding of the relationship between the factors and their simultaneous effects on the result.

DISCUSSION

The development of a bilayer tablet for fixed-dose combinations can offer several benefits such as increasing the effectiveness of one drug by combining it with another drug. In addition, it can provide a more convenient dosing regimen, improve patient adherence, and reduce the risk of adverse drug reactions. To achieve the desired therapeutic effect, the bilayer tablet was designed to release the two medications at different time intervals. To formulate the bilayer tablet, the first layer was designed for immediate release, and the second layer was designed for sustained release. Different excipients were selected based on a literature survey to ensure the stability and effectiveness of the final product. For example, sodium starch glycolate and croscarmellose sodium were used as super disintegrants, and HPMCK100m was used as a polymer to control the release rate of the drug Also micro crystalline cellulose was used as a diluent (Khaled *et al.,* 2014). The solubility of the poorly water-soluble drugs, telmisartan and cilnidipine, was enhanced using beta-cyclodextrin complex in a 1:1 ratio (Kausalya *et al*., 2011). The pre-formulation study was conducted to determine the melting point and solubility of the drugs, and no interaction was observed between the drugs and excipients, as confirmed by FTIR and DSC analysis (Hu *et al.*, 2012; Zhang *et al*., 2012; Lin, 2021). The wet granulation method was used to prepare the granules, and the flow properties of the granules were observed to be excellent. The double compression method was used to formulate the bilayer tablet, with the sustain layer being compressed with sufficient hardness and the immediate layer being compressed with less hardness. The bilayer tablet was evaluated for various parameters such as weight variation, thickness, diameter, friability, and hardness, and all formulations showed satisfactory results (Dholariya *et al*., 2014; Tuyen *et al.,* 2021). The in-vitro dissolution study revealed that the immediate release layer F7 batch showed 95.51% drug release, while the F7 sustain release batch showed 98.46% drug release, with HPMC K100m providing a better sustain release effect for up to 12 hours. In the future, the bilayer tablet technology can be further optimized for simultaneous drug release to achieve synergistic effects, increase drug solubility, reduce drug incompatibility, and improve patient compliance. Further studies can also be conducted to investigate the pharmacokinetics and pharmacodynamics of the bilayer tablet to evaluate its safety and efficacy in human subjects.

Stability study of the optimized batch. The stability study of optimized batches was monitored up to 1 month, 2 months and 3 months at the accelerated stability conditions and relative humidity (40ºC +- 2ºC, R.H. 75% +- 5%). There was no large difference observed in the evaluation of the optimized batch (ICH 2003).

CONCLUSIONS

In this study, a bilayer tablet formulation of antihypertensive drugs telmisartan and cilnidipine was developed. Telmisartan was incorporated into an immediate-release layer while cilnidipine was formulated into a sustained-release layer to achieve a desired pharmacological effect. The bilayer tablet was prepared using a special technique involving wet granulation, and beta-cyclodextrin was employed to improve the solubility of telmisartan. Various super disintegrants, including sodium starch glycolate and cross-carmellose sodium, were used in different amounts to optimize the immediate-release layer. The best formulation was found to be F7, which demonstrated excellent super disintegrant effect. For the sustained-release layer, HPMC K-100 M was utilized, and it provided satisfactory sustained release up to 12 hours. A 3^2 factorial design was employed for formulation optimization, and drug-excipient compatibility investigation using DSC showed no interaction between the drug and excipients. FTIR analysis demonstrated the presence of peaks for the drugs. An in vitro drug release study using the USP type II apparatus showed that the telmisartan immediate release optimized batch exhibited 95.51% drug release in 15 minutes, while the cilnidipine sustain optimized release batch showed 96.46% drug release up to 12 hours. The optimized formulation

stability study was show the satisfactory result. The optimized formulation maintains the physical and chemical quality. The bilayer tablet demonstrated a synergistic effect and improved patient compliance by combining the two drugs.

FUTURE SCOPE

The bilayer tablet technology can be used for simultaneous drug release to get synergistic effects, increase drug solubility, reduce drug incompatibility and improve patient compliance. Currently designed bilayer tablets can be studied for human pharmacokinetics and pharmacological effects.

Authors Contribution Statement. Dr. Amar Zalte has help in design of experiment and monitored progress of project. Pooja Kadu conceptualized, performed laboratory work, gathered, and analysed the data with regard to this work. Dr. Vishal Guleccha gave necessary inputs towards the design of the manuscript. Pooja Kadu wrote manuscript, Dr. Amar Zalte and Dr. Vishal Guleccha did proof reading of manuscript.

Acknowledgement. Authors are highly thankful to Padmashree Dr. Vithalraovikhepatile foundation's college of pharmacy for providing the facility to carry the research work. Authors are also thankful to Dr P. Y. Pawar, Dr R. L. Sawant, Prof. K.N. Tarkase, Prof. M. A. Raskar for guidance during my project work. Also thankful to Dr Venkateswarlu Ronda, Scientist, Indian Institute of Millets

Conflict of Interest. None.

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How to cite this article: Pooja Kadu, Amar Zalte and Vishal Gulecha (2023). Design and Optimize a Bilayer Tablet of Antihypertensive Drugs using a 3^2 Factorial Design. *Biological Forum – An International Journal, 15*(2): 794-803.