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Formulation and Evaluation of Bilayer Matrix Tablet of Candesartan and Simvastatin

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Abstract

The present study was undertaken with an aim formulation and evaluation of Bilayer Tablets containing Candesartan and Simvastatin by Direct compression and wet granulation method to formulate a stable, safe and convenience dosage form for the better management of most common cardiovascular disorders blood pressure. The formulations of Bilayer tablets showed good results in case of Candesartan immediate release layer physicochemical parameters and prepared using concentration of super disintegrant sodium starch glycolate for the fast release layer and sustained release layer of simvastatin containing HPMC K100 M and ethyl cellulose for the delay the drug release up to 10-12 hrs. The FTIR analysis indicates that the drug is pure. Pre compression and post compression parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayer tablets. The data obtained from in vitro release study shows that there is a delay in release of drug simvastatin from the sustained layer that is just because of its hydrophobic characteristics of the polymer ethyl cellulose and the mechanism involved in the release of drug is due to erosion of polymer surface from the matrix.

Key Words:

Bilayer Matrix Tablet, Sustained Release, Candesartan, Simvastatin, Antihypertensive

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1. INTRODUCTION

The main goal of controlled drug administration is to decrease the frequency of doses. Modified release medication products are designed to improve patient compliance and convenience while optimizing a therapy regimen by delivering the drug gradually and continuously throughout the full dose interval. Nowadays, more than 90% of the formulations produced are taken orally[1]. The new era of controlled release formulation development is the bilayer tablet. Another name for it is a dual or multi-component tablet. The bilayer pill outperforms the conventional dose form. It works well for releasing two medications in succession. Additionally, it can separate two

kinds of incompatible compounds. It can also be used with sustain release tablets, which have two layers: one for the initial dose, which is quick release, and the other for the maintenance dose. Both rapid and sustained release layers are present in Bilayer tablets. The first dose is administered by the instant release layer, which also contains superdisintegrants, which accelerate drug release and achieve a quick commencement of effect.Another name for it is a loading dose. The second layer, known as the sustained release (maintenance dose) layer, releases the medication over an extended period of time.

Bilayer tablets are presently being developed by a number of pharmaceutical companies for a number of reasons, including increased therapeutic efficacy and patent extension. Bilayer tablet creation for controlled release is appropriate for the sequential release of two drugs in combination and the separation of two incompatible substances[2]. By physically separating APIs, bi-layer tablets can be the main solution for preventing chemical incompatibilities and facilitating the creation of various drug release profiles. The oral drug delivery system, tablet types, bilayer tablet manufacturing, different tablet presses used, quality and GMP requirements for high production output, recent advancements in the field of bilayer technology, and the reasons why development and production of high-quality bi-layer tablets must be done on specially designed tablet presses, including layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, and reduced yield.[3]

Candesartan cilexetil is the oral form of candesartan. Because to inadequate absorption, its oral bioavailability is only about 40%. During absorption from the upper gastrointestinal tract, it is quickly and entirely transformed into the active ingredient candesartan.[4]The kidneys are primarily responsible for the removal of candesartan, with the biliary or intestinal systems playing a minor role[5]. Due to its strong and extended binding to the receptor in the target tissues, candesartan cilexetil's effective half-life is longer than its plasma half-life of 4–9 hours[6].

simvastatin is recommended as a dietary supplement. It is a semi-synthetic version of the first FDA-approved statin, lovastatin. Simvastatin lessens the creation of cholesterol and the difficulties that come with dyslipidemia. Elevated levels of low-density lipoprotein (LDL) cholesterol can cause arterial damage, which may result in heart problems and stroke.Simvastatin targets the synthesis of cholesterol, while statin therapy is used to reduce cholesterol levels. This molecule's biosynthesis follows a multi-step process. This pathway's rate-limiting step is the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. Mevalonic acid is created using acetyl-CoA as a substrate, and further reactions result in the production of cholesterol. Simvastatin inhibits HMG-CoA reductase and operates on the rate-limiting step, which lowers cholesterol levels.

The aim of the present work is to formulate and evaluate bilayer tablet of Candesartan and simvastatin for controlled antihypertensive effect and to achieve immediate release of Candesartan and sustained release of simvastatin using bilayered tablet[7].

2. Materials and Methods:

2.1. Materials

Candesartan and Simvastatin was obtained from Kamla institute of pharmaceutical sciences, Bhilai, chhattisgarh; Dicalcium Phosphate, Microcrystalline Cellulose, lactose, Sodium Starch

Glycolate, Ethyl cellulose, HPMC K 100, PVP, Magnesium Stearate, Talc were obtained from lobachemiepvt. Ltd., Mumbai. All other chemicals used were of analytical grade.

2.2. Methodology

2.2.1. Physico chemical parameters

Solubility determination[8]

A minute quantity of the drug sample was taken in a test tube and solubility of the drug dissolving in 1 ml of various solvents like water, DMSO, ethanol, DMF, phosphate buffer, chloroform etc was observed.

Partition coefficient

To determine the partition coefficient of Candesartan and simvastatin, 10mg each of Candesartan and simvastatin was accurately weighed and taken in two different volumetric flasks of 25 ml containing 10ml of each n-octanol and aqueous phase. The flask was occasionally shaken for 6hours and kept for 24 hours until equilibrium was reached. The phases were separated by using the separating funnel and the aqueous phase was analyzed spectrophotometrically for the amount of drug partitioned in aqueous phase after appropriate dilution.

UV spectrum of Candesartan and simvastatin

A 0.001% w/v solution of Candesartan and simvastatin in Ethanol and 0.1 N HCl was made and UV scanning was done between 200-400nm using UV double beam spectrophotometer, "Shimadzu UV 1800 double beam spectrophotometer" and compared with the standard.

2.2.2. FTIR spectrum of Candesartan and simvastatin

The infrared spectrum of the Candesartan and simvastatin was obtained by KBr pellet technique using ShimadzuCorpn., Japan; IR-Prestige 21 FTIR Spectrophotometer. The samples were placed into a pellet before measuring their infrared absorption spectra. To prepare the pellets, a few milligrams of the sample were ground together in a mortar with about 100 times the quantity of potassium bromide (KBr). The finely ground powder was introduced into a stainless steel die. The powder was then pressed in the die between polished stainless steel anvils at a pressure ofabout 9 t/in^2. The infrared spectrum of drug was then taken and compared with standard.

2.2.3. Estimation of Candesartan and Simvastatin in analytical sample

Preparation of stock solution of Candesartan and simvastatin

Candesartan and simvastatin (10mg) each was accurately weighed and dissolved in sufficient volume of Ethanol in 100ml volumetric flask. The final volume was made up to the mark with 0.1 N HCl to obtain concentration of 100µg/ml. This stock solution was used to prepare further standard solution of drug.

Preparation of calibration curve of Candesartan in 0.1 N HCL

From stock solution the aliquots viz., 0.5, 0.75, 01, 1.25, 1.5 & 1.75 ml was transferred into a series of 10ml volumetric flask and the volume made up to mark with 0.1N HCl. Thus, a range of concentration of drug solution between 5-17.5µg/ml was obtained. All solutions were filtered using whatman filter paper (#41). The absorbance of all the resultant solution was measured against blank using UV at 262 nm for Candesartan.

Preparation of calibration curve of simvastatin in 0.1 N HCL

From stock solution the aliquots viz., 0.3, 0.45, 0.6, 0.75, 0.9 & 1.05 ml was transferred into a series of 10ml volumetric flask and the volume made up to mark with 0.1N HCl. Thus, a range of concentration of drug solution between 3-10.5µg/ml was obtained. All solutions were filtered using whatman filter paper (#41). The absorbance of all the resultant solution was measured against blank using UV at 239 nm for simvastatin.

2.2.4. Formulation of Bilayer tablets

Immediate release layer of Candesartan

The immediate release layer of Candesartan was prepared by the direct compression method. Sodium starch glycolate, were used in varying amounts as shown in table 1. Batch C1 to C3 contained 2%, 3%, and 5% of sodium starch glycolate, respectively. Prepared powder was evaluated for its micrometrics properties.

Ingredients (mg)	Qty. (mg/tab)		
	C1	C2	C3
Candesartan	20	20	20
MCC	51	50	48
Lactose	25	25	25
Sodium starch glycolate	2	3	5
Magnesium stearate	1	1	1
Talc	1	1	1
Total	**100 mg/tab**		

Table 1.Composition of the immediate release layer

Sustained Release Layer of Simvastatin

The sustained release layer of Simvastatin is prepared by the wet granulation method. HPMC K100M and ethyl cellulose should be used in various amounts as shown in table. Batch S1 was prepared with HPMC and ethyl cellulose in a ratio of 1:1. Batch S2 prepared to check the effect of HPM with ethyl cellulose in a ratio of 2:1 and Batch S3 is to be prepared with HPMC with ethyl cellulose in a ratio of 1:2 respectively. Prepared granules were evaluated for its micrometrics properties.

Ingredients (mg)	Qty. (mg/tab)		
	S1	S2	S3
Simvastatin	30	30	30
HPMC	56	84	28
Ethyl cellulose	56	28	84
Bentonite	5	5	5
10% Starch paste	q.s	q.s	q.s
Magnesium stearate	2	2	2
Talc	1	1	1
Total	**150 mg/tab**		

Table 2.Composition of sustained release layer

2.3. Evaluation of Prepared Powder and granules[2]

2.3.1. Bulk Density:

Weigh accurately 10 gm of powder/granules, which was previously passed through 30# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting and read the unsettled apparent volume (Vo). Calculate the apparent bulk density in gm/ml by the following equation.

$$\text{Bulk Density} = \frac{\text{Mass of powder (M)}}{\text{Bulk Volume(Vo)}}$$

2.3.2. Tapped Density:

Weigh accurately 10 gm of powder/granules, which was previously passed through 30# sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample. Tap the cylinder 500 times initially and measure the tapped volume (V1) to the graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2) to the nearest graduated unit. If the difference between the two volumes is less than 2% then final the volume (V2). Calculate the tapped density in gm/ml by following equation.

$$\text{Tapped Density} = \frac{\text{Mass of powder (M)}}{\text{Tapped Volume(V2)}}$$

2.3.3. Compressibility Index:

Compressibility index is used as an important parameter to determine the flow behaviour of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by equation.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

2.3.4. Hausner's Ratio:

Hausner's ratio is used to predict the flowability of the powder/granules. This method is similar to compressibility index. Hausner's ratio can be represented by equation.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.3.5. Angle of Repose:

The angle of repose of API powder will be carried out by funnel method. Accurately weighed powder blend is taken in a funnel. Height of the funnel is adjusted in such ways that tip of the funnel just touches the apex of the powder blend. The powder/granules blend is allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured and angle of repose will be calculated using the following equation.

$$\Theta = \tan^{-1} h/r$$

Where, Θ is the angle of repose

h is height of pile

r is radius of the base of pile

2.4. Evaluation Parameters of Bilayer Tablet[9]

2.4.1. Weight variation Test or Uniformity of Weight:

It was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated as shown in Table 3.

Sr. No.	Average weight of tablet(mg)	% of deviation
1	80mg or less	10%
2	80-250mg	7.5%
3	250mg or more	5%

Table 3. Uniformity of Weight

2.4.2. Thickness:

Tablet was selected at random from individual formulations and thickness was measured using vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within ± 0.5% variation of standard value.

2.4.3. Hardness:

Hardness of the tablet was tested by placing the tablet longitudinally in between the two plungers of the Monsanto tablet hardness tester and the obtained hardness was mentioned in terms of kg/cm2. Limits for Hardness are 4-6kg/cm2.

2.4.5. Friability Test:

The friability of the tablets was determined by Roche Friabilator in which the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25RPM and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets were placed in the friabilator and allowed to rotate for 100 revolutions. Later the tablets were dedusted and the tablets were reweighed. Percent friability is given by the formula; Where W0 is the weight of the tablets before the test W is the weight of the tablets after the test. Limits for friability should not be more than 1%.

$$\text{Friability} = \frac{Winitial - Wfinal}{Winitial} X\ 100.$$

2.4.6. Disintegration Test

It is determined by using USP device which consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 mesh screen at the bottom end of basket rack assembly. To test for disintegration time, one tablet is placed in each tube and the basket arch is positioned ina1liter beaker of water at 37°C ± 2°C. A standard motor driven device is used to move the basket assembly up and down. To be incompliance with the USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified.

2.4.7. In-vitro Drug Release Study for Candesartan and Simvastatin[10-11]

In-vitro drug release of bilayer tablets was determined using a USP type -II dissolution test apparatus at 100 rpm. The dissolution was studied using 900 ml of simulated gastric fluid 0.1N

HCl (without enzyme, pH 1.2) for the first 2 hr and half dissolution model was followed for the sustained release layer for 12 hr. Filter through whatman filter paper and replaced by an equal volume of dissolution medium sample were suitably diluted and analyzed by UV at 262 & 239 nm respectively.

3.Result & Discussion:

3.1. Solubility studies

Solubility of drug in selected solvent is necessary for the successful preparation of formulation and determination of exact concentration of drug in particular media. The solubility of Candesartan & simvastatin in different solvent was determined and reported in Table 4 & 5.

Sl. No.	Solvent	Solubility
1	Water	-
2	DMSO	+
3	Ethanol	+
4	DMF	+

Table 4. Solubility of Candesartan in different solvents

Sl. No.	Solvent	Solubility
1	Water	-
2	Methanol	+
3	Ethanol	+
4	Chloroform	+
5	Dilute solutions of mineral acids	+
6	Dilute solutions of alkali hydroxides	+

Table 5. Solubility of Simvastatin in different solvents

3.2. Partition coefficient:

Partition coefficient of the drug was taken out in Octanol/0.1N HCl and Octanol/water. The result reported in table 6 & 7.

Sl. No.	Phases	Result
1	Octanol /0.1N HCl	1.5
2	Octanol/water	2.125

Table 6. Partition coefficient of Candesartan in different solvents

Sl. No.	Phases	Result
1	Octanol/0.1N HCl	1.8
2	Octanol/water	2.3

Table 7. Partition coefficient of Simvastatin in different solvents

3.3. UV spectrum of Candesartan and simvastatin

UV scanning was done between 200-400nm using UV double beam spectrophotometer, “Shimadzu UV 1800 double beam spectrophotometer. The absorption maximum for Candesartan was observed at 262 and for simvastatin at 239nm. The UV spectrum of Candesartan and simvastatin is shown in figure 1 and 2.

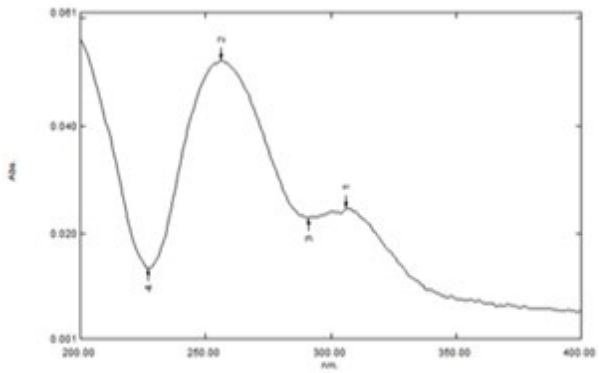

Figure 1. UV spectrum of Candesartan

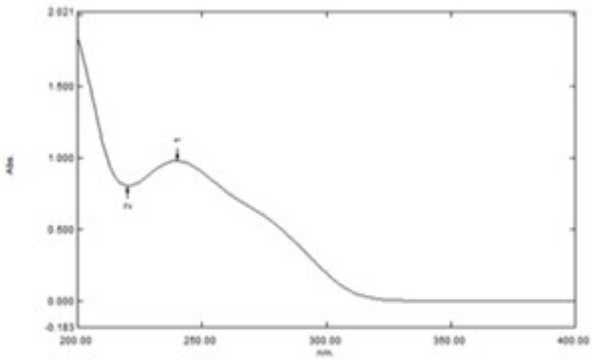

Figure 2. UV spectrum of Simvastatin

3.4. FTIR spectrum of Candesartan and simvastatin

The KBr disc of the Candesartan and Simvastatin was prepared and scanning was done by IR spectrophotometer "Shimadzu Corpn., Japan; IR-Prestige 21 FTIR Spectrophotometer". The result is recorded in table 8 & 9. The IR spectra are shown in figure 3 and 4. The spectrum obtained has well resolved peaks, which ascertained the purity of drug. The sample IR was interpreted and matched with reference IR spectrum reported in Florey, 2005 which infers that the compound contains all the peaks to be obtained as authentic sample of drug samples.

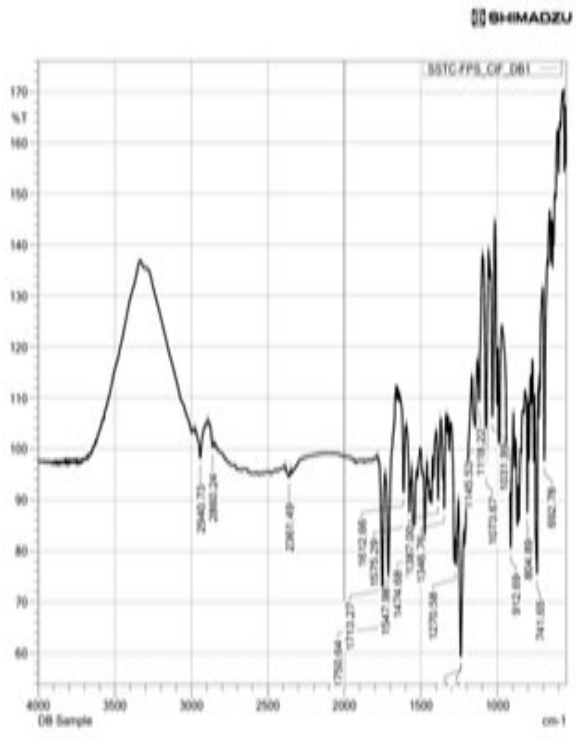

Figure 3. Characteristic absorption of Candesartan at various Wave numbers

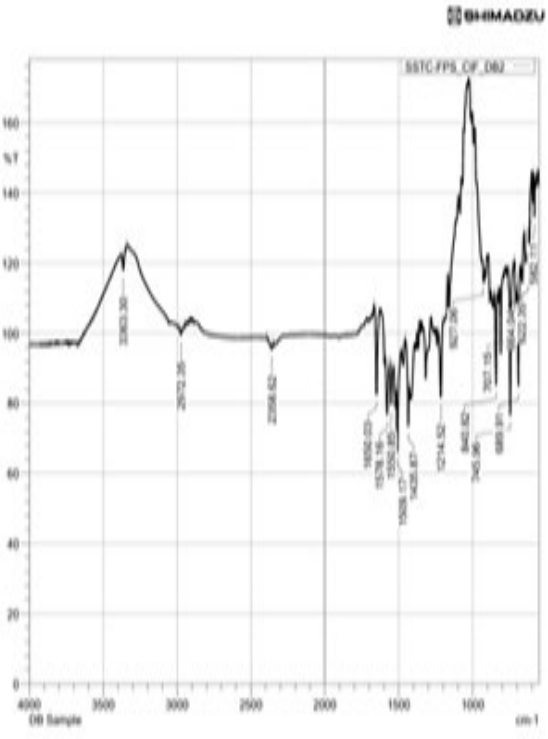

Figure 4. Characteristic absorption of Simvastatin at various Wave numbers

S.No.	Frequency of band (Cm^{-1})	Indication	Inference
1.	1750.64	C=O	Carboxylic acid Stretching
2.	2940.73	OH	Carboxylic acid stretching
3.	2362-2320	N-NH-N	Azide stretching
4.	1650-1580	N-H	Imine stretching
5.	2145-2120	N=C-N	Carbodiimide Stretching
6.	1031	C-O-C	Ether Stretching
7.	1650-1600	C=C	Aromatic ring…

Table 8. Characteristic absorption of Candesartan at various Wave numbers

S.No.	Frequency of band (Cm^{-1})	Indication	Inference
1.	3363.30	C-OH	Aromatic Stretching
2.	1214.52	C=O	Acid Ester Stretching
3.	927.06	C-O-C	Ether Stretching
4.	1650.03	C=C	Aromatic Ring..

Table 9. Characteristic absorption of Simvastatin at various Wave numbers

3.5. Preparation of calibration curve of Candesartan and simvastatin

The calibration curve was plotted taking concentration on X-axis and absorbance on Y-axis. The values are reported in table 10 for Candesartan and table 11 for simvastatin. The drug followed Beer Lambert's law in the concentration range of 5–17.5 µg/ml with good accuracy, as evident from the regression coefficient obtained from calibration curve for Candesartan (Fig 5) and 3-10.5 for simvastatin (fig.6).

S.No.	Concentration (µg/ml)	Absorbance at 262 nm	R^2 value
1	5	0.524	Y= 0.1026x + 0.018 R^2= 0.999
2	7.5	0.791	
3	10	1.054	
4	12.5	1.302	
5	15	1.546	
6	17.5	1.817	

Table 10. Calibration curve of Candesartan in 0.1N HCl

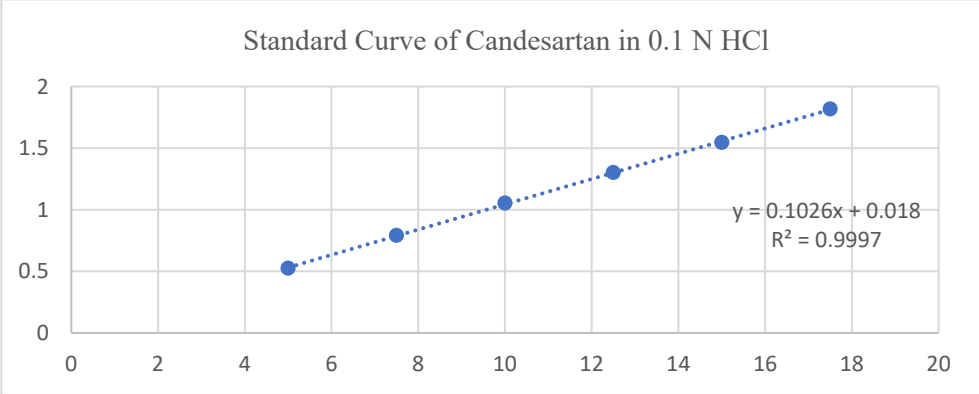

Fig 5: Calibration curve of Candesartan in 0.1N HCl

S.No.	Concentration (µg/ml)	Absorbance at 239 nm	R^2 value
1	3	0.212	Y= 0.0713 - 0.0032 R^2 = 0.999
2	4.5	0.317	
3	6	0.423	
4	7.5	0.532	
5	9	0.636	
6	10.5	0.747	

Table11. Calibration curve of Simvastatin in 0.1N HCl

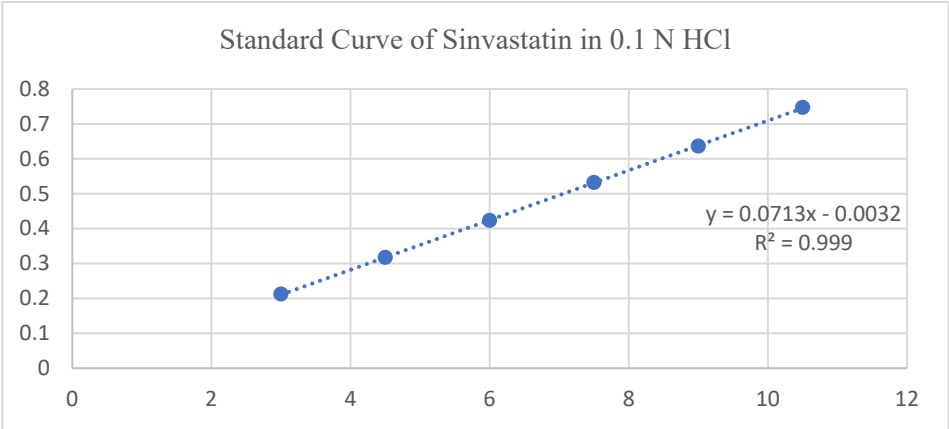

Fig 6: Calibration curve of Simvastatin in 0.1N HCl

3.6. Evaluation of Prepared Powder and granules

Flow Properties ofPrepared Powder for direct compression

The Powder blend for all 3 formulations were evaluated for bulk density which ranged from 0.270 ± 0.25 to 0.321 ± 0.35 gm/ml, tapped density ranged from 0.310 ± 0.25 to 0.362 ± 0.37 gm/ml, Carr's index ranged from 11.32 ± 1.85 to 12.90 ± 1.26 %, Hausner's ratio from 1.128 ± 0.012 to 1.148 ± 0.057 and Angle of repose ranged from 25.02 ± 1.58 to 26.24 ± 2.25. All these results indicate that, the power blend possess excellent to good flow ability and compressibility properties.

Batch Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Ɵ)
C1	0.270 ± 0.25	0.310 ± 0.25	12.90 ± 1.26	1.148 ± 0.057	25.03 ± 2.52
C2	0.285 ± 0.33	0.325 ± 0.40	12.30 ± 1.2	1.140 ± 0.015	26.24 ± 2.25
C3	0.321 ± 0.35	0.362 ± 0.37	11.32 ± 1.85	1.128 ± 0.012	25.02 ± 1.58

All values are expressed as mean ± standard deviation, n=3

Table 12: Pre-compression Evaluations of Batches of C1 to C3

3.7. Flow Properties of Prepared granules as sustained release layer

The Granules blend for all 03 formulations were evaluated for bulk density which ranged from 0.252 ± 0.25 to 0.274 ± 0.30 gm/ml, tapped density ranged from 0.292 ± 0.29 to 0.320 ± 0.21 gm/ml, Carr's index ranged from 13.68 ± 1.20 to 14.37 ± 1.19%, Hausner's ratio from 1.158 ± 0.010 to 1.168 ± 0.007 and Angle of repose ranged from 22.52 ± 1.32 to 28.60 ± 2.12. All these results indicate that, the power blend possess excellent to good flow ability and compressibility properties.

Batch Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Ɵ)
S1	0.265 ± 0.22	0.307 ± 0.41	13.68 ± 1.20	1.158 ± 0.010	23.56 ± 1.36
S2	0.252 ± 0.25	0.292 ± 0.29	13.69 ± 1.10	1.159 ± 0.012	28.60 ± 2.12
S3	0.274 ± 0.30	0.320 ± 0.21	14.37 ± 1.19	1.168 ± 0.007	22.52 ± 1.32

All values are expressed as mean ± standard deviation, n=3

Table 13: Pre-compression Evaluations of Batches of S1 to S3

3.8. Evaluation of Bilayer Tablet

Post-Compression Evaluation of Bilayer tablets

All the tablet preparations were evaluated for various physical parameters. Table below includes the values (mean ± SD) of weight variation, hardness, thickness, friability, disintegration time and in-vitro drug release of batches S1C1 to S3C3 prepared using different combinations of HPMC and Ethyl cellulose. All the formulated (S1C1 to S3C3) tablets passed weight variation test as the % weight variation was within the pharmacopeia limits of ± 7.5% of the weight. Thickness of all tablets was in the range between 4.22 ± 0.037 mm to 4.57 ± 0.047 mm. Hardness of tablets was in range between 5.48 ± 0.018 to 5.61 ± 0.058 kg/cm2. Friability was in range between 0.32 ± 0.03 to 0.78 ± 0.032 %. Friability values were less than 1 % in all cases shows good mechanical strength at the time of handling and transports. Disintegration time from 28 ± 0.14 sec to 31 ± 0.17 sec. Thus, all the physical parameters of the manually compressed tablets were quite within control.

Batch Code	Weight variation (n=20)	Thickness (mm) (n=3)	Hardness (kg/cm2) (n=3)	% Friability(n=5)	Disintegration time (sec)
C1S1	249.40 ± 0.18	4.22 ± 0.037	5.48 ± 0.018	0.73 ± 0.03	31 ± 0.17

C2S2	250.60 ± 0.07	4.57 ± 0.047	5.61 ± 0.0 58	0.68 ± 0.15	29 ± 0.29
C3S3	251.83 ± 1.07	4.36 ± 0.041	5.48 ± 0.03	0.73 ± 0.04	28 ± 0.14

All values are expressed as mean ± standard deviation, n=3

Table 14: Post-Compression Evaluation of Bilayer tablets

3.9. In-vitro Drug Release Study for Candesartan and Simvastatin

All the tablet preparations were evaluated for its in-vitro drug dissolution study in 0.1 N HCL for 2 hours and then for rest of the time in phosphate buffer. The ratio of polymers for formulation C1S1 is 1:1, C2S2 is 2:1 and for C3S3 is 2:1 as discussed earlier. In the study it was found that the concentration of Ethyl cellulose can influence the release of drug from the formulation significantly, as we increase the concentration of ethyl cellulose in all the formulation there is a decrease in drug release from the sustained layer of the formulations which is due to the hydrophobic characteristics of ethyl cellulose. Whereas, In case of immediate release layer the release of drug is almost similar. A complete release of drug was found within an hour for all the immediate release layer of the formulations.

Si. No.	Formulation Code							
	Time in Min.	C1	C2	C3	Time in Hr.	S1	S2	S3
1	5	9.2	10.8	12.11	1	10.01	10.26	9.8
2	10	18.88	21.4	26.05	2	17.75	19.18	16.07
3	15	38.1	40.05	56.47	3	25.75	28.1	21.96
4	20	44.4	48.1	60.47	4	30.37	37.02	25.75
5	25	54.7	61.47	69.64	5	39.63	45.94	34.58
6	30	58.04	68.66	73.41	6	44.26	54	38.79
7	35	64.05	72.91	78.88	7	51.41	63.78	42.58
8	40	70.21	78.21	86.94	8	53.94	72	46.36
9	45	78.94	87.01	89.64	9	59.83	81	50.99
10	50	87.4	92.51	100	10	64.88	90.54	53.94
11	55	94.17	100	100	11	72.03	93.49	58.56
12	60	100	100	100	12	80.02	96.42	67.82

Table 15: In-vitro Drug Release Study for Candesartan and Simvastatin Bilayer tablets

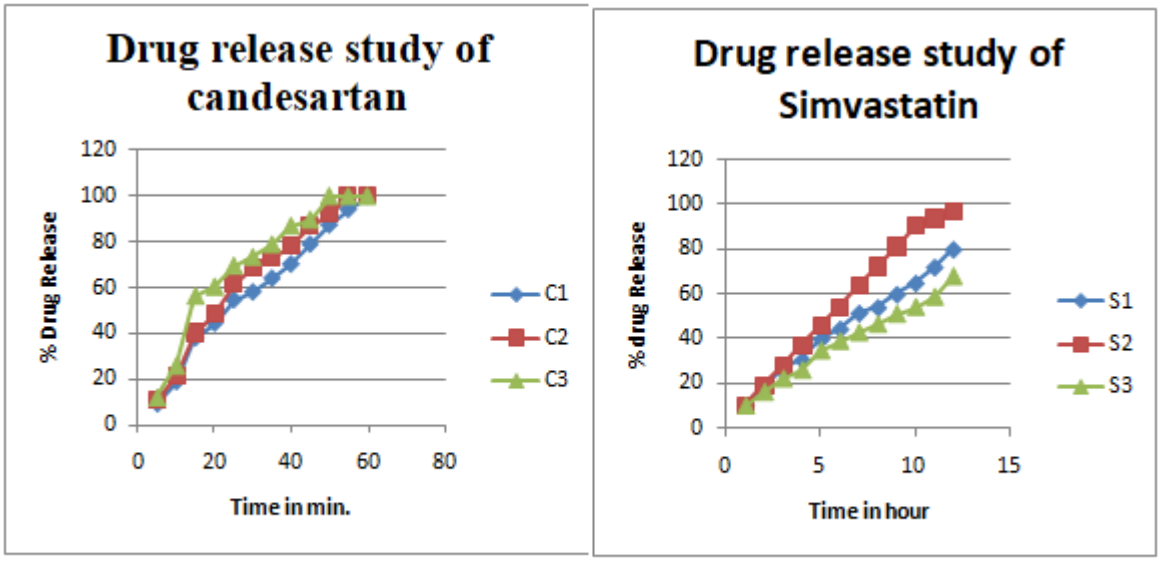

Fig.7. In-vitro Drug Release Study for Candesartan and Simvastatin

4. Conclusion:

The present study was undertaken with an aim formulation and evaluation of Bilayer Tablets containing Candesartan and Simvastatin by Direct compression and wet granulation method to formulate a stable, safe and convenience dosage form for the better management of most common cardiovascular disorders or blood pressure. The formulations of Bilayer tablets showed good results in case of Candesartan immediate release layer physicochemical parameters and prepared using concentration of super disintegrant sodium starch glycolate for the fast release layer and sustained release layer of simvastatin containing HPMC K100 M and ethyl cellulose for the delay the drug release up to 10-12 hrs. The FTIR analysis indicates that the drug is pure. Pre compression and post compression parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayer tablets. The data obtained from in vitro release study shows that there is a delay in release of drug simvastatin from the sustained layer that is just because of its hydrophobic characteristics of the polymer ethyl cellulose and the mechanism involved in the release of drug is due to erosion of polymer surface from the matrix. It can be concluded that by considering the concentration of super disintegrant as a SSG for immediate release layer and the concentration of polymer as a HPMC K100M and ethyl cellulose for sustained release layer, we successfully developed Bilayer tablet. It was observed that the bioavailability of SR layer increased as compared to conventional administration.

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