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ORIGINAL ARTICLE

Formulation and Evaluation of Bilayer Tablet of Carbimazole as Immediate Release & Propranolol HCL as Sustained Release

Sujit Tambe*, Rushikesh Meher, Shankar Dhobale, Suresh Jadhav, Dushyant Gaikwad
VJSM's Vishal Institute of Pharmaceutical Education and Research Ale, Tal –Junnar, Dist-Pune (412411), Maharashtra, India.
Email:rushikeshmeher333@gmail.com

ABSTRACT

The objective is to formulate and evaluate the bilayer tablet containing carbimazole as immediate release and propranolol hcl as sustain release. Propranolol hcl is used complementary in therapy of hyperthyroidism. Propranolol & carbimazole used to treat hyperthyroid tremor and tachyacardia. Propranolol HCl has been used in conjunction iodine to prepare mildly thyrotoxic patient for surgery but preferable to make the patient euthyroid with carbimazole. Bilayer tablet prepared in which one layer is of sustained release and another is of immediate release. Immediate release layer was formulated by wet granulation using sodium starch glycolate in 2-8 % and cross linked povidone in 2-5 %. Other ingredient used for formulation of immediate release was mannitol, talc and magnesium stearate. Sustain release layer of propranolol HCl was formulated by using ethyl cellulose as non- swellable polymer by direct compression method and other ingredients used are talc, magnesium stearate, starch and lactose. Various pre-formulation and studies such as identification test, melting point, compatibility study, solubility were checked. Also the micrometrics properties of powder blend such as bulk density tapped density, hasuner's ratio, carr's index and angle of repose were evaluated. Post compression studies such as the hardness, weight variation, friability; drug content uniformity, thickness and in vitro drug release were performed. The result of the c5p1 batch was within limit and found to be as optimized batch. The drug release from the optimized batch was found 92.91 % for immediate layer within 1hr and 91.91% drug release of sustained release layer for 8hr. The optimized layers were selected to prepare the bilayer tablet. All the results were found within limit. The optimized batches are c5 of carbimazole and p1 of propranolol. The parameter selected for immediate release tablet was c5 (sodium starch glycolate) and p1 (ethyl cellulose) for optimized formulation. The principle behind drug release was diffusion and release kinetics by zero order.

Keywords:-*Bilayer Tablet, Carbimazole, Propranolol HCl, Sustained Release, Immediate Release, Ethyl Cellulose, Wet Granulation, Direct Compression.*

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INTRODUCTION

The main aim behind this formulation is to overcome the disease and the clinical symptoms associated with it. Tablet is solid unit dosage form that has most patient acceptance among different dosage form. Tablet is used widely because these are easy to administer as compared to other dosage form. These are cheapest dosage form, stable, easy to dispense and deliver the accurate dose to the patient. Bilayer tablet is tablet containing two layers of different drugs that are incompatible or to enable development of different drug release profile such as immediate release and sustain release. Hyperthyroidism is condition related to thyroid gland. Thyroid gland produces T3 and T4 which controls how cell uses energy.. Hyperthyroidism is condition when thyroid gland makes too much T3 and T4. This excess produced T3 and T4 causes tachycardia & tremor. The main advantage of combining two drugs is that Carbimazole against hyperthyroidism and Propranolol against Systolic hypertension [1].

Antithyroid action of Carbimazole is Carbimazole convert to methimazole [5]. Methimazole is the agent that reduces the uptake and concentration of inorganic iodine by thyroid it also reduces the formation of di-iodotyrosine and thyroxine. Propranolol HCL is used because the systolic hypertension is common

symptom is hyperthyroidism especially in people in people with age 50 years or older. Systolic hypertension increases blood pressure by decreasing systemic vascular resistance increasing heart rate and raising cardiac output. Carbimazole is absorbed 90-100 % in intestine and converted to active metabolite methimazole. It show about 80 % protein binding. The half life of Carbimazole is 5.3-5.4 hours [5].

Its peak plasma concentration occurs rapidly so suitable for immediate release layer. Propranolol is completely absorbed after oral administration. Propranol shows 90% plasma protein binding. But due to short plasma half life about 3 to 6 hrs it given in sustained or extended release layer [6].

Carbimazole is prepared as immediate release layer by using sodium starch glycolate and cross-povidone which acts as superdisintegrant. Propranolol is prepared as sustain release layer by using ethyl cellulose which acts as rate controlling polymer. Both the layer is compressed by the direct compression method. Various pre-compression studies such as Bulk density, Tapped density, Hausner's rato, Carr's index, Angle of repose were performed. Post-compression studies such as Hardness, Friability, Weight variation, Drug content uniformity, In vitro drug release studies were performed by using 0.1N HCL as buffer solution [8].

MATERIAL AND METHODS

Carbimazole obtained as a gift sample from Glenmark pharmaceuticals Limited mumbai and Propranolol HCL is obtained as gift sample from Flemingo pharmaceuticals Ltd, Thane. Mannitol, sodium starch glycolate, cross-povidone, ethyl cellulose, lactose, magnesium stearate, talc (research lab).

METHOD

The bilayer tablets of Carbimazole and Propranolol HCL were prepared by formulating immediate release layer of Carbimazole and sustain release layer of propranolol HCL separately and two layers were combined together by using single punch.

Immediate release layer of Carbimazole was prepared by using wet granulation method. Various superdisintegrants were used for preparation of this layer. All ingredients except talc and magnesium stearate were taken and mixed with granulating fluid of composition PVP K30 alcohol to produce dough mass. The mass then passed through 40# sieve to produce granules. Granules passed to polythene bag and mixed well for 3 min. The remaining excipient such as talc (Glidant) and magnesium stearate as lubricant added to blend and mix well for 3 min.

Sustain release layer of Propranolol HCl was prepared by direct compression method. The drug and polymer (ethyl cellulose) were passed through 22# sieve and transfer it to the polythene bag and mix it for 3 min. The remaining excipients were added. Finally add talc (glidant) and magnesium stearate as lubricant to the bag and mix well.

The optimized batch Carbimazole (batch) and Propranolol HCl (batch) for formulation of bilayer tablet. As mentioned the two layers of bilayer tablet were prepared separately. First the die is filled with the sustain release layer in tablet punching machine giving single layer, then the sustain release layer is applied over it and compressed to form bilayer tablet under by using mm thick flat punch.

Table 1: Formulation of Immediate Release Layer of Carbimazole

Sr.no.	Ingredients	Weight(mg)								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
1.	Carbimazole	20	20	20	20	20	20	20	20	20
2.	Mannitol	57	52	47	52	47	42	47	42	32
3.	Sodium starch glycolate	10	10	20	10	15	20	10	15	20
4.	Cross-povidone	5	5	5	10	10	10	15	15	15
5.	Talcum Powder	5	5	5	5	5	5	5	5	5
6.	Magnesium stearate	3	3	3	3	3	3	3	3	3
	Total	100	100	100	100	100	100	100	100	100

Table 2: Formulation of Sustain Release Layer of Propranolol HCl

Sr.no.	Ingredients	Weight(mg)		
		P1	P2	P3
1.	Propranolol HCL	50	50	50
2.	Ethyl cellulose	25	50	75
3.	Lactose	57	32	7
4.	Talc	5	5	5
5.	Starch	10	10	10
6.	Magnesium stearate	3	3	3
	Total	150	150	150

PREFORMULATION STUDY:[2, 3, 8, 9]

Identification test by UV-Vis. Spectrophotometer [2, 3]

For Carbimazole

50 mg of Carbimazole was weighed accurately and transferred it to the volumetric flask 50 ml. Add ethanol to dissolve the drug make the volume up to 25 ml with respective solvent. Consider this as stock solution (1000 mcg/ml). Further dilutions were made by using the stock solution and scanned with respective blank in UV spectrophotometer (SHIMADZU U.V. 1800) in the range 40-200 nm.

For propranolol HCl:

50mg of Propranolol HCL was weighed accurately and transferred it to the volumetric flask 50 ml. Add ethanol to dissolve the drug make the volume up to 25 ml with respective solvent. Consider this as stock solution (1000 mcg/ml). Further dilutions were made by using the stock solution and scanned with respective blank in UV spectrophotometer (SHIMADZU U.V. 1800) in the range 40-200 nm.

Melting point determination: [2, 3]

Melting points of Carbimazole and propranolol were determined by using capillary method.

Determination of solubility [2, 3]

Qualitative Solubility

Qualitative solubility determined by dissolving 5 mg drug in 5ml solvent such as water, ethanol, chloroform, acetone and 0.1N HCL solution.

COMPATIBILITY STUDY, BY FT-IR SPECTROSCOPY [2, 3]

For this study powdered drug is mixed with dried potassium bromide in ratio 1:100.i.e. 1mg drug is with 100mg Kbr to form the transparent pellets. This pellets then scanned by from 4000 to 400 cm^{-1} ambient temperature.(Perkin Elmer Spectrum-65).

PRE-COMPRESSION EVALUATION [2, 3, 8, 9]

BULK DENSITY

The weighed powder is transferred to measuring cylinder and total volume is meaured. The bulk density is determined by using formula:

Bulk density = (weight of powder) / (bulk volume) ×100

TAPPED DENSITY

Tapped density is calculated by using tapped density apparatus by tapping 100 times and by using the formula:

Tapped density = (weight of powder) / (tapped volume) ×100

Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density and is indicative of the flowability.

The formula for Hausner's ratio is

Hausner's ratio= tapped density / bulk density

Compressibility index

It is calculate by using formula

Compressibility index/ carr's index (%) = tapped density -bulk density/ tapped density ×100

ANGLE OF REPOSE

It is the angle between pile of powder and horizontal surface. It is done by fix funnel method.

The whole powder blend pass through funnel until the pile is formed and then height and radius are measured. The angle of repose is then calculated by following formula

Angle of repose $=\theta=\tan^{-1}(h/r)$

Where, h= height of the pile.

r= radius of the pile.

Post-Compression Evaluation [2, 3, 8, 9]

Uniformityweight: [2, 3]

These test 20 tablets are taken randomly. Comparison between the weight of individual tablet and average tablet is done.

Table 3: Limits for tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
>324	5%

Thickness

Thickness is measured by instrument called vernier caliper. It is measured in mm unit.

Hardness

Hardness is one of the important parameter for tablet evaluation. It determines the tablet strength during handling as well as the hardness determines the disintegration and dissolution time. Monsanto hardness tester used to determine hardness. It expressed in kg/cm^2.

Friability

It determines the ability of tablet to withstand abrasion, shock during handling storage and transportation. For this test Roche Friabilator is used. The mechanism involve is dropping of tablet from fixed distance to check its strength. Accurately weigh 6-10 tablets in Friabilator and rotate it at 25 rpm. Rotate the Friabilator drum for 100 rotations. Remove the tablets, loose the dust and weigh again. The maximum limit for the loss of tablet is between 0.5-1.0 percent. If the loss is more than this limit it is not acceptable.

Broken tablets are not taken. Percentage friability is calculated by following formula.

Percentage friability = [Initial weight-final weight] ×100

Content uniformity: [2, 3]

FOR CARBIMAZOLE:

10 tablets were taken and crushed by using the mortar and pestle to form the powder. From these powder 50 mg was taken and transferred to the 100 ml volumetric flask. This powder was dissolved by using the distilled water and remaining volume make up is done by the distilled water. This volume was filtered and from that filtrate 1ml volume was taken and diluted by using the pH 0.1 N HCL buffer and absorbance was taken by using the U.V. spectrometer at 291.8 nm. (SHIMADZU U.V. 1800).

For Propranolol HCl:

10 tablets were taken and crushed by using the mortar and pestle to form the powder. Form these powder 50 mg was taken and transferred to the 100 ml volumetric flask. These powder was dissolved by the using the distilled water and remaining volume make up is done by the distilled water. These volume was filtered and from that filtrate 1 ml volume was taken and diluted by using the pH 6.8 phosphate buffer and absorbance was taken by using the U.V. spectrometer at 288.3nm

***In vitro* drug dissolution studies:** [2, 3]

In vitro drug release was studied for immediate release tablet (Carbimazole)USP type II((paddle)apparatus,(Electrolab dissolution tester TDT-08L) with 900 ml dissolution medium taken maintained at temperature 37+_1^{0}C,for 1 hr and at rotation 50 rpm standard for the paddle. Dissolution media used was 0.1 N HCL (pH1.2). 5ml sample was withdrawn at each 10 min interval.

This volume is replaced with same quantity of dissolution medium to maintain sink condition. The collected sample was analysed by using UV spectrophotometer at 291.8 nm and cumulative % drug release was determined.

***In vitro* drug release was studied for sustained release tablet (Propranolol HCl)**

USP type II((paddle)apparatus, (Electrolab dissolution tester TDT-08L) with 900 ml dissolution medium taken maintained at temperature 37+_1^{0}C,for 8 hr and at rotation 50 rpm standard for the paddle. Dissolution media used was 0.1 N HCL (pH1.2). 5ml sample was withdrawn at each 1 hour interval.

This volume is replaced with same quantity of dissolution medium to maintain sink condition. The collected sample was analysed by using UV spectrophotometer at 288.3nm and cumulative % drug release was determined.

In vitro drug release was studied for bilayer tablet

USP type II (paddle) apparatus, (Electrolab dissolution tester TDT-08L) with 900 ml dissolution medium taken maintained at temperature 37+_1^{0}C,for 15 hr and at rotation 50 rpm standard for the paddle. 0.1 N HCL was used as buffer to maintain pH. 5ml sample was withdrawn at each 10 min interval.

This volume is replaced with same quantity of dissolution medium to maintain sink condition. The collected sample was analysed by using UV spectrophotometer at 291 nm and 288nm .Cumulative % drug release was determined.

RESULTS AND DISCUSSION

Pre-formulation studies

The UV absorption maximum of 10µg/ml in ethanol for Carbimazole is 291.8 nm and for propranolol HCL is 288.3 in the range 200-400 nm.

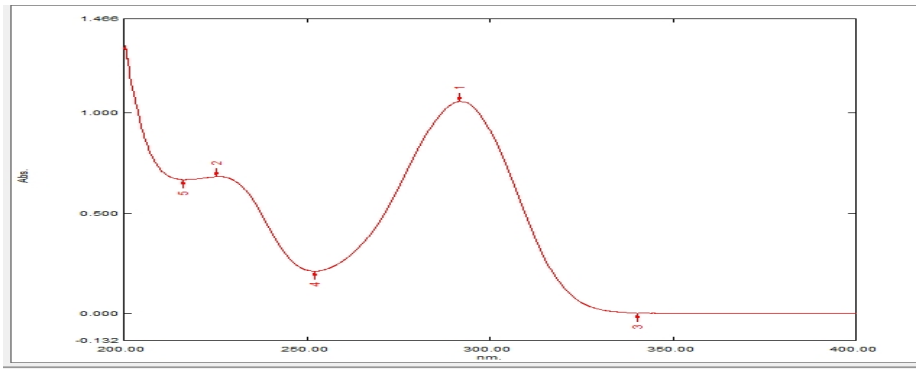

Figure 1: Absorbance Maximum of Carbimazole.

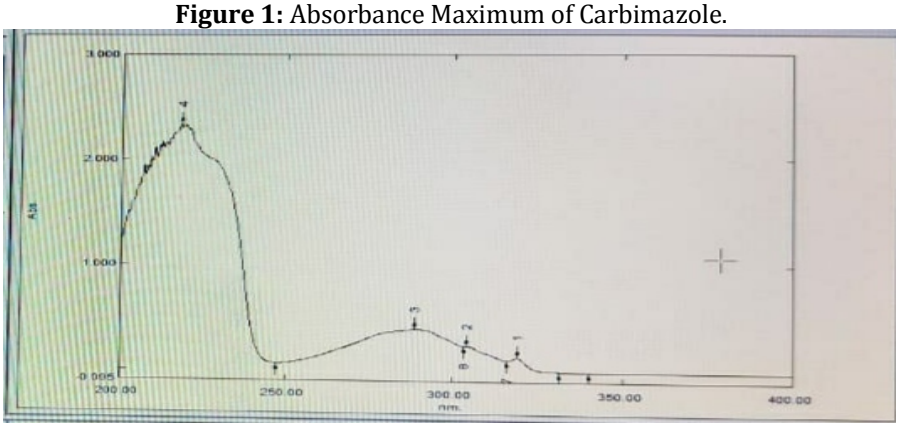

Figure 2: Absorbance Maxima Of Propranolol HCl

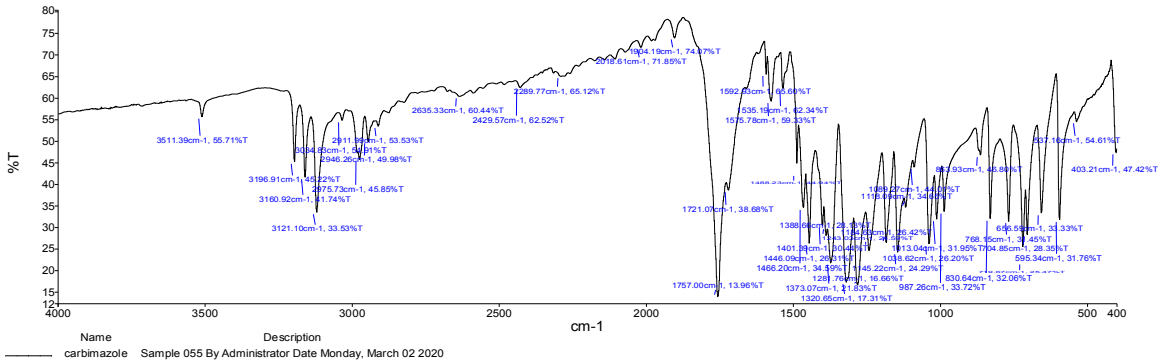

Figure 3:FTIR of Carbimazole And Excipients.

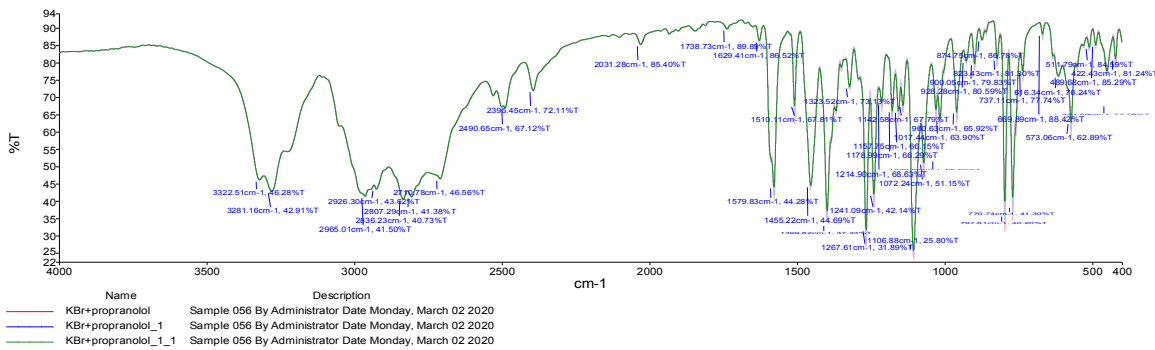

Figure 4:FTIR of Propranolol Hcl And Excipients

Table 4 : Preformulation Study of Carbimazole and Propranolol HCL

Sr.no.	Parameter	Carbimazole	Propranolol HCL
1.	Identification by U.V. Vis spectrophotometer	291.8nm	288.3nm
2.	Melting point	123.5^{0}C	164.0^{0}C
3.	Solubility	Slightly soluble in water, ether, acetone. Sparingly soluble in ethanol.	Highly soluble in water and ethanol slightly soluble in chloroform, Insoluble in ether.
4.	Compatibility studies	Compatible	Compatible

Pre-compression evaluation

Pre-compression evaluation of Carbimazole as immediate release and Propranolol as sustain release includes various micrometrics properties such as Bulk density, Tapped density, Angle of repose, Carr's index, Hausner' ratio. Bulk density is important factor that affects packaging and transportation. Compressibility index is the ability of powder to decrease its volume under pressure. High compressibility index indicate poor flow. The high angle of repose indicates the poor flow. The range of 16^0 to 26^0 indicates the good flow properties.

Table 5:Pre-Compression Evaluation Of Immediate Release Layer Blend (Carbimazole)

Sr.no.	Parameter	C1	C2	C3	C4	C5	C6	C7	C8	C9
1.	Bulk density(g/ml)	0.5435	0.5354	0.5245	0.5349	0.5429	0.5154	0.5246	0.5149	0.5198
2.	Tapped density(g/ml)	0.6333	0.6122	0.6034	0.6119	0.6135	0.5998	0.6029	0.5997	0.5999
3.	Compressibility Index (%)	14.17	12.54	13.07	12.58	11.50	14.07	12.98	14.14	13.35
4.	Hausner's ratio	1.16	1.14	1.15	1.14	1.13	1.16	1.14	1.16	1.15
5.	Angle of repose (degree)	24.7^0	22.4^0	23.1^0	22.2^0	21.6^0	23.7^0	22.8^0	24.6^0	23.4^0

Table 6: Pre-Compression Evaluation Of Sustained Release Powder Blend (Propranolol HCl)

Sr.no.	Parameter	P1	P2	P3
1.	Bulk density (g/ml)	0.4344	0.4262	0.4385
2.	Tapped density (g/ml)	0.4953	0.4944	0.5263
3.	Compressibility index (%)	12.29	13.79	16.68
4.	Hausner's ratio	1.14	1.16	1.20
5.	Angle of repose (degree)	20.22^0	21.34^0	21.6^0

Post-compression evaluation of tablet

After compression tablets where evaluated for weight variation, thickness, hardness, dissolution test, friability. Uniformity of weight is important to ensure that there even distribution of active ingredient. Uneven distribution may result into many problems such as problem to achieve therapeutic effect or some cases toxic effect may occur. For this 20 tablets were taken and their average weight is calculated and compared with the individual tablet. Not more than 2 tablet deviate from the average weight. Thickness of tablet is important as quality control test that affect packaging, disintegration rate and dissolution rate of tablet. Thickness is measured by using Vernier Caliper. Hardness of tablet determines the structural integrity of tablet during transportation, handling and storage. Hardness also decides breaking point of tablet. Hardness should be within limit 3-5 kg/cm^2. Monsanto hardness tester used to determine the hardness of tablets. Friability is determined by using Roche Friabilator. Friability not more than 1% is acceptable. Dissolution and content uniformity performed as per USP standards.

Table 7: Post-compression evaluation of immediate release layer tablet (carbimazole)

Sr.no.	Parameters	C1	C2	C3	C4	C5	C6	C7	C8	C9
1.	Uniformity of weight (mg)	98	98	97	98	99	97	97	98	98
2.	Thickness(mm)	1.5	1.6	1.6	1.6	1.8	1.7	1.5	1.5	1.6
3.	Hardness(kg/cm^2)	3.5	3.4	3.4	3.4	3.2	3.3	3.5	3.5	3.4
4.	Friability (%)	0.58	0.64	0.67	0.65	0.79	0.72	0.59	0.55	0.67
5.	Drug content	90.87	91.93	92.76	93.34	97.21	94.65	90.76	89.99	93.21
6.	% drug release	85.45	87.56	88.23	88.16	92.98	90.2	85.43	86.98	88.22

Table 8: Post-compression evaluation of sustained release layer tablet (propranolol hcl)

Sr.no.	Parameters	P1	P2	P3
1.	Uniformity of weight(mg)	149	147	148
2.	Thickness (mm)	3.5	3.4	3.2
3.	Hardness (kg/cm^2)	6.5	7	7.2
4.	Friability (%)	0.53	0.76	0.80
5.	Drug content	95.23	94.11	92.77
6.	% drug release	91.61	86.41	82.99

Table 9: Post compression evaluation bilayer tablet of c5 and p1 optimised batch

Sr.no.	Parameters	C5P1
1.	Uniformity of weight (gm)	248
2.	Thickness (mm)	5.3
3.	Hardness (kg/cm^2)	5.2
4.	Friability (%)	0.58
5.	Drug content (immediate release) Drug content (sustain release)	97.23 95.76
6.	% drug release (immediate release) % drug release (sustain release)	92.91 91.91

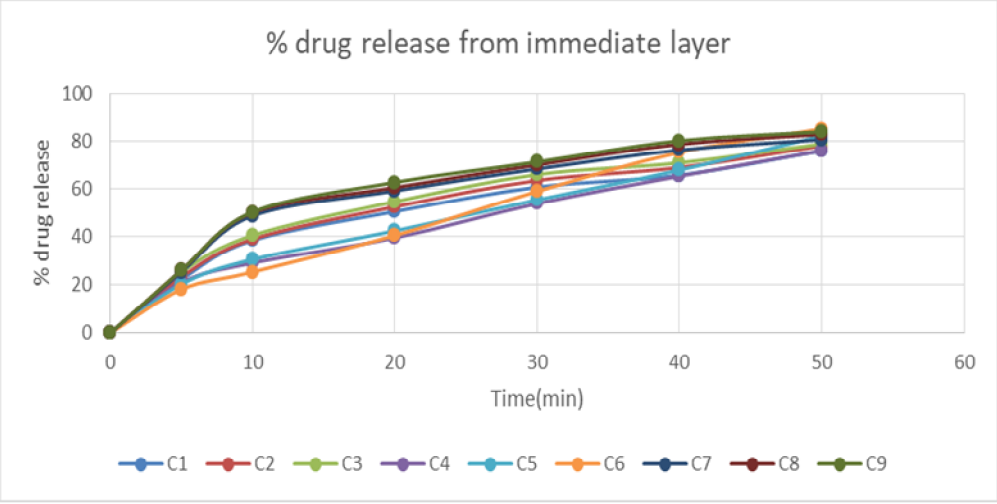

Figure 5: % drug release immediate release layer (carbimazole)

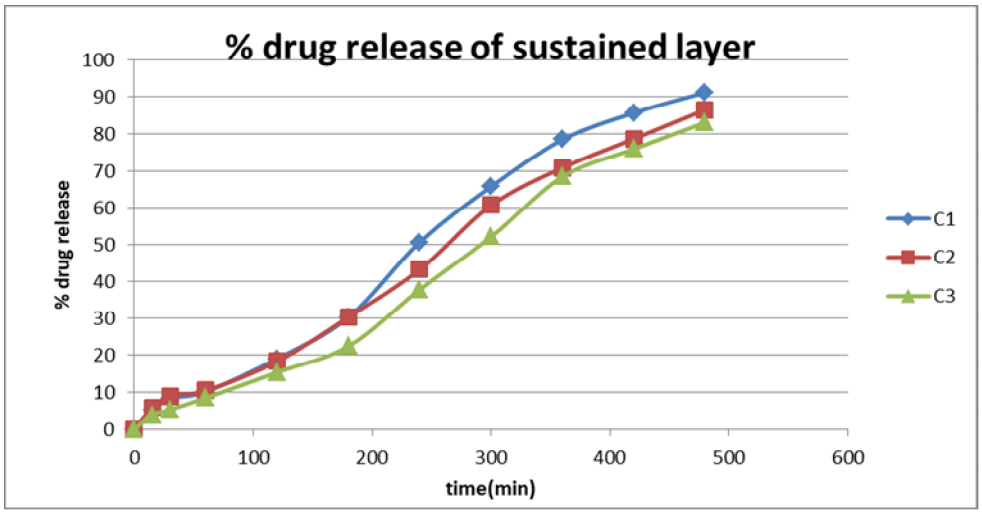

Figure6:% drug release of the sustained released layer (propranolol hcl)

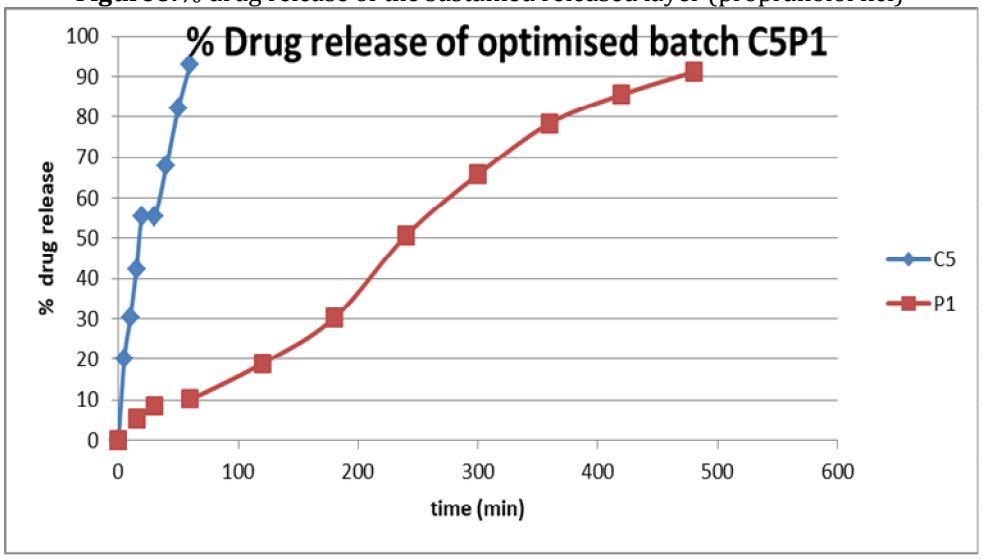

Figure 7: % drug release optimized formulation c5p1

Table 10: drug release kinetics of carbimazole tablets.

Time (min)	Cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
5	20.23	79.77	2.236	1.902	0.699	1.306	20.23	4.305	0.337
10	30.42	69.58	3.162	1.842	1.000	1.483	10.19	4.113	0.529
20	42.37	57.63	4.472	1.761	1.301	1.627	11.95	3.863	0.779
30	55.32	44.68	5.477	1.650	1.477	1.743	12.95	3.548	1.094
40	67.78	32.22	6.325	1.508	1.602	1.831	12.46	3.182	1.460
50	82.17	17.83	7.071	1.251	1.699	1.915	14.39	2.612	2.030
60	92.91	7.09	7.746	0.851	1.778	1.968	10.74	1.921	2.721

Table 11: Drug release kinetics of propranolol hcl

Time(min)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
15	5.22	94.78	3.873	1.977	1.176	0.718	5.22	4.559	0.083
30	8.37	91.63	5.477	1.962	1.477	0.923	3.15	4.508	0.134
60	10.12	89.88	7.746	1.954	1.778	1.005	1.75	4.479	0.163
120	18.95	81.05	10.954	1.909	2.079	1.278	8.83	4.328	0.314
180	30.23	69.77	13.416	1.844	2.255	1.480	11.28	4.117	0.525
240	50.65	49.35	15.492	1.693	2.380	1.705	20.42	3.668	0.974
300	65.78	34.22	17.321	1.534	2.477	1.818	15.13	3.247	1.395
360	78.46	21.54	18.974	1.333	2.556	1.895	12.68	2.782	1.860
420	85.57	14.43	20.494	1.159	2.623	1.932	7.11	2.435	2.207

DISCUSSION

The absorption maxima of Carbimazole and Propranolol hcl were found to be 291.8 nm and 288.3 nm respectively. All the excipients used in formulation of bilayer tablet of Carbimazole and Propranolol hcl are compatible. Various precompression parameters such as bulk density, tapped density, angle of repose, carr's index, hausner's ratio were performed. Various postcompression parameters such as uniformity of weight, thickness, hardness, friability, drug content, percentage drug release were performed. Among all the batches c5p1 was found to be optimized batch. The bulk density, tapped density, compressibility index, hausner's ratio, angle of repose of c5 layer was found to be 0.5429 g/ml, 0.6135 g/ml, 11.50%, 1.13, 21.6^0 respectively. The bulk density, tapped density, compressibility index, hausner's ratio, angle of repose of p1 layer was found to be 0.4344g/ml, 0.4953 g/ml, 12.29%, 1.14, 20.22^0 respectively. the results of post compression parameters such as uniformity of weight, thickness, hardness, friability, drug content, percentage drug release of c5 layer was found to be 99 mg, 1.8mm, 3.2 kg/cm^2. The results post compression parameters of c5 layer such as uniformity of weight, thickness, hardness, friability, drug content, and percentage drug release were found to be 99 mg, 1.8 mm, 3.2 kg/cm^2, 0.79%, 97.21, 92.98% respectively. The results post compression parameters of p1 layer such as uniformity of weight, thickness, hardness, friability, drug content, and percentage drug release were found to be 149mg, 3.5mm, 6.5 kg/cm^2, 0.53 %, 95.23, 91.61% respectively. The results post compression parameters of optimized layer in bilayer tablets such as uniformity of weight, thickness, hardness, friability was found to be 248 mg, 5.3 mm, 5.2kg/cm^2, 0.58% respectively. Drug content of immediate release layer was found to be 97.23 and drug content of the sustained release layer was found to 95.76. Drug release of immediate layer was found to be 92.91% within 1 hr. Drug release of sustained release was found to be 91.91% for 8 hrs. The mechanism involve in drug release from the optimized batch c5p1 is by zero order. Therefore the bilayer tablets were prepared from optimized immediate release layer of carbimazole and optimized sustained release layer of propranolol hcl. After preparing the bilayer tablets again post compression parameters were performed. The batch c5p1 containing sodium starch glycolate of 15 mg and ethyl cellulose of 25 mg was found to be optimized batch.

KINETIC MODELS

Dissolution study of bilayer tablet evaluated against Zero order, Higuchi, First order, Hixson, Kors-peppas. The mechanism of drug release determined by using Higuchi equation for Carbimazole as immediate release and zero order for Propranolol HCl as sustain release.

CONCLUSION

The prepared tablet shows satisfactory results for weight variation, Hardness, Thickness, Friability, Drug content and percentage drug release. The optimized formulation i.e. C5 (sodium starch glycolate) was selected for the immediate release layer and P1 Ethyl cellulose) was selected for control release layer. The drug release kinetics by zero order and involves both by dissolution and diffusion. The immediate release layer of Carbimazole useful for hyperthyroidism and sustain release layer of propranolol useful against systolic hypertension.

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AUTHORS CONTRIBUTIONS
All authors contributed equally.

CONFLICT OF INTERESTS
Declare none.

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