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FORMULATION AND IN-VITRO CHARACTERIZATION OF LOSARTAN POTASSIUM AND REPAGLINIDE BILAYER TABLETS

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Abstract:
The purpose of this study is to formulate and evaluate bilayer anti-hypertensive and anti-diabetic tablets. Bilayer tablet contains Losartan potassium for immediate release and Repaglinide for a sustained release. The bilayer tablets were prepared using crospovidone and sodium starch glycolate as super-disintegrants for the immediate release layer, hydroxyl propyl methyl cellulose K 100M and hydroxyl propyl methyl cellulose K 15M as polymers at various concentrations to retard the release of drug for a period of time. Immediate release layer was prepared by direct compression and wet granulation method was followed for sustained release. FT-IR studies revealed that there was no incompatibility between drugs and excipients. The tablets were evaluated for weight variation test, hardness, thickness, friability, tablet disintegration time, content uniformity and in vitro dissolution studies. In vitro drug release studies were performed using the type-II dissolution apparatus (paddle) using 0.1N Hydrochloric acid for first 2 hours and the remaining hours with 6.8 pH phosphate buffer. Among all the formulations, optimized formulation F5 showed a maximum of 99.4% drug release at 45 minutes for Losartan potassium and Repaglinide has an in vitro drug release of 99.87%. Therefore, bilayer tablets in combination of these two drugs can be used to improve the management of hypertension (high blood pressure) and diabetes mellitus. –II.

Keywords: *Bilayer tablet, Losartan Potassium, Crospovidone, and Sodium starch glycolate, Repaglinide, Hydroxy propyl methyl cellulose K100M, Hydroxy propyl methyl cellulose K15M.*

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INTRODUCTION:

When two or more active pharmaceutical ingredients must be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate a multilayer tablet. The bilayer tablets are prepared with drug layer for immediate release while the second layer is designed as to release the drug later, as a second dose, or for a prolonged or conventional[1] manner. Bilayer tablet is suitable for the sequential release of two drugs in combination and separate two incompatible substances. Each layer may contain a different medicinal agent with variable release profiles, and they are designed for many reasons such as controlling the rate of administration of one or two different active pharmaceutical ingredients and the separation of the incompatible active pharmaceutical ingredients, the ones with the others, release of active pharmaceutical ingredients from one layer using the functional property of the other layer. Repaglinide [2] is used alone or with other medicines to control high blood sugar levels. It is used in people with type 2 diabetes [3]. Losartan Potassium is an angiotensin II receptor antagonist that is used to treat hypertension [4], and help protect the kidney damage from diabetes. It is also used to reduce the risk of stroke in patients with high blood pressure and an enlarged heart. Lowering high blood pressure helps prevent strokes, heart attacks and kidney problems. The present work focuses on the immediate release dosage form of Losartan potassium which gives faster onset of action, and reduces the high blood pressure. To prepare sustained release dosage form of Repaglinide which gives controlled onset of action for a longer period of time with the desired release pattern.

MATERIALS AND METHODS:

Materials: Losartan Potassium and Repaglinide were obtained as a gift sample from Hetero Drugs Pvt. Ltd. (Hyderabad, India). Crospovidone and Sodium Starch Glycolate were donated by Granules India and Dow Corning. HPMC K 100 M and HPMC K 15 M were obtained as a gift sample from Colorcon. Polyvinyl pyrrolidone K 30, Spray Dried Lactose, Lactose Monohydrate came from MERCK. Hydrochloric acid and Methanol were obtained as a gift from Rankem..Magnesium Stearate was donated by Peter Griven GMBH. Talc was obtained as a gift sample from Luzenac Pharma.

EXPERIMENTAL WORK:

Preformulation studies

Physicochemical interaction of drugs and excipients

The absorption spectra of the drugs,superdisintegrants and all the polymers [5,6] used as a combination polymers did not show a significant interaction. The graphs are shown in Figure 1.

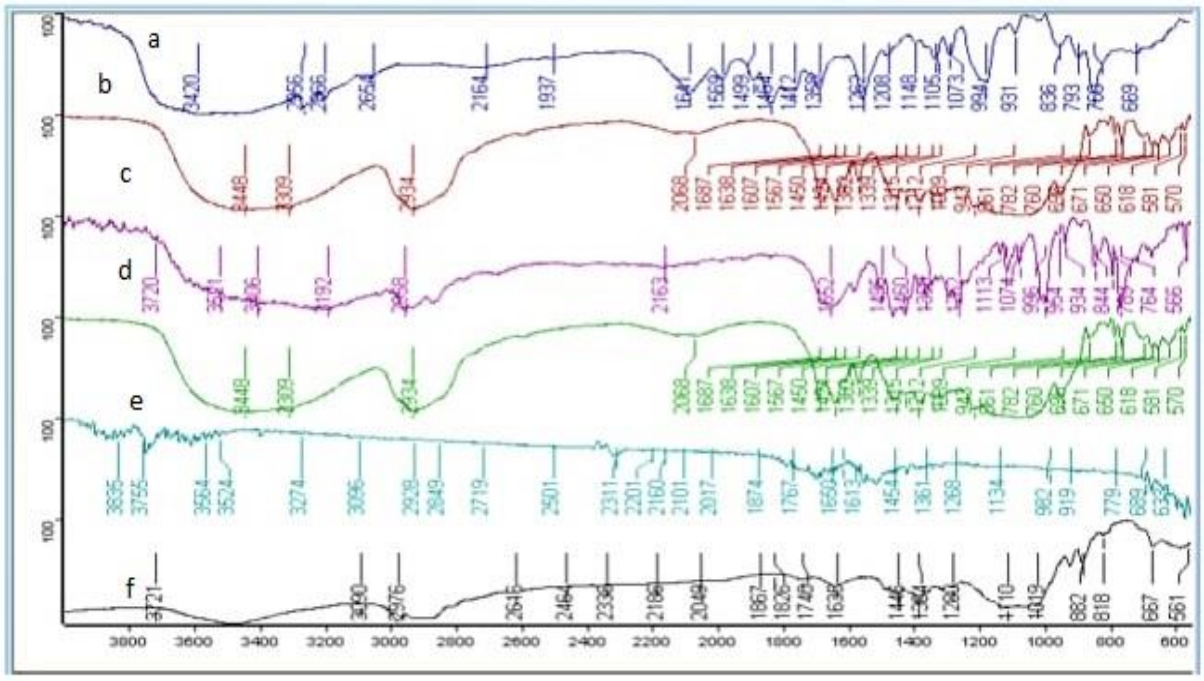

Fig 1: IR overlay of drug and excepients
(a)-losartan potassium, (b)-repaglinide, (c)-crospovidone, (d)-sodium starch glycolate, (e)-HPMC K 15 M, (f)- HPMC K 100 M

Manufacturing process of the immediate release [7] **layer of losartan potassium**

The procedure for the preparation was direct compression. All ingredients were mixed, except magnesium stearate and talc. Finally, dye was added together with magnesium stearate and talc,later the powder mixture was punched with 12 mm size punch.

Manufacturing process of the Sustained release [8,9] **granules of Repaglinide**

wet granulation method was followed,all the ingredients weremixed,except magnesium stearate and talc with water and a wet mass was formed. The formed mass was passed through mesh 10#and the formed granules were dried and then passed through mesh 24# and punched with 12mm size punch.

Evaluation of tablets

All tablets were evaluated [10,11] for various parameters such as hardness, thickness, friability, disintegration time, drug release in vitro dissolution studies.

Thickness

From each batch six tablets were randomly selected and their thickness was measured using vernier callipers. The average thickness with the standard deviation of the tablets of each batch was measured and are tabulated in Table 3.

Hardness

The tablet crushing load is the force required to break the tablet by compression. Monsanto hardness tester is used to measure hardness . From each batch, six tablets were selected randomly and evaluated. The tablets must have a certain amount of hardness or strength and the resistance and friability to withstand the mechanical shocks of manufacturing, packaging and shipping hardness. Hardness is tabulated in Table3**.**

Friability

The friability test is performed to evaluate the effect of friction and shock, which can often cause the tablet to chip, clog or break. Roche friabilator was used for this purpose. Pre-weighed samples of twenty tablets were placed in the friabilator, which was then operated at 25 RPM for 4 minutes, that is, 100 revolutions. After 100 revolutions, the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight. A conventional tablet should have less than 0.5-1% of the friability of the weight tabulated in Table 3.

Weight variation test

Select twenty tablets randomly from each lot and weigh individually. Average weight and standard deviation of 20 tablets were calculated. The lot passes weight variation test, if not more than two of the individual weights deviates from average weight by more than the percentage shown in the table and none should deviate more than the double percentage shown. The average weight, standard deviation of the tablets in each batch were given in Table 3.

Disintegration time

The in vitro disintegration time was determined by the use of a disintegration test apparatus and a tablet was placed in the apparatus. The complete disintegration time in seconds for the of the tablet without palpable mass in the apparatus was measured. The results are shown in Table 3**.**

Assay

The content uniformity test was done by uv method. Twenty tablets were weighed and randomly pick the tablets then immediately crush it. Take required quanity of crushed tablet and the powder was transferred into the volumetric flask and mix with suitable diluent. Then it was checked by uv method and the assay was calculated.The results are shown in Table 3.

RESULTS AND DISCUSSION:

In vitro dissolution studies [12]:

The in vitro dissolution test was carried out using the USP type II apparatus .The solution was carried out using 0.1 N HCl for the first 2 hours and with phosphate buffer pH 6.8 during the remaining hours. The paddle was rotated at 100 rpm at the temperature (37 ° C ± 0.5 ° C). The sampling was carried out at regular intervals and was replaced by means after each sampling interval. The samples are analyzed spectrophotometrically at λ max of the drug. The in vitro dissolution studies were tabulated in Table 4.

Table 1: Formulation trials of Bilayer tablets

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Immediate release layer									
Losartan potassium	50	50	50	50	50	50	50	50	50
Crospovidone	50	75	100	125	150	NA	NA	NA	NA
Sodium starch glycolate	NA	NA	NA	NA	NA	50	75	100	125
Polyvinyl pyrrolidone	5	5	5	5	5	5	5	5	5
Lactose monohydrous	191.5	166.5	141.5	116.5	91.5	191.5	166.5	141.5	116.5
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Colour	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
IR layer wt	300	300	300	300	300	300	300	300	300
Sustained release layer									
Repaglinide	4	4	4	4	4	4	4	4	4
HPMC k 100 M	2	4	6	8	10	NA	NA	NA	NA
HPMC k 15 M	NA	NA	NA	NA	NA	2	4	6	8
pvp	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Spray dried lactose	192.5	190.5	188.5	186.5	184.5	192.5	190.5	188.5	184.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
SR layer wt	200	200	200	200	200	200	200	200	200
Total tablet weight	500	500	500	500	500	500	500	500	500

Table 2:Pre compression parameters for Losartan Potassium blend and Repaglinide granules

Formulation	Bulk density(g/ml)	Tapped Density(g/ml)	Hausner's Ratio	Carr's index(%)	Angle of Repose (θ)
L1	0.682±0.004	0.752±0.002	1.16±0.02	20.60±0.65	26.3±0.98
L2	0.575±0.013	0.824±0.004	1.25±0.03	18.98±0.87	29.8±0.17
L3	0.823±0.215	0.685±0.002	1.13±0.02	19.24±1.11	28.3±0.76
L4	0.672±0.153	0.814±0.003	1.9±0.02	21.29±0.87	29.4±0.88
L5	0.426±0.023	0.615±0.001	1.8±0.01	20.52±0.76	28.5±0.12
L6	0.765±0.012	0.734±0.004	1.23±0.03	17.85±0.65	25.8±0.23
L7	0.521±0.006	0.624±0.003	1.14±0.01	18.76±0.45	29.7±0.92
L8	0.678±0.032	0.654±0.004	1.19±0.02	20.32±0.96	26.9±0.47
L9	0.479±0.041	0.856±0.002	1.21±0.019	19.43±0.12	27.6±0.80
R1	0.532±0.002	0.822±0.006	1.12±0.01	18.60±0.45	21.3±0.98
R2	0.474±0.003	0.814±0.003	1.28±0.02	14.98±0.89	26.3±0.17
R3	0.872±0.241	0.689±0.001	1.23±0.02	19.24±0.21	21.9±0.76
R4	0.634±0.231	0.715±0.002	1.9±0.03	20.29±0.34	23.8±0.88
R5	0.398±0.021	0.619±0.001	1.8±0.01	21.52±0.65	28.1±0.12
R6	0.763±0.014	0.718±0.002	1.16±0.02	18.85±0.43	25.3±0.23
R7	0.426±0.003	0.654±0.004	1.18±0.01	16.76±0.29	26.3±0.92
R8	0.732±0.051	0.783±0.002	1.20±0.03	15.32±0.72	24.7±0.47
R9	0.564±0.041	0.691±0.002	1.17±0.02	17.43±0.14	27.2±0.80

Table 3: Post compression parameters for bilayer tablets

Batch	Thickness	Hardness	Friability	Disintegration time	Weight variation	Assay%	
						Losartan	Repaglinide
F1	5.89±0.015	8.2	0.14	12m 53s	498±1.95	85.18±0.01	87.49±0.23
F2	5.92±0.013	8.7	0.17	11m 47s	495±1.23	89.72±0.04	89.45±0.41
F3	5.86±0.025	8.5	0.27	9m 18s	500±1.35	92.17±0.21	85.41±0.18
F4	5.88±0.014	7.8	0.25	6m 41s	512±1.29	97.36±0.11	95.13±0.56
F5	6.12±0.032	9.5	0.1	5m 30s	500±1.56	99.18±052	99.37±0.11
F6	5.99±0.153	7.6	0.21	8m 32s	506±1.8	96.43±0.03	97.92±0.29
F7	5.96±0.231	8.3	0.18	9m 12s	503±1.2	94.65±0.01	98.51±0.04
F8	6.1±0.051	7.9	0.16	11m 24s	499±1.25	93.47±0.06	91.33±0.12
F9	5.92±0.061	8.8	0.13	7m 86s	498±1.12	97.23±0.21	92.43±0.34

Table 4: *In-vitro* percent drug release of Losartan potassium immediate release layer (L1-L9)

Time (min)	Losartan IR layer %Drug Release								
	L1	L2	L3	L4	L5	L6	L7	L8	L9
0	0	0	0	0	0	0	0	0	0
5	25.2±0.05	26.8±0.321	18.1±0.208	19.24±0.01	13.8±0.1	17.27±0.03	18.92±0.01	12.9±0.30	14.71±0.01
10	69.2±0.37	58.2±0.264	46.17±0.026	52.41±0.03	34.89±0.01	39.72±0.02	42.79±0.03	28.9±0.26	32.4±0.04
15	81.2±0.20	74.1±0.2	67.87±0.02	78.26±0.02	67.41±0.32	59.27±0.02	61.91±0.02	60.21±0.20	65.4±0.24
30	82.3±0.15	79.2±0.1	73.79±0.026	84.2±0.1	89.7±0.26	79.14±0.03	78.28±0.04	78.4±0.26	84.7±0.41
45	73.6±0.01	76.1±0.35	85.89±0.030	95.3±0.05	99.4±0.26	83.59±0.04	85.29±0.02	85.89±0.36	89.3±0.31
60	69.2±0.15	71.9±0.55	81.27±0.02	88.1±0.15	91.6±0.15	77.98±0.01	79.63±0.01	81.23±0.02	87.72±0.26

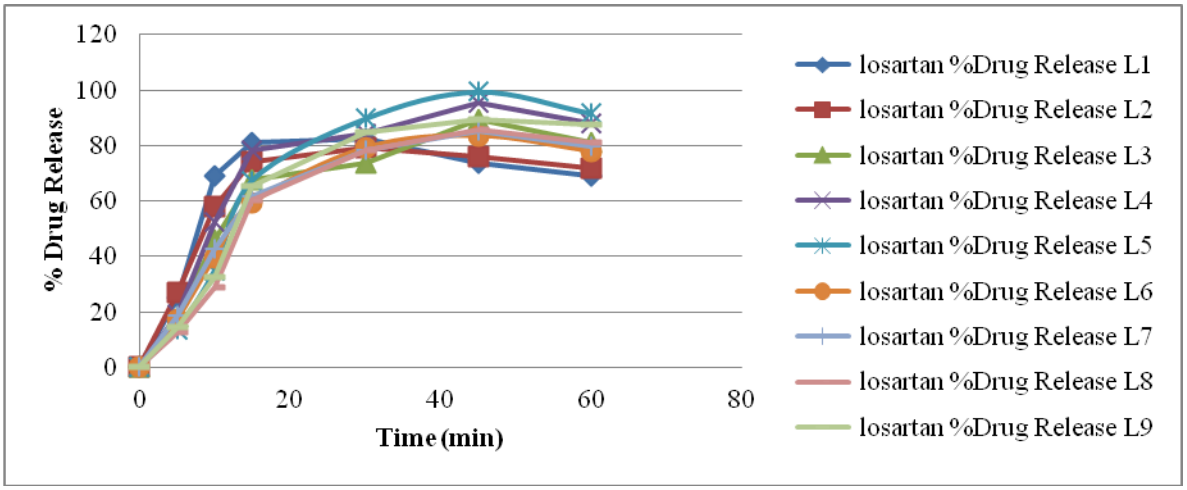

Fig 6: *In- vitro* dissolution % drug release profile of bilayer tablet (L1-L9)

Table 4: *In-vitro* percent drug release of Repaglinide sustained release layer (R1-R9)

Time (min)	Repaglinide SR layer % drug release								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
0	0	0	0	0	0	0	0	0	0
0.5	8.92±0.01	9.82±0.04	12.4±0.15	4.2±0.01	1.8±0.17	7.21±0.13	8.54±0.02	2.4±0.01	1.2±0.29
1	28.41±0.02	32.25±0.02	39.67±0.02	15.7±0.23	12.8±0.26	24.78±0.03	28.67±0.01	14.9±0.02	13.2±0.13
2	58.67±0.02	68.91±0.06	56.37±0.02	38.27±0.02	30.21±0.24	42.56±0.01	52.91±0.04	28.0.547±0.36	32.8±0.34
4	69.27±0.02	78.96±0.07	72.81±0.03	64.89±0.14	58.7±0.12	68.24±0.04	67.29±0.01	49.4±0.72	60.81±0.23
6	73.24±0.55	80.12±0.02	81.82±0.02	86.71±0.01	87.49±0.32	72.93±0.01	75.81±0.12	72.9±0.21	82.47±0.62
8	78.27±0.02	85.6±0.01	83.97±0.02	94.78±0.03	99.87±0.02	89.37±0.05	89.4±0.48	92.72±0.18	93.6±0.01

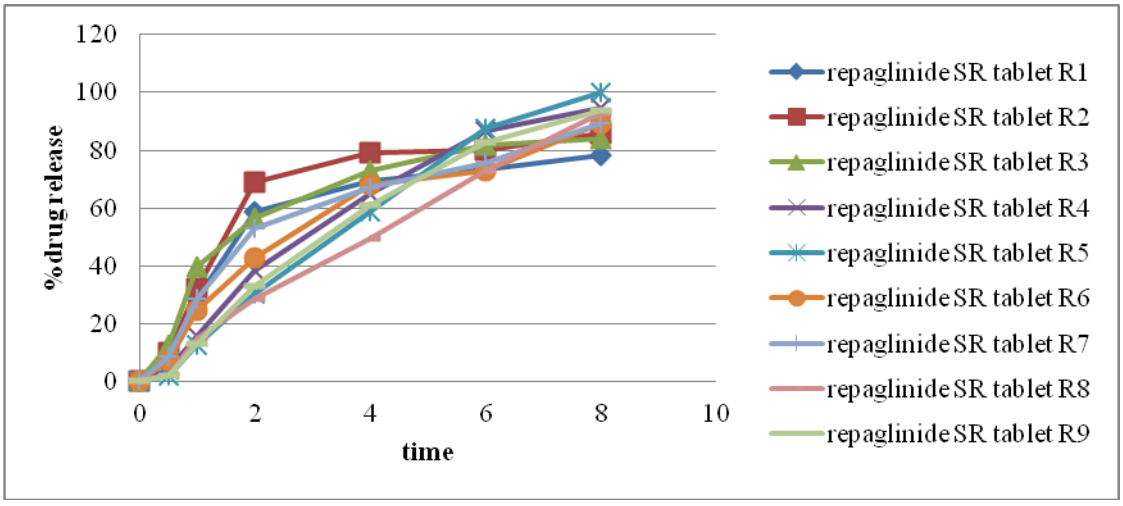

Fig 7: In- vitro percent % drug release of bilayer tablet (R1-R9)

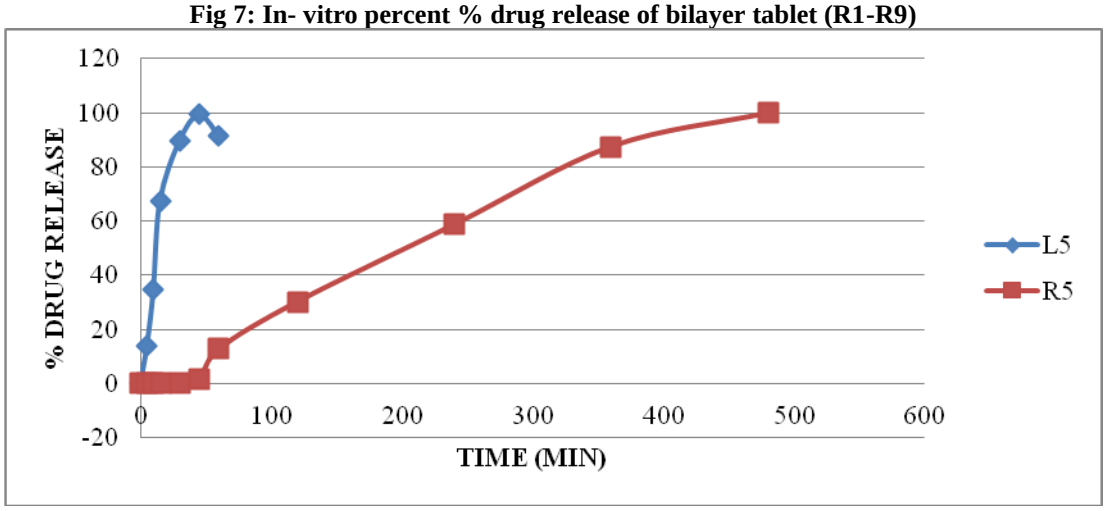

Fig 8: In vitro Percent % drug release of optimized formulation

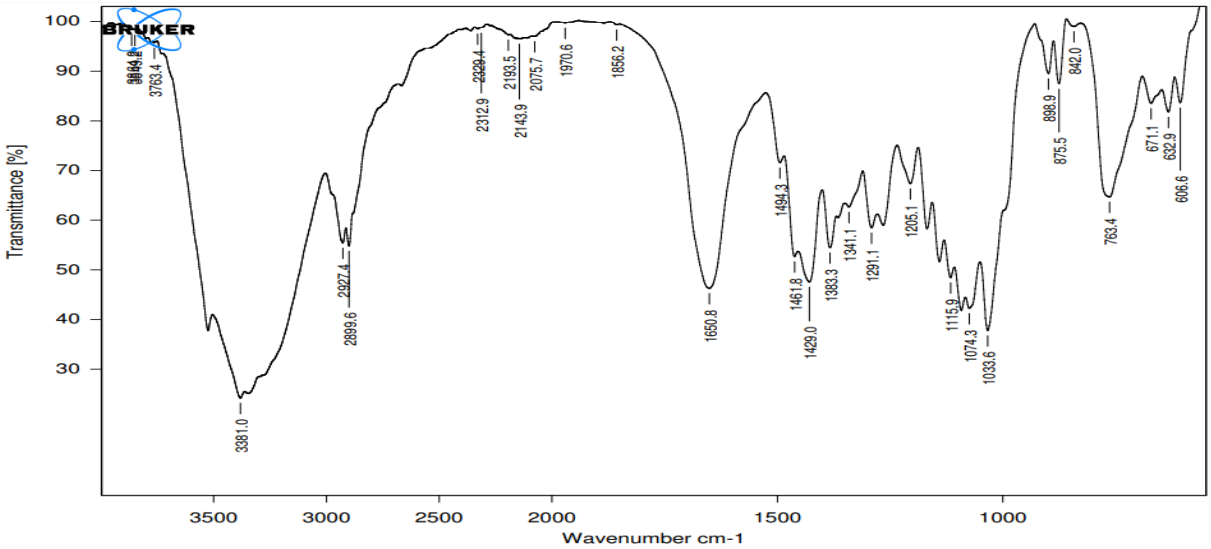

Fig 9: IR overlay of optimized formulation

CONCLUSION:

The present research was carried out to develop a bilayer tablet of Losartan potassium and Repaglinide by using different super disintegrants in various concentrations for immediate release, where polymers are used to retard the release of Repaglinide. The FT-IR studies revealed that there was no interaction between the drugs and the excipients. Different formulations were prepared in increasing concentrations of super disintegrants and polymers. Direct compression was performed for immediate release and wet granulation for the sustained release layer. Various batches were prepared and evaluated, among the nine formulations, F5 formulation was optimized and showed the maximum drug release compared to the other formulations.

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