IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND IN VITRO EVALUATION OF BILAYER TABLETS OF ALISKIREN AND EMPAGLIFLOZIN FOR THE TREATMENT OF HYPERTENSION AND DIABETES

Archana V. Rajdeo[*1], Jyoti N. Patil[2], Samruddhi S. Patil[3]

[1,2]Department of Quality Assurance, PRES Institute of Pharmacy, Loni, Ahmednagar.

[3]Department of Pharmaceutics, PRES Institute of Pharmacy, Loni, Ahmednagar.

Abstract

The current work focuses on the development and evaluation of bilayer tablet of Empagliflozin and Aliskiren in the treatment of Diabetes and hypertension. The release of Aliskiren and Empagliflozin was controlled by formulating it into an immediate and sustained release layer respectively. Both layers were prepared by wet granulation. The compatibility of polymers and excipients along with pure drugs was evaluated using FTIR studies. The tablets were prepared and Pre-and Post-compression parameters, In-vitro dissolution testing, release rate kinetics and stability studies were evaluated. The FT-IR spectra's confirms the absence of chemical interaction between drug and polymers. Both pre- and post-compression parameter was discovered to be within acceptable bounds. For the bi-layered tablet, one formulation of each layer was chosen based on the in vitro dissolving profile data. AIRF6 from immediate release formulations, which demonstrated a 30-minute drug release of 98%. 99 percent of the medication was released in 12 hours when using EERF5, a sustained release formulation. For three months, stability tests conducted on bi-layered tablet batches at 40ºC and 75% relative humidity revealed no appreciable changes in the drug's composition, release profile, or outward look. Thus, combining both immediate and sustained release layers led to the effective development of a unique bilayer tablet formulation of Empagliflozin and Aliskiren. The rationale for this fixed-dose combination is to co-administer two drugs acting by different mechanisms of action together, reduce dosing frequency, and increase patient compliance.

Keywords: Hypertension, Diabetes, Bilayer Tablet, Aliskiren, Empagliflozin.

Introduction

Whenever it comes to patient compliance, the oral route is the most preferred delivery method. Numerous pharmaceutical companies have focused their research efforts on repurposing current medications in novel dosage formulations. The oral film is one such relatively recent dosage form. It is a thin film made of hydrophilic polymers that dissolves quickly on the tongue or in the buccal cavity. Formulation development for youngsters has proven to be a difficult undertaking. One of the most important variables affecting adherence to treatment plans, among other things, is how well paediatric oral drug formulations taste. While older children and teenagers generally accept solid dosage forms, younger children typically choose liquid formulations since they are simpler to ingest 3. Keeping the ease of administration and swallowing in mind, pharmaceutical research has led to the development of Oral Disintegrating Tablets (ODTs). ODTs have been defined as "A solid dosage form containing medicinal substances which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue". United States Food and Drug Administration further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity, with an Invitro disintegration time of approximately 30s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative. The lower bioavailability, long onset time and Dysphagia patients because of this the manufacturer shifted towards parenteral and liquid orals. But the liquid orals like syrup, suspension, emulsion etc. have the issue of perfect dosing mainly and parenteral are painful drug delivery, which result into patient noncompliance. Every pharmaceutical company has desire to formulate the innovative oral dosage form which has the higher bioavailability, rapid action and most patient compliance. Tablets and capsules are the most popular solid dosage forms. Many patients having a problem to swallow tablets and hard gelatin capsules especially geriatric and pediatric patients and do not take their medicine as prescribed. In the present situation the major focus has turned towards combination therapy for the treatment of different diseases and disorders. Combination therapy has an edge over monotherapy because it reduces the dose dependent side effects and improves the total clinical performance of the drugs. Bi-layer tablets are innovative drug delivery systems where mixing of two or more drugs in a single unit having various release profiles which increases patient compliance, prolongs the drug action. Two layer tablets may be developed for sustain release, one layer for the immediate release of the drug and second layer for extended release thus controlling a prolonged blood level. Layers may be colored differently to find the product.

Aliskiren

Aliskiren is the first drug in the renin inhibitor drug class and is used for the treatment of hypertension. It was developed by Speeded and Novartis and initially approved by the FDA in early 2007. Aliskiren has been proven to efficacious in reducing blood pressure when used alone or in conjunction with other antihypertensive agents. Aliskiren is used for the treatment of hypertension in children above 6 years and adults. This drug may also be used in conjunction with antihypertensive such as calcium channel blockers and thiazides in products form to provide additional blood pressure control. Aliskiren is a renin inhibitor. Renin is secreted by the kidneys when blood volume and renal perfusion decrease. It normally cleaves the protein angiotensinogen to form angiotensin I. Angiotensin I is then converted to angiotensin II, an active protein. Angiotensin II is a potent vasoconstrictor that causes the release of Catecholamines into the circulation. It also promotes the

secretion of aldosterone in addition to sodium reabsorption, increasing blood pressure. Additionally, angiotensin II acts on the adrenal cortex where it stimulates aldosterone release. Aldosterone increases sodium reabsorption and potassium excretion in the nephron. Aliskiren prevents the above process via binding to renin at its active site, stopping the cleavage of angiotensin, in turn inhibiting the formation of angiotensin I. This ends the cascade of angiotensin II mediated mechanisms that normally increase blood pressure.

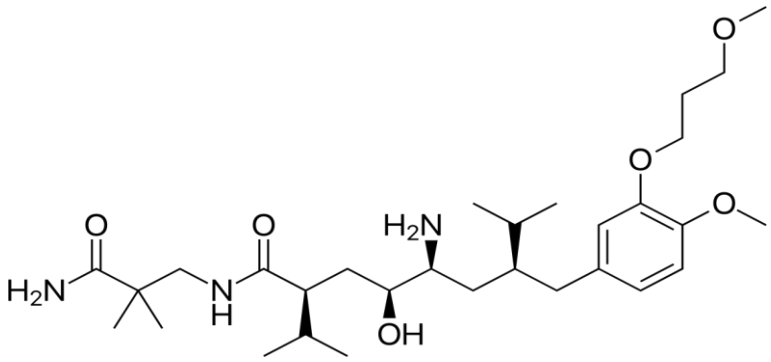


Fig. no. 1 Structure of Aliskiren

Empagliflozin

Empagliflozin is an inhibitor of sodium-glucose co-transporter (SGLT2), the transporters primarily responsible for the reabsorption glucose in the kidney. It is used clinically as an adjunct to diet and exercise, often in combination with other drug therapies, for the management of type 2 diabetes mellitus. The first known inhibitor SGLTs, polarizing, was isolated from the bark of apple trees in 1835 and researched extensively into the 20th century, but was ultimately deemed inappropriate for clinical use given its lack of specificity and significant gastrointestinal side effects.

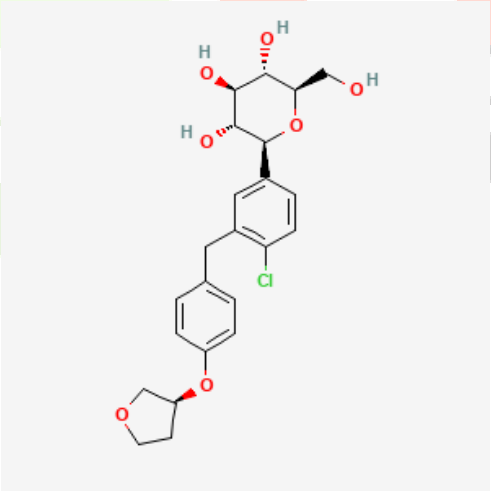


Fig. no. 2 Structure of Aliskiren

Method and Results

Preformulation Studies Determination of λmax

□max for Empagliflozin was Found at 224 nm. □max of Aliskiren was found to be 279 nm.

Solubility

It was determined as per procedure given in material and method part. The drug Empagliflozin is slightly soluble in water (pH 1-7.4), slightly soluble in ethanol, sparingly soluble in methanol. The drug Aliskiren is soluble in water, slightly soluble in ethanol and soluble in methanol.

Determination of Melting Point

Table 1: Melting Point for Empagliflozin

Test	Specification / limits	Observations
Melting Point	151-153°C	152°C

Table 2: Melting Point for Aliskiren

Test	Specification / limits	Observations
Melting Point	98-99 °C	98°C

Calibration Curve for Aliskiren

Method was developed for estimation of Aliskiren showed maximum absorption at wavelength 279 nm in 0.1 N HCl. The value of regression coefficient was found to be 0.998 which showed linear relationship between concentration and absorbance. The standard calibration curve obeyed Beer's law at the given concentration range of 05 µg/ml to 25 µg/ml in 0.1 N HCl.

Table No. 3: Results for Aliskiren Linearity by UV Spectroscopy

Sr. no.	Concentration(µg/ml)	Absorbance
1	0	0
2	05	0.124
3	10	0.226
4	15	0.344
5	20	0.458
6	25	0.569
Correlation coefficient		**0.998**

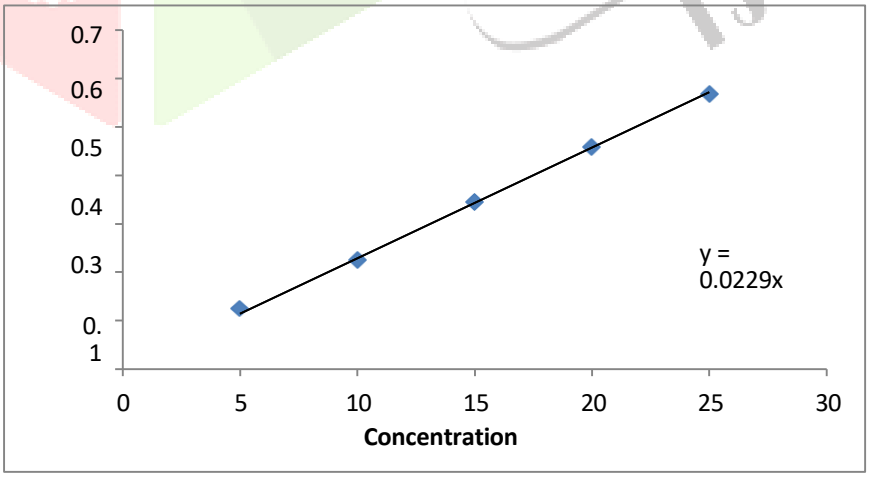


Figure No. 3: Calibration curve of Aliskiren by UV Spectroscopy Calibration Curve of Empagliflozin

And also method was developed for estimation of Empagliflozin showed maximum absorption at wavelength 224 nm in Phosphate buffer of pH 6.8. The value of regression coefficient was found to be 0.9986 which showed linear relationship between concentration and absorbance. The standard calibration curve obeyed Beer's law at the given concentration range of 5 µg/ml to 25µg/ml.

Table No. 4: Results for Empagliflozin by UV Spectroscopy

Sr. no.	Concentration(µg/ml)	Absorbance
1	0	0
2	05	0.151
3	10	0.284
4	15	0.411
5	20	0.555
6	25	0.669
Correlation coefficient		**0.9986**

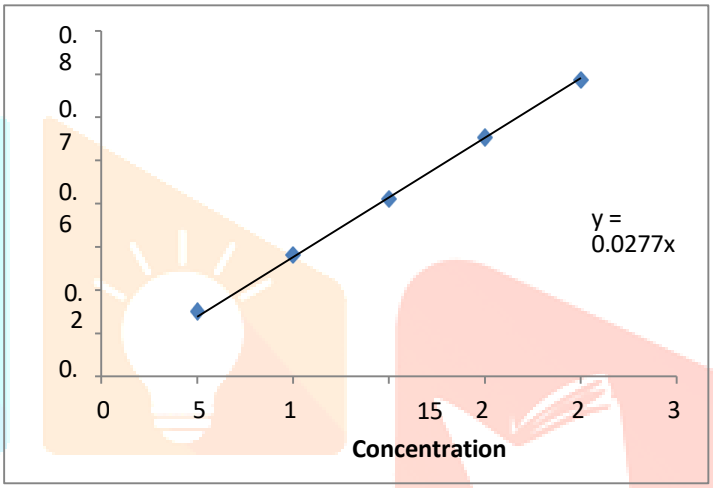


Figure No.4: Calibration Curve for Empagliflozin by UV Spectroscopy Physical Characteristics

Loss on Drying

Table no: 5: Loss on Drying for Empagliflozin

Test	Specification / limits	Observations
Loss on drying	Not more than 0.2 %	0.1%

Table no: 6 Loss on Drying for Aliskiren

Test	Specification / limits	Observations
Loss on drying	Not more than 0.2 %	0.2%

FT-IR Spectroscopy

FT-IR spectroscopy was carried out to check the compatibility between drug and excipients. Infrared spectroscopy was conducted and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The sample (drug and drug-excipient mixture in 1:1 ratio) in KBr (200-400mg) was compressed in to discs by applying a pressure of 5 tons for 5 min in hydraulic press. The interaction between drug-excipients was observed from IR- spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drugs excipients.

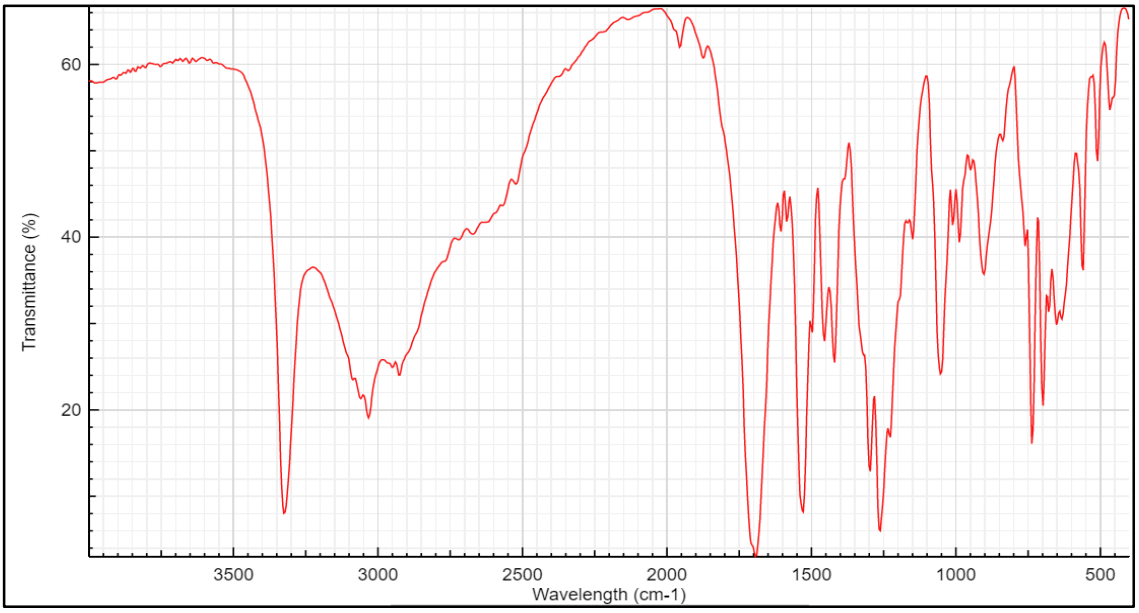
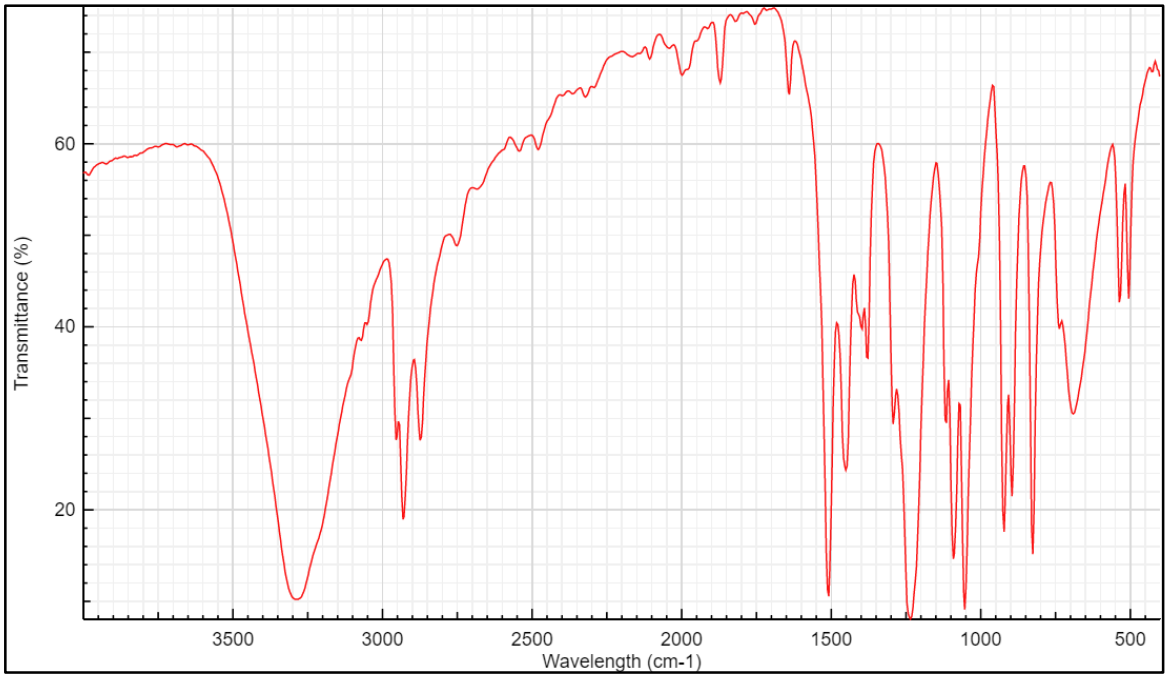


Figure no. 5: IR Spectra of Aliskiren

Sr.no	Functional group	Wave no.(cm^{-1})
1	O-H stretching	3374
2	- Secondary NH stretching	3324
3	Aromatic C-H stretching	3011
4	Aliphatic C-H bending	2884
5	-C-N Stretching	1248
6	-C=O Stretching	1288

Figure no.6 : IR Spectrs of Empagliflozin



Sr.no	Functional group	Wave no.(cm^{-1})
1	-NH stretch	3398
2	-OH stretch	3332
3	=C-H symmetric stretch	3041
4	-NH stretch Combination band	2062
5	-C=O stretching	1710
6	-C=C stretch ring	1444

Sr. no	Functional group	Wave no.(cm^{-1})
1	-OH stretching	3126
2	-CH stretching	2987
3	$-CH_2$ stretching	1503
4	-C-H stretching	1387
5	-C-O stretching	1211

EVALUATION OF PRE-COMPRESSION PARAMETERS

Flow properties:

Flow properties of Aliskiren and Empagliflozin were carried out and results are shown in the Tables 9 and 10 which were found to be as per the limits.

For Aliskiren Immediate release Layer

Table no.7: Flow properties of Aliskiren Immediate release Layer

Batch code	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's index (%)	Hausner's ratio	Angle of repose
AIRF1	0.536±0.001	0.626±0.004	12.611±0.218	1.136±0.031	19.495±0.355
AIRF2	0.575±0.004	0.646±0.005	15.085±0.227	1.172±0.019	18.371±0.276
AIRF3	0.554±0.005	0.625±0.004	15.772±0.108	1.165±0.023	19.422±0.174
AIRF4	0.684±0.002	0.683±0.002	13.898±0.176	1.154±0.015	16.246±0.155
AIRF5	0.611±0.009	0.583±0.008	11.766±0.205	1.142±0.008	17.914±0.040
AIRF6	0.655±0.003	0.756±0.007	11.147±0.156	1.123±0.026	17.102±0.078

For Empagliflozin Extended release Layer

Table no. 8: Flow properties of Empagliflozin Extended release Layer

Batch code	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's index (%)	Hausner's ratio	Angle of repose
EERF1	0.583±0.006	0.695±0.004	13.778±0.205	1.155±0.010	19.603±0.278
EERF2	0.560±0.007	0.688±0.001	14.485±0.329	1.168±0.018	18.461±0.064
EERF3	0.624±0.003	0.683±0.004	11.224±0.187	1.164±0.010	18.200±0.089
EERF4	0.644±0.006	0.704±0.002	16.530±0.126	1.233±0.011	22.547±0.279
EERF5	0.596±0.005	0.711±0.005	11.153±0.248	1.121±0.029	18.134±0.078
EERF6	0.594±0.005	0.728±0.003	12.117±0.398	1.257±0.030	18.187±0.103

POST-COMPRESSION EVALUATION PARAMETERS

Post Compression Evaluation of Aliskiren IR

Immediate release tablets of Aliskiren were successfully prepared by Wet Granulation method. The prepared formulations were evaluated for post compression parameters. The results of all formulations were found to be within limits (weight variation 198.7- 201.2, hardness range 4.15–6.36 kg/cm2, friability <1%, drug content 97.64–99.60%. and disintegration time 2–4 minutes) and all the values were reported in Table 7.11. In vitro drug release studies of immediate release tablets were carried out using USP type II dissolution apparatus in 900 mL of 0.1 N HCl at 45 rpm up to 30 minutes. The formulations AIRF1- AIRF6 showed drug release 67–99%. From that above data formulation AIRF6 was optimized for bilayer tablet as it reflects good disintegration and dissolution characters. These results are represented in Table 11 and Figure 9.

Table no.9: Post Compression Evaluation of Aliskiren IR

Batch code	Weight variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	drug content (%)	Disintegration time (min)
AIRF1	200.9±1.58	5.96±0.06	2.86±0.03	0.75±0.08	98.11±1.18	3.40
AIRF2	201.2±1.61	4.19±0.11	2.90±0.09	0.59±0.03	97.64±1.81	3.44
AIRF3	199.8±1.61	6.36±0.04	2.89±0.06	0.57±0.05	98.64±1.27	3.09
AIRF4	199.7±2.00	6.18±0.08	2.86±0.02	0.66±0.04	99.60±0.93	3.25
AIRF5	201.1±2.53	4.15±0.05	2.91±0.05	0.64±0.02	99.42±1.31	3.65
AIRF6	200±1.82	4.54±0.12	2.88±0.08	0.70±0.03	99.50±1.80	2.54

Table no. 10: In vitro drug release data of Aliskiren IR (AIRF1- AIRF6)

Time	AIRF1	AIRF2	AIRF3	AIRF4	AIRF5	AIRF6
0	0	0	0	0	0	**0**
5	14 ± 3.23	19 ± 3.47	22 ± 3.58	24 ± 27	26 ± 4.97	31 ± 3.89
10	21 ± 3.55	29 ± 3.30	33 ± 4.20	35 ± 3.30	41 ± 3.66	44 ± 3.64
15	37 ± 3.18	39 ± 4.55	45 ± 4.22	49 ± 4.11	55± 3.84	59 ± 3.84
20	49 ± 4.25	54 ± 4.61	59 ± 3.75	63 ± 4.63	67 ± 5.25	78 ± 4.33
25	58 ± 3.86	65 ± 3.78	66 ± 3.57	74 ± 4.98	80± 4.98	90± 3.87
30	67 ± 4.67	74 ± 3.79	77 ± 4.51	85 ± 4.87	97 ± 4.81	98 ± 3.55

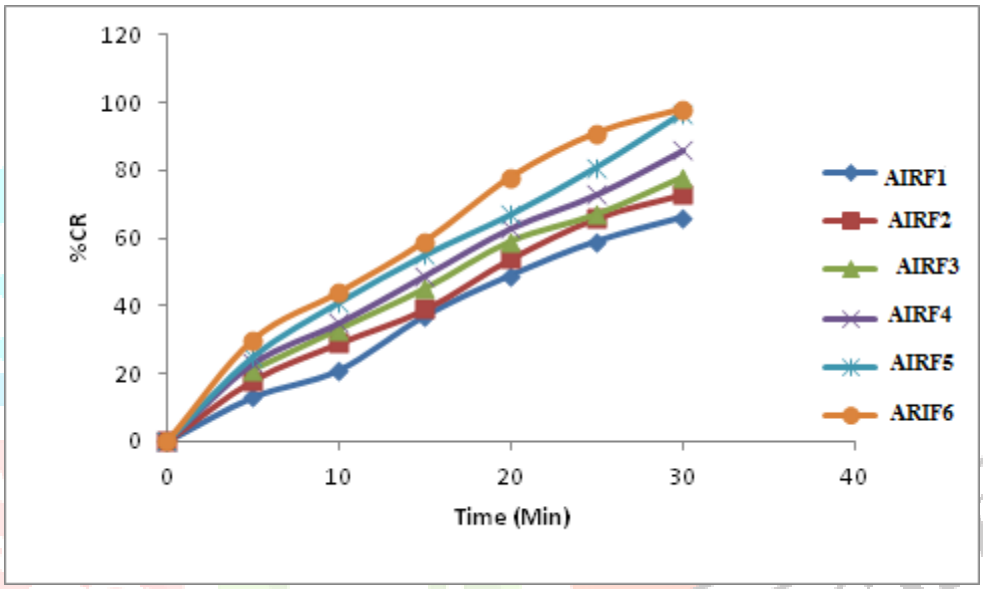


Figure No.7: In vitro drug release data of Aliskiren IR (AIRF1- AIRF6)

Post Compression Evaluation of Empagliflozin Extended release Layer Empagliflozin Extended release layer of bilayer tablet was prepared by wet granulation method using common granulating agent and diluent for all the formulations, having varying concentrations of polymers and gums which were used either individually or in combination, Post compression parameters were evaluated for all the formulations. The results of all formulations were found to be within limits (weight variation 300.75-302.9, hardness range 4.34–6.24 kg/cm2, friability <1%, drug content 97.42–99.37%, and all the values were reported in Table 7.13. In vitro drug release studies of extended release tablets were carried out using USP type II dissolution apparatus in 900 mL of 6.8 buffer solutions at 45 rpm up to12 hr. The formulations EERF1- EERF6 showed drug release up to 99%. From that above data formulation EERF5 was optimized because drug release extended up to 12 Hr with maximum drug release were shown in table 14.and figure 13. For bilayer tablet as it reflects good disintegration and dissolution.

Table no. 11: Post Compression Evaluation of Empagliflozin ER

Batch code	Weight Variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	content (%)
EERF1	302.7±1.42	5.39±0.11	3.34±0.09	0.31±0.07	99.37±1.18
EERF2	302.9±2.30	4.34±0.03	3.30±0.14	0.36±0.03	98.60±1.02
EERF3	302.5±1.60	6.15±0.05	3.31±0.03	0.44±0.04	97.42±1.27
EERF4	301.85±1.15	6.24±0.07	3.28±0.05	0.37±0.03	98.56±0.84
EERF5	300.75±1.38	5.15±0.04	3.30±0.06	0.43±0.07	98.42±1.26
EERF6	302.40±1.32	4.53±0.03	3.33±0.03	0.49±0.03	97.62±0.60

Time (hrs)	EERF1	EERF2	EERF3	EERF4	EERF5	EERF6
0	0	0	0	0	**0**	0
1	10 ± 3.38	12 ± 3.65	13± 3.33	14 ± 3.97	12± 3.91	11 ± 3.25
2	19 ± 3.98	21 ± 3.37	19 ± 3.64	19 ± 3.65	16± 3.69	13 ± 3.63
3	27 ± 3.43	32 ± 4.25	29± 3.65	32 ± 3.77	28± 3.43	24 ± 4.01
4	38 ± 3.99	39 ± 3.83	39± 4.28	41 ± 3.23	35± 4.21	30 ± 4.25
5	49 ± 3.72	48 ± 3.54	47± 4.24	49 ± 3.62	43± 3.64	38 ± 3.45
6	59 ± 4.46	55 ± 3.68	55± 3.99	59 ± 3.84	56± 3.08	45 ± 3.23
7	66 ± 3.23	63 ± 3.59	59 ± 3.88	60 ± 4.10	56± 3.68	53 ± 3.64
8	79 ± 3.45	80 ± 4.37	72± 4.11	74 ± 3.5	63± 3.28	58 ± 4.21
9	86 ± 3.88	89 ± 3.47	83± 3.98	84 ± 4.13	80± 4.15	62 ± 3.82
10	99 ± 3.31	98 ± 3.98	97± 3.66	98 ± 3.98	84± 3.75	74 ± 4.30
11					95± 3.49	82 ± 4.16
12					99± 3.93	88 ± 4.43

Table no.12: In vitro drug release data of Empagliflozin ER (EERF1- EERF6)

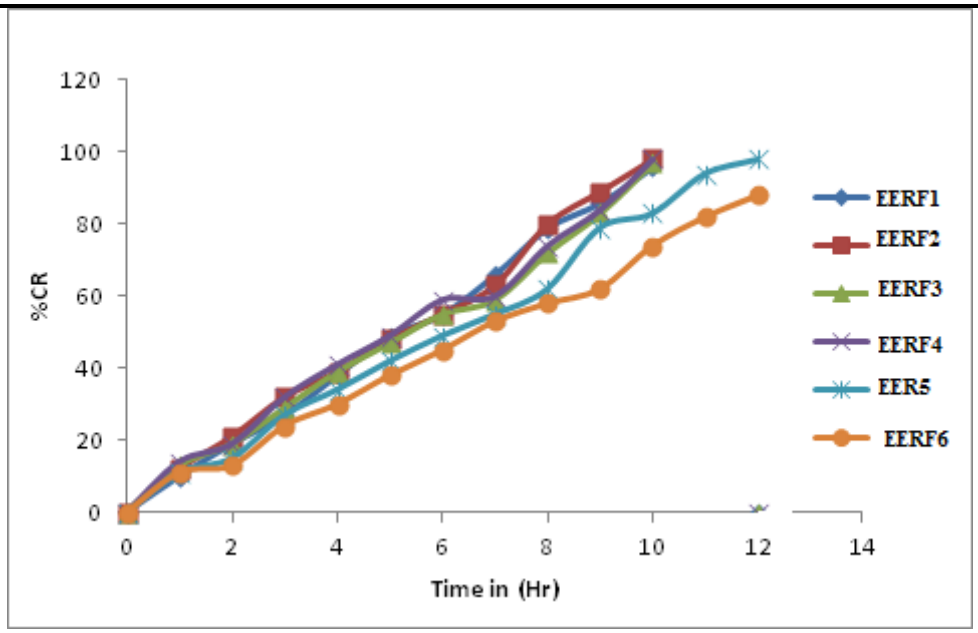


Figure No.8: In vitro drug release data of Empagliflozin ER (EERF1- EERF6)

EVALUATION OF BILAYER TABLETS:

Bilayer tablets were prepared successfully after selecting the optimized formulations of immediate release layer (**AIRF6**) and sustain release layer (**EERF5**) using 10 mm punches, The prepared bilayer tablets were evaluated for post compression parameters and results were found to be within the limits mentioned in the above section and were shown in Table7.15. In vitro drug release studies of bilayer tablets were carried out using USP dissolution apparatus type II in 900 mL of 0.1 N HCl for first 30 minutes and in 900 mL of 6.8 phosphate buffer solution up to 12 hours. From the results, drug release of Aliskiren IR layer was found to be 98 % in 30 minutes and that of the Empagliflozin ER layer was 99 % at the end of 12 hours drug release of bilayer tablet and values are represented in the Table and Figure.

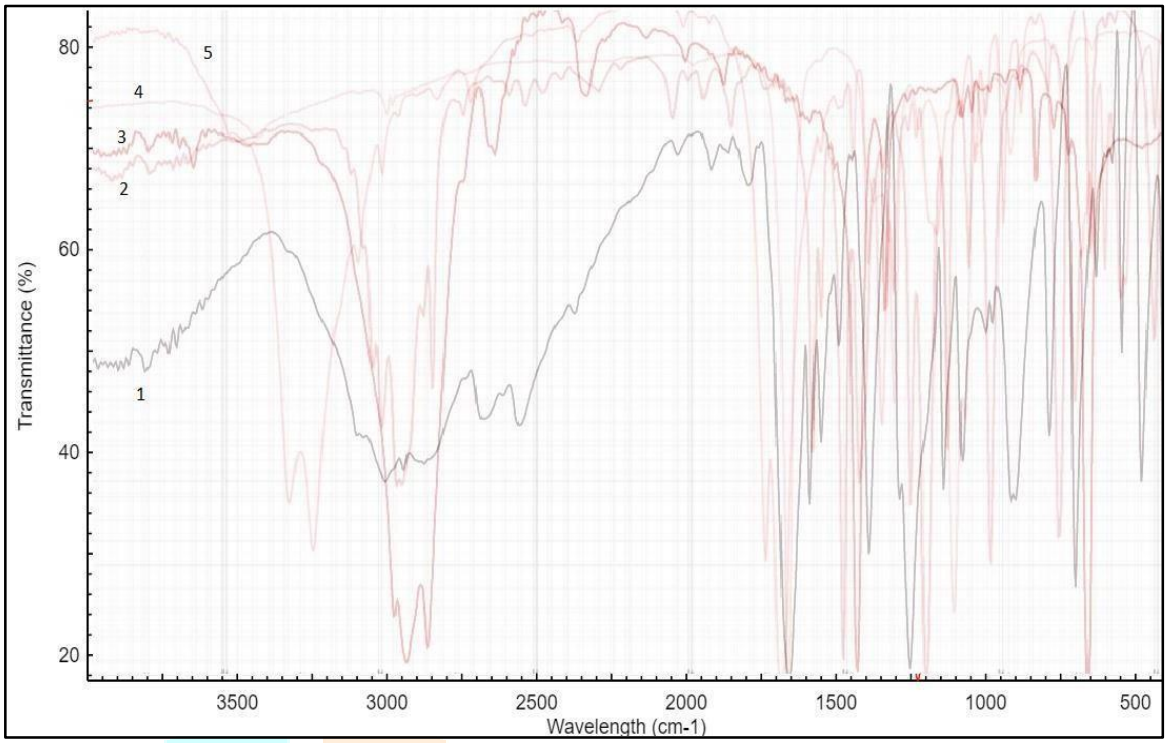


Figure no.9: Overlay Spectra of FTIR Spectrum

Post-compression parameters for bi-layered tablet

Table no.13: Post-compression parameters for bi-layered tablet

Formulation	Weight variation Mean ± SD	Hardness Mean ± SD	Friability Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD
Bilayer Tablet	500.75±0.46	7.05±0.15	0.38±0.01	6.31±0.15	98.23±0.53

STABILITY STUDIES

Table no. 14: Stability Study Data

Stability period	40^0C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release	
				IRL (30 min)	SRL (720min)
Initial	7.04±0.68	0.39±0.02	98.22±0.533	99±4.7	96±3.33
1 month	7.06±0.50	0.46±0.07	98.04±0.752	99±7.7	95±4.33
2 month	6.49±0.46	0.54±0.06	97.95±0.793	97.8 ±4.9	96±3.33
3 month	5.84±0.51	0.64±0.05	96.43±0.922	99±5.4	96±3.33

The bi-layered tablets were subjected to short term stability study, storing the formulation at 40^0C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and *in vitro* drug release rate were observed. As shown in table 7.

Conclusion

In the current study, a bi-layered tablet containing Empagliflozin and Aliskiren was created using the wet granulation method. The immediate release layer of the tablet was created using super disintegrants such sodium starch glycolate and croscarmellose, while the sustained release layer was created utilizing polymers like HPMC K4M and HPMC K100M. For the preparation of the bi-layered tablet, the best formulations for each layer were chosen. Bi-layered tablets were tested for drug content homogeneity, hardness, weight fluctuation, friability, in vitro drug release, and drug polymer interaction. Following are the findings of the aforementioned studies: The medication and all of the excipients are compatible, according to FTIR measurements. Using the wet granulation process, both the immediate and sustained release layers were created. Pre- and post-compression parameters were assessed for the produced tablets of both layers. For the bi-layered tablet, one formulation of each layer was chosen based on the in vitro dissolution profile data. AIRF6 from formulations for immediate release, as they demonstrated 98% drug release in less than 30 minutes. 99 percent of the medication was released in 12 hours when using EERF5, a sustained release formulation. The observations lead to the conclusion that the bi-layered tablets that were created with the use of super disintegrants, release retardant polymers, and various excipients were able to display every characteristic of a bi-layered tablet. The chosen immediate and sustained release layer was used to create the bilayer tablets.

References

1. Karandikar A, Kedar V, Surve C. Oral Strips: A Novel Drug Delivery Technology. International journal of Science and Technology 2020; 11(12): 6010-6019.
2. Bhattarai M, Gupta AK. Fast dissolving oral films: a novel trend to oral drug delivery system. Sunsari Technical College Journal 2015;2(1):58-68.
3. Ghadi R, Garse H, Dr. Dand N, Dr. Kadam V, Waghmare N. Design And Evaluation Of Novel Bi-Layered Tablet For The Effective Treatment of Hypertension. Indo American Journal of Pharmaceutical Research 2013;3(12):1530-1543.
4. Lee L. Diffusion-controlled matrix systems. In: Kydonieus A. ed. Treatise on Controlled Drug Delivery, Marcel Dekker, Inc., New York,1992; 155– 98.
5. Peppas NA. Hydrogels in Medicine and Pharmacy, vols. I, II and III, CRC Press, Boca Raton FL, 1988.
6. Jha AK, Bhattacharya A, Verma P. Formulation and in vitro evaluation of sustained release matrix tablets of metoprolol succinate using hydrophilic polymers. International Journal of PharmTech Research. 2009; 1(4): 972-77.
7. Prajapati SK, Richhaiya R, Singh VK, Singh AK, Kumar S, Chaudhary RK. Formulation and evaluation of once daily sustained release matrix tablet of Aceclofenac using natural gums. Journal of Drug Delivery and Therapeutics 2012; 2(1): 16-24.
8. Ganesh S, Radhakrishnan M, Ravi M, Prasannakumar B, Kalayani J. In vitro evaluation of the effect of

combination of hydrophilic and hydrophobic polymers on controlled release zidovudine matrix tablets. Indian J Pharm Sci. 2008; 70(4): 461-5.

9. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose on release profile and kinetics of diltiazem HCl from matrices. Tropical Journal of Pharmaceutical Research 2009; 8(5): 425-32.
10. Derakhshandeh K, Soleymani M. Formulation and in vitro evaluation of nifedipinecontrolled release tablet: Influence of combination of hydrophilic and hydrophobic matrix forms. Asian Journal of Pharmaceutics 2010; 4(4): 185-93.
11. Wadher KJ, Kakde RB, Umekar M. Formulation of sustained release metformin hydrochloride matrix tablets: Influence of hydrophilic polymers on the release rate and in vitro evaluation. International Journal of Research in Controlled Release 2011
12. Srihari R, Patan A, Reddy PS, Sasikanth K, Brahmaiah B and Nama S: An emerging trend on bilayer tablets, International Journal of Innovative Drug Discovery, 2013; 3(21):45-50.
13. Singh NP, Ganarajan G, Kothiyal P. Bilayer tablet: a review. World journal of pharmacy and pharmaceutical sciences.2015;4(11):703-717.
14. Akhtar M, Jamshaid M, Zaman M., Mirza AZ. Bilayer tablets: A developing novel drug delivery system. Journal of Drug Delivery Science and Technology 2020: 102079.
15. Gopinath C, Bindu VH, Nischala M. An overview on bilayered tablet technology. Journal of global trends in pharmaceutical sciences. 2013;4(2):1077-1085.
16. Roshani K, Panda P, Vishwakarma D K and Verma N K. A brief review on bilayer floating tablet International Journal of Advances in Pharmaceutics 2017;06(03):70- 78
17. Sowmya C, Reddy SG, Tabasum VV, Varma V. An overview on bi-layer tablets. International Journal of Pharmacy Technology. 2012;4(2):2143-2156.
18. Patel P, Patel CJ, Tyagi S, Kumar U, Patel J, Chaudhari B. Novel Approach Of Bilayered Tablets: An Overview. PharmaTutor 2012 available on https://www.pharmatutor.org/articles/novel-approach-bilayered-tablets-overview.
19. Mehraj Ud Din, Shahista Mohi Din, Shukla TP. An Overview on Bilayered Tablet Technology American-Eurasian Journal of Scientific Research 2014; (1): 06-15.
20. Deshpande RD, Gowda DV, Mahammed N, Maramwar DN. Bi-layer tablets-An emerging trend: a review. International journal of pharmaceutical sciences and research. 2011;2(10):2534-2544.
21. Nizami F and Malviya Y. Recent Advancement and Challenges in Bilayer Tablet Technology: An Overview Current Research in Pharmaceutical Sciences 2021; 11(04: 91-97.
22. Reddy T Pradeep, Rao V Divya, Kumar K Ravi. BI-Layer technology- an emerging trend: A review. International Journal of Research and Development in Pharmacy and Life Sciences. 2013; 2(3): 404-411.
23. Patel J B, Patil BR. A Comprehensive Review on Technological Aspects in Bilayer Tablet Manufacturing. World Journal of Pharmaceutical Research. 2022;11(3):1947-1963.
24. Patel M, Sockan G , Mani T. Challenges in the formulation of bilayered tablets: A Review. Int. J. of Pharm. Res. and dev. 2010;29(2):30-42.

25. Singh A, Das S, Gupta S, Ghosh S.The Challenges of Producing Bilayer Tablet: A Review. Journal of Drug Delivery & Therapeutics. 2021; 11(4-S):171-175
26. Ratnaparkhi MP, Vyas Ram Ganesh Bilayered Tablet Technology with Recent Advancement - A Review Research J. Pharm. and Tech. 2014;7(10): 1158-1164
27. Kaushik SK, Easwari TS, Sharan G, Sharma A. Novel Approach of Bilayer Tablet Technology: A ReviewInternational Journal for Pharmaceutical Research Scholars (IJPRS)2014;3(I-4):260-268.
28. Devtalu SV , Patil AE , Bari1MM , Dr. Barhat S D. A Review on Novel Approach Bilayer Tablet Technology. International Journal of Pharmaceutical Sciences Review and Research.2013;21(1):46-52.
29. Ghosh R , Haque MA , Paul T R , Bhuiyan A A , Dewan I, Bilayered Tablet Technology: An Overview World Journal of Pharmaceutical Research · 2014;3(4):150-163.
30. Malathi P, Khan AB. Recent Apporaches in bilayered technology. International Journal of Pharmaceutical Sciences and Research. 2012;3(12):4681-4688.
31. Ghugarkar P , Swain K , Suggala V , Adsare P , Shaik D. Review on Bilayer Tablet Technology. World Journal of Pharmaceutical Research 2015; 4(07):1438-1452.
32. George N, Pillai MK, Haribabu Y. Bilayer Floating Tablets: An Updated Review. Research Journal of Pharmacy and Technology. 2022; 15(3):1337-2.