Formulation And In Vitro Evaluation of Bilayer Tablet for The Treatment of Hypertension and Diabetes

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Abstract—**In the present work bi-layer tablet of Aliskiren and Empagliflozin were prepared by wet granulation method. Using super disintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and for sustained release layer polymer like HPMC K4M and HPMC K100M was used. Best formulation of each layer was selected for bi-layer tablet and bilayer tablet were prepared. Bi-layered tablets were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction.**

The above studies lid to following:
FTIR studies indicate that the drug is compatible with all the excipients.
Both immediate and sustained release layer were prepared by wet granulation method. The prepared tablet of both layers was evaluated for pure and post compression parameters.
The stability research revealed that after three months, the tablets had not changed much.
The produced bilayered tablets using super disintegrants, release retardant polymers, and various excipients were able to display all the characteristics of a Bi-layered tablet, according to the observations.

I. INTRODUCTION

The most popular method of administering medication is orally. Patients and doctors prefer tablets as the best oral dosing type. A bilayer tablet is useful for the sequential release of two medications in tandem, with one layer providing sustained release and Immediate release is an additional layer.1 Bilayer tablets offer several significant advantages over control tablets with a single layer. For instance, by combining layers with distinct release patterns or by mixing slow-release and immediate-release layers, these tablets which are frequently used to prevent bilayer tablets have made it possible to design controlled drug delivery with predetermined release profiles. Conventional dose forms typically result in significant variations in the drug's concentration in the bloodstream and tissues, which can lead to unwanted toxicity and ineffectiveness. The idea of regulated drug delivery systems was inspired by factors including inconsistent absorption and repeated doses. By localizing the medication at the site of action, lowering the necessary dose, or ensuring consistent drug delivery, sustained or controlled delivery systems aim to either decrease the frequency of dosing or increase the drug's effectiveness. Ensuring patient compliance and improving medication efficacy are the main goals of sustained release drug administration. By physically separating APIS, bi-layer tablets can prevent chemical incompatibilities and allow for the creation of distinct drug release patterns (immediate release with prolonged release). Bi-layer tablets can separate two incompatible substances and be used for the sequential release of two medications in combination. They can also be used for sustained release tablets, where the first layer is immediately released as the initial dose and the second layer is the maintenance dose. Both rapid and sustained release layers are present in bilayer tablets. The first dose is administered by the quick release layer.

It has super disintegrants that accelerate the rate of drug release and achieve a rapid onset of effect (loading dose), while the sustained release (maintenance dose) layer delivers the drug over an extended period of time. The most common chronic noncommunicable diseases and multifactorial disorders impacting both developed and emerging nations are type 2 diabetes mellitus and hypertension. countries. Diabetes mellitus and hypertension are mostly caused by hereditary and lifestyle factors. Over the past three decades, the prevalence of type 2 diabetes has increased from 1.2% to 11%. Patients

with type 2 diabetes are two to four times more likely to die from cardiovascular causes than those without the disease. Heart disease is the most frequent cause of death for diabetic patients. Additionally, amputations, blindness, end-stage renal disease, and peripheral vascular disease are common comorbidities in diabetes individuals. Therefore, combination therapy is crucial for preventing diabetes in hypertensive patients. One of the main dangers associated with heart disease is hypertension.

Figure 1: Bilayer Tablet

The primary cause of stroke is hypertension, which is also a significant risk factor for myocardial infarction, sudden cardiac death, coronary artery disease, and its consequences. The prevalence of hypertension increases with age; for instance, approximately 50% of individuals between the ages of 60 and 69 have hypertension, and the prevalence increases further above the age of 70. Nevertheless, it is well known that several potential cardiovascular drug molecules have bioavailability problems related to acid instability, enzymatic degradation, and low water solubility, which could lead to inconsistent and insufficient oral absorption.

Due to their significant first pass metabolism and short duration of action, they also have a short half-life. As a result, they must be administered repeatedly, which is uncomfortable for the elderly population. High blood glucose is the hallmark of diabetes mellitus, a chronic metabolic disease. Hyperglycemia in concentration. Diabetes mellitus comes in two varieties. Insulin is used to manage type-1 diabetes. Treatment for type2 diabetes starts with nutrition, but oral hypoglycemic medications are frequently required. Oral antidiabetic medications come in several different kinds. When using medication to treat any illness, the best dosing schedule is one that swiftly reaches and maintains the targeted therapeutic drug concentration in plasma. consistent during the entire course of treatment. One of the major dangers associated with heart disease is hypertension. Although it is a significant risk factor for cardiovascular death and morbidity, it is not a disease in and of itself. The primary cause of stroke, a significant risk factor for coronary artery disease, and its aftereffects, myocardial infarction, and unexpected cardiac death. The bilayer tablet will be ready to show the various ways that pharmaceuticals work in a single system. Aliskiren is an immediate release medication, while empagliflozin is a sustained release medication. distinct advantages of combination therapy over monotherapy include the reduction of dose-dependent adverse effects, the elimination of dose-related danger by a low-dose combination of two distinct drugs, The clinical and metabolic effects that result from the maximum dosage of each component of the combined tablet are minimized when two separate medications are used in low dosages. The inclusion of one agent may counteract some of the negative effects of the other. Therefore, the goal of the current effort is to develop and assess bilayer tablets of antihypertensive and antidiabetic medications for better disease management, to lessen side effects, and to increase patient compliance.

The necessity of a bilayer tablet

- To administer fixed dose combinations of various APIs, extend the life cycle of drug products, create novel drug delivery systems such chewing devices and floating tablets for gastro-retentive drug delivery, and extend the buccal/mucoadhesive delivery system
- To create a swellable or erodible barrier for release, the overall surface area available for the API layer can be altered by sandwiching with one or two inactive layers.
- To control the release of API from one layer by separating incompatible active pharmaceutical ingredients (APIs) from one another using the functional property of another layer (e.g., osmatic property).
- Managing the pace at which one or two distinct active medicinal substances are delivered.

1.1 Advantages

- Stable and economical (chemical & microbiological)
- Taste and odor can be covered with a coating.
- Precise and consistent dosage.
- Generally easy to swallow.
- Prevents medication interactions.
- Enables both quick and continuous release of drugs.

1.3 Disadvantages

- A reduced yield of production.
- Inadequate control over the weight of each layer.
- Children and unconscious individuals may find it difficult to swallow.
- Certain medications are challenging to compress.
- Drugs with poor solubility or dissolution may have reduced bioavailability.

1.4 Ideal Qualities

- Defect-free (contamination, chips, and fractures).
- Robust enough to manage transportation and handling.
- Stable throughout the shelf life, both chemically and physically.
- Offers consistent and repeatable medication release.

1.5 Applications

- Give two medications that have distinct release characteristics.
- Give doses for loading and maintenance.
- Applied to formulations with modified release.
- Floating tablets: one-layer floats while the other instantly releases the medication.

Types of Bilayer Tablets

- Homogeneous: Same drug, different release patterns (immediate + extended).
- Heterogeneous: Different drugs or incompatible substances.

Tablet Press Types

1. Single-sided press
   - Simple, low cost.
   - Limitations: poor weight control, weak layer separation, quality issues.
2. Double-sided press
   - Better control and precision.
   - Uses compression force monitoring.
   - Limitation: requires higher compression force.

II. DIFFERENT METHODS FOR BI-LAYER TABLETS

a) OROS pulls technology This system is mostly composed of two or three levels, of which one or more are drug-essential layers and the remaining layers are push layers. The medication and two or more distinct agents make up the majority of the drug layer. Thus, the drugs in this drug layer are weakly soluble. Osmotic and suspending agents are also added. The tablet is encased in a semi-permeable membrane.

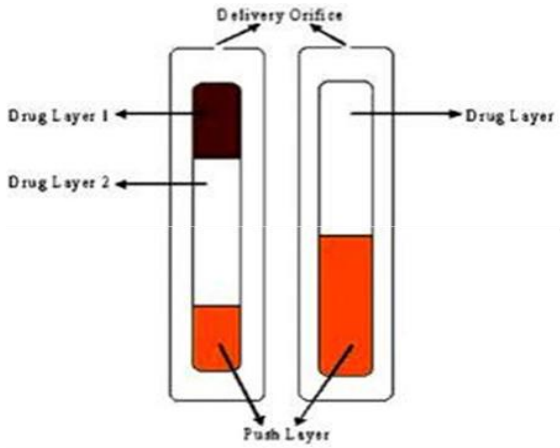


Figure 2: OROS push pull technology

b) EN SO TROL Technology E-Shire Laboratory uses an integrated strategy to drug delivery that focuses on identifying and incorporating the identified enhancer into controlled release technologies in order to improve solubility by an order of magnitude or to generate an optimal dose form.

Figure 3: EN SO TROL Technology

c) DUREDASTM Technology the Dual Release Drug Delivery technology from Elan Drug Technologies is another name for this technology. DUREDAS TM Technology is a bilayer tablet that can deliver two medications at varying rates of release in a single dosage form, or it can give rapid or sustained release of two pharmaceuticals. Within a single tablet, the tableting technique can produce both a modified release hydrophilic matrix complex and an instant granulate. A mixture of hydrophilic polymers gives the dosage form its modified-release characteristics.

d) DUROS Technology An exterior cylindrical titanium alloy reservoir makes up the system. This reservoir shields the drug molecules from enzymes and has a high impact strength. The DUROS technology is a tiny medicine dispensing device that functions similarly to a tiny needle and continuously releases a little amount of concentrated form over the course of several months or a year.

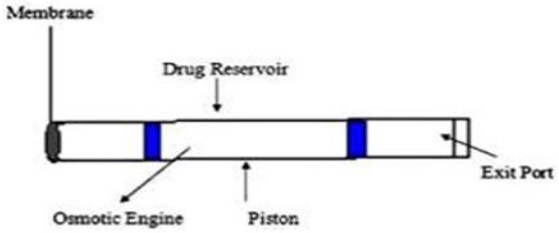


Figure 4: DUROS Technology

Basic Formulation Steps

1. Fill first layer
2. Compress first layer
3. Remove upper punch
4. Fill second layer
5. Final compression

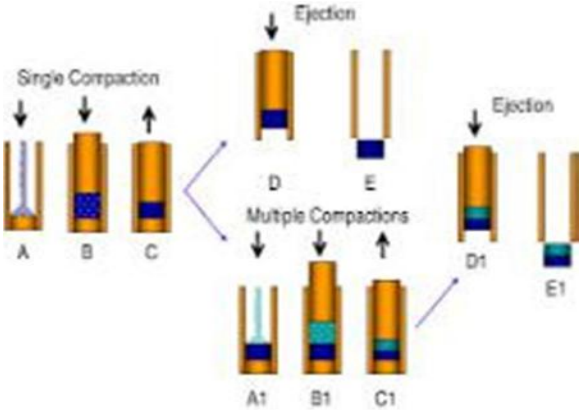
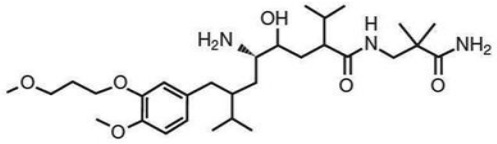


Figure 5: Compression steps of bilayer tablet

III MATERIALS AND METHODS

Drug and excipient profile



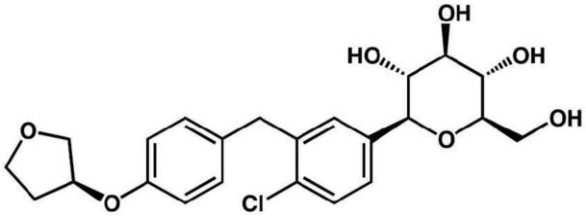
Structure 1: Aliskiren

Table 1: Pharmacokinetic data of Aliskiren

Bioavailability	Absolute bioavailability 47-51%
Vd	135 L
Half- life	2.3 hours
PKa	9.49

Table 2: Physicochemical parameter of Aliskiren

Sr. no.	Physicochemical parameter	Observation
1	Description	Slight whitish crystalline powder
2	Molecular formula	$C_{30}H_{53}N_3O_6$
3	Molecular weight	551.8
4	Chemical name (IUPAC)	5-amino-N-(2-carbamoyl-2-mathylpropyl)-4-hydroxi-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-8-methylnonanamide
5	Melting point	95–100 °C
6	Solubility	Freely soluble in water
7	Category	Antihypertensive agent
8	Mode of action	Renin inhibitor



Structure 2: Empagliflozin

Table 3: Pharmacokinetic data of Empagliflozin

Bioavailability	Absolute bioavailability 81%
Vd	73.8L
Half-Life	12.4 hours
PKa	12.57
Elimination	Eliminated 54% in urine Eliminated 41% in FECES

Experimental Work

III. PRE-FORMULATION & EVALUATION

1. Pre-formulation Studies
First step in dosage form development.
Focus: physicochemical properties of drug & excipients.
Aim: Ensure stable, safe, and effective formulation.
Melting point:
Melting point of the Aliskiren and Empagliflozin were determined by capillary method in triplicate
Solubility:
Tested in water, methanol, alcohol, isopropyl alcohol.

Table 10: Solubility Study
λmax determination:
Drugs scanned (200–400 nm) using UV spectrophotometer.
Empagliflozin: ~224 nm
Aliskiren: ~279 nm

IV. CALIBRATION CURVES

4.1 Calibration Curve for Empagliflozin:
The initial stock solution was made by precisely weighing 100 mg of empagliflozin and dissolving it in 100 ml of phosphate buffer 6.8. To create the II stock solution, 10 ml of the aforementioned solution was diluted to 100 ml using the same solvent. To obtain 5, 10, 15, 20, 25, and 30 µg/ml of the final solution, the aliquot amount of II stock solution was further diluted. The calibration curve was shown as concentration against absorbance across the range of 5–30 µg/mL with correlation after the absorbance was measured in the appropriate solvents against 224 nm.

4.2 Calibration Curve for Aliskiren:
The initial stock solution was made by precisely weighing 100 mg of Aliskiren and dissolving it in 100 ml of 0.1 N HCl. To create the II stock solution, 10 ml of the aforementioned solution was diluted to 100 ml using the same solvent. To obtain 5, 10, 15, 20, 25, and 30 µg/ml of the final solution, the aliquot amount of II stock solution was further diluted. The calibration curve was plotted as concentration against absorbance over the range of 5-30 µg/mL with correlation after the absorbance was measured in the appropriate solvents against 279nm.

4.3 Physical Characterization:
Loss on Drying (LOD)

- Measures moisture content.
- Formula:
  % LOD = (W2 − W3) / (W2 − W1) × 100

% LOD = (W2-W3)/ (W2-W1) X 100
Where, W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample

4.4 Drug–Excipient Compatibility:
Ensures no interaction affecting stability.
Methods:
Storage study:
40°C / 75% RH (accelerated)
4°C (control)
FT-IR Spectroscopy:
Detects interaction via peak shifts (4000–400 cm^{-1}).
Pre-compression Parameters (Flow Properties):
Angle of Repose:
The funnel method was used to calculate the granules' angle of repose. The funnel was placed on a burette stand at a specific height of 2.5 cm. After passing the powder sample through the funnel, a pile was formed. Granules were prevented from being added as soon as the pile reached the funnel's tip. Without upsetting the pile, a circle was drawn across it. The pile's radius was recorded. The average value was obtained when the identical process was carried out three times. The following formula was used to get the angle of repose:

$$\text{Tan } \theta = h/r \text{ (or) } \theta = \tan -1 (h/r)$$

Where, h and r are the height and radius of the powder cone.

Table 11: Angle of repose as an indication of granule flow properties

Angle of repose (º)	Type of flow
<25	Excellent
25-30	Good
30-40	Poor
>40	Very poor

4.5 Bulk Density
Weigh the dry granules precisely into a graduated 100 ml measuring cylinder, record the volume, and use the formula to get the bulk density. Bulk density is calculated by dividing the raw powder's weight by its volume.

Tapped Density A graduated 100 ml measuring cylinder filled with a known mass of dry granules was used to determine it. To achieve a constant volume of powder bed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 10 cm every second for 100 taps.
Tapped Density = Weight of the tapped powder / Volume of the tapped powder

4.6 Carr's Index:
The flow property of the granules was determined by % Carr's Index.
it was calculated by the following formula.
Carr's Index = Tapped Density-Bulk Density / Tapped Density ×100

Table 12: Carr's index as an indication of granule flow prope

Carr's Index (%)	Type of flow
5 –15	Excellent
12 – 16	Good
18 – 21	Fair to Possible
23 -35	Poor
33-38	Very Poor

4.7 Hausner's Ratio: Flow property
Hausner's Ration is an indication of flowability of the granules. It was calculated by following formula.
Hausner's Ratio = Tapped Density /Bulk Density

Table 13: Hausner's ratio as an indication of granule flow properties

Flow character	Hausner's ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Possible	1.26-1.34
Poor	1.35- 1.45
Very Poor	1.46 - 1.59
Very very Poor	>1.60

4.8 Formulation of Bilayer Tablets
Immediate Release Layer (Aliskiren)
Using the formulas listed in Table 14, Aliskiren and sodium starch glycolate were blended uniformly using PVP K30 as a binder to create the immediate release granules utilizing the wet granulation process. After passing the cohesive material through a sieve #20, it was dried at 60°C for an hour, yielding a moisture level of 12%, as measured by an IR moisture balance.

Table 14: Formulation of immediate release layer

Sr. No.	Ingredients	AF1 (mg)	AF2 (mg)	AF3 (mg)	AF4 (mg)	AF5 (mg)	AF6 (mg)
1	Aliskiren	50	50	50	50	50	50
2	Lactose	82	79.5	82	79.5	77	77
3	Croscarmellose sodium	10	12.5	–	–	5	10
4	Sodium starch glycolate	–	–	10	12.5	10	5
5	Microcrystalline cellulose	35	35	35	35	35	35
6	PVP K-30	5	5	5	5	5	5
7	Magnesium stearate	10	10	10	10	10	10
8	Talc	8	8	8	8	8	8
Total (mg)		200	200	200	200	200	200

Formulation of the sustained release layer:

Table 15: Formulation of sustained release layer

Sr. No.	Ingredients	EF1 (mg)	EF2 (mg)	EF3 (mg)	EF4 (mg)	EF5 (mg)	EF6 (mg)
1	Empagliflozin	120	120	120	120	120	120
2	Lactose	52	44.50	37	52	44.50	37
3	HPMC K4M	45	52.5	60	–	–	–
4	HPMC K100M	–	–	–	45	52.5	60
5	Microcrystalline cellulose	60	60	60	60	60	60
6	PVP K-30	6	6	6	6	6	6
7	Magnesium stearate	8	8	8	8	8	8
8	Talc	9	9	9	9	9	9
Total (mg)		300	300	300	300	300	300

Post compression Evaluation of Aliskiren and Empagliflozin

The tablets prepared were evaluated for the following parameters:
Thickness, Weight variation, Hardness, Friability, Disintegration Time, Drug content, In-vitro Dissolution Studies, Stability Studies

4.9 Tablet thickness:
Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Caliper's. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main metric scale is read first then read "hundredths of mm" of imperial scale (count the number of divisions until the lines concedes with the main metric scale. The imperial scale number is multiplied with 0.02.

V. WEIGHT VARIATION TEST

Table no 16: IP standards of Uniformity of weight

Sr. No.	Avg. Wt of Tablet (mg)	% of Deviation
1	Less than 80 mg	10%
2	More than 80 mg but less than 250 mg	7.5%
3	More than 250 mg	5%

5.1 Hardness:
The hardness of each batch of tablet was checked by using Monsanto hardness tester. The average hardness of 5 determinations was recorded.

5.2 Friability:
10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Percentage friability was calculated by

$$\% \text{ Friability} = \frac{\text{Initial wt - Final wt.}}{\text{Initial weight}} \times 100$$

5.3 Disintegrating Time:
The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve.

5.4 Drug Content:
The tablets were crushed in a mortar and accurately weighed amount of average tablet weight was taken from the crushed blend and transferred in to a 100 mL volumetric flask.

5.5 Dissolution Studies:
a) Empagliflozin (Sustained Release)
- Medium: pH 6.8 buffer
- Time: up to 20 hours
- Speed: 45 rpm
- Temp: 37°C

b) Aliskiren (Immediate Release)
- Medium: 0.1 N HCl
- Time: 45 min
- Speed: 100 rpm

c) Bilayer Tablet Evaluation
Dissolution in:
- N HCl (initial 45 min)
- pH 6.8 buffer (up to 24 hrs)

d) Drug Release Kinetics Models
Used to understand release mechanism:
- Zero-order: Constant release
- First-order: Concentration-dependent
- Higuchi model: √time dependent (matrix diffusion)
- Korsmeyer–Peppas: Mechanism identification (n value)

Table17: Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model

Sr. No.	'n' value	Drug Release
1	0.45	Fickian release
2	0.45 < n> 0.89	Non-Fickian release
3	0.89	Case II transport
4	Higher than 0.89	Super case II transport

e) Stability Studies:
Conditions: 40°C / 75% RH (2–3 months)
Packaging: Aluminum foil, closed containers
Checked periodically for stability

VI. RESULTS AND DISCUSSION

A. Pre-formulation Studies

1 Determination of λmax
- max for Empagliflozin was Found at 224 nm.
- max of Aliskiren was found to be 279 nm.

2 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.

B. Determination of Melting Point:

Table 18: Melting Point for Empagliflozin

Test	Specification / Limit	Observations
Melting Point	151-153	152

Table 19: Melting Point for Aliskiren

Test	Specification / Limit	Observations
Melting Point	98-99	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. 20: Results for Aliskiren Linearity by UV Spectroscopy

Sr. No.	Concentration (ug/ml)	Absorbance
1	0	0
2	05	0.124
3	10	0.226
4	15	0.334
5	20	0.458
6	25	0.569
Correlation Coefficient		0.998

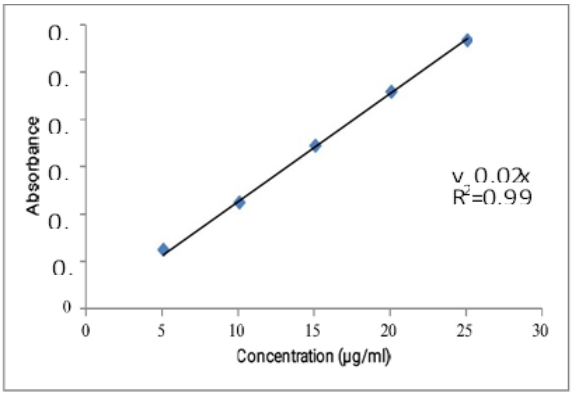


Figure No. 6: Calibration curve of Aliskiren by UV

D. 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 5µg/ml to 25µg/ml.

Table No. 21: 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

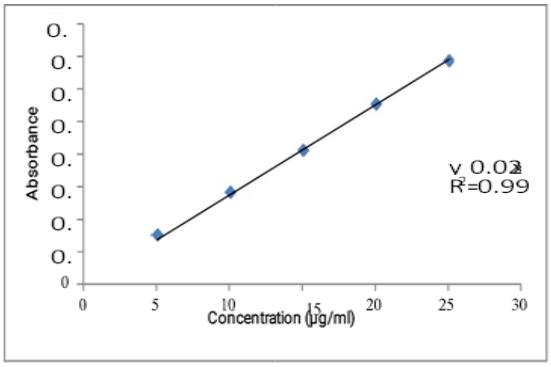


Figure No. 7: Calibration Curve for Empagliflozin by UV Spectroscopy

VII. PHYSICAL CHARACTERISTICS

Loss on Drying

Table no. 22: Loss on Drying for Empagliflozin

Test	Specification/Limits	Observation
Loss on drying	Not more than 0.2%	0.1%

Table no. 23: Loss on Drying for Aliskiren

Test	Specification/Limits	Observation
Loss on drying	Not more than 0.2%	0.2%

Excipient Compatibility Studies Compatibility studies of Empagliflozin It were determined as per procedure given in material and method part. The following table illustrates the result.

Table no. 24: Excipient Compatibility for Aliskiren

Sr. No	Drug+ Excipients	Ratio	Condition	Conclusion
1	Aliskiren + Lactose	1:1	A white or almost white crystalline powder	Compatible
2	Aliskiren + HPMC K4M	1:1		Compatible
3	Aliskiren + HPMC K100M	1:1		Compatible
4	Aliskiren + Microcrystalline cellulose	1:1		Compatible
5	Aliskiren + PVP K-30	1:1		Compatible
6	Aliskiren + Magnesium stearate	1:1		Compatible
7	Aliskiren + Talc	1:1		Compatible

Table no.25: Excipient Compatibility for Empagliflozin

Sr. No	Drug+ Excipients	Ratio	Condition	Conclusion
1	Empagliflozin + Lactose	1:1	A white or almost white crystalline powder	Compatible
2	Empagliflozin + Croscarmellose sodium	1:1		Compatible
3	Empagliflozin + Sodium starch glycolate	1:1		Compatible
4	Empagliflozin + Microcrystalline cellulose	1:1		Compatible
5	Empagliflozin + PVP K-30	1:1		Compatible
6	Empagliflozin + Magnesium stearate	1:1		Compatible
7	Empagliflozin+ Talc	1:1		Compatible

The compatibility studies of the drugs with polymers are studies using FT-IR spectroscopy.

VIII. 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

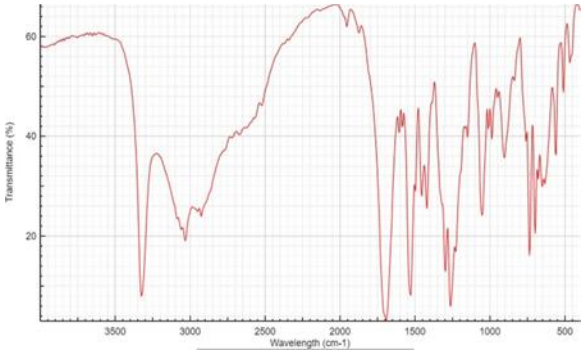


Figure no. 8: IR Spectra of Aliskiren

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

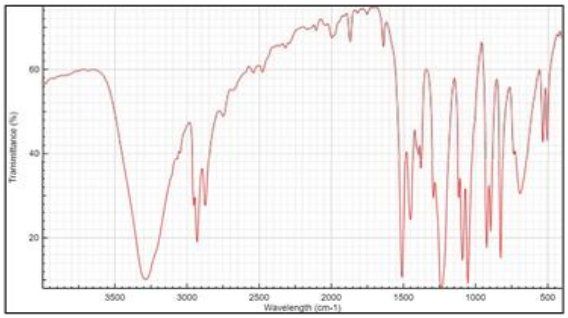


Figure no. 9: IR Specters of Empagliflozin

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

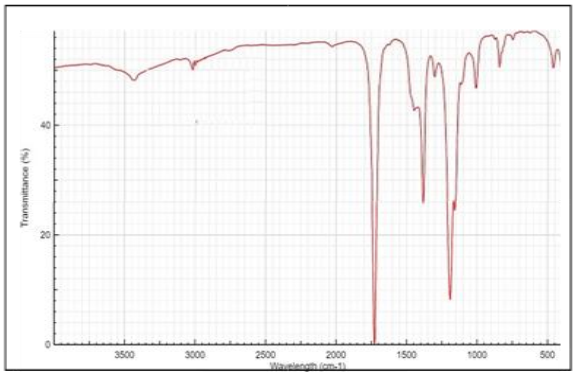


Figure no.10: IR Spectra of Calcium Carbonate (Talc)

Sr.no	Functional group	Wave no.(cm^{-1})
1	-C=O stretching	1709
2	-C-O stretching	1229
3	=C-O Fingerprint	729

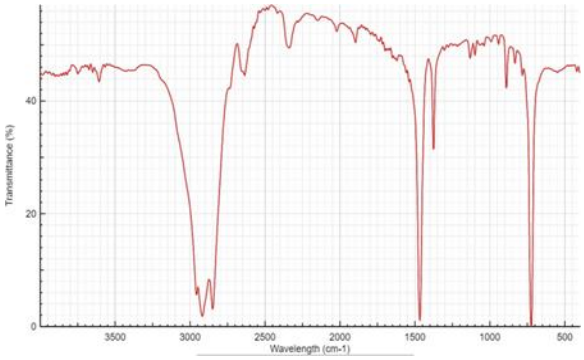


Figure no.11: IR Spectra of Magnesium Stearate

Sr. no	Functional group	Wave no.(cm^{-1})
1	Carboxylate stretching	2917 2850
2	COO- Asymmetric twin bands	1497 1477

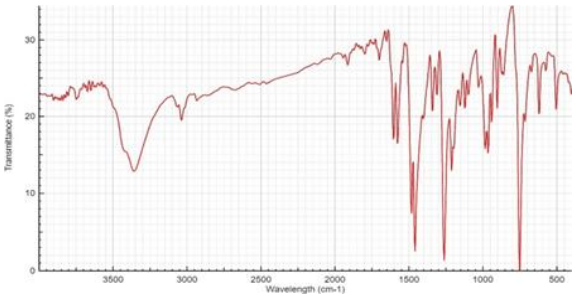


Figure no. 12: IR Spectra of Micro Crystalline Cellulose

Sr. no	Functional group	Wave no.(cm^{-1})
1	-OH stretching	3423
2	-CH stretching	2917
3	$-CH_2$ stretching	1479
4	-C-H stretching	1388
5	-C-O stretching	1210

Sr. no	Functional group	Wave no.(cm^{-1})
1	-OH stretching	3126
2	-CH stretching	2987
3	-CH2 stretching	1503
4	-C-H stretching	1387
5	-C-O stretching	1211

Table no.26: 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

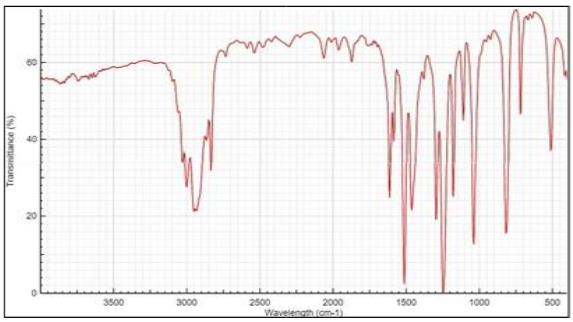


Figure no. 13: IR Spectra of Croscarmellose Glycolate

IX. EVALUATION OF PRE-COMPRESSION PARAMETERS

A. Flow properties:

Flow properties of Aliskiren and Empagliflozin were carried out and results are shown in the Tables 25 and 26 which were found to be as per limits.

For Aliskiren Immediate Release Layer

For Empagliflozin Extended-Release Layer

Table no. 27: 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
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

X. POST-COMPRESSION EVALUATION PARAMETERS

Post Compression Evaluation of Aliskiren IR

Table no. 28: 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±1.5 8	5.96±0.06	2.86±0.03	0.75±0.0 8	98.11±1.1 8	3.40
AIRF2	201.2±1.6 1	4.19±0.11	2.90±0.09	0.59±0.0 3	97.64±1.8 1	3.44
AIRF3	199.8±1.6 1	6.36±0.04	2.89±0.06	0.57±0.0 5	98.64±1.2 7	3.09
AIRF4	199.7±2.00	6.18±0.08	2.86±0.02	0.66±0.0 4	99.60±0.9 3	3.25
AIRF5	201.1±2.53	4.15±0.05	2.91±0.05	0.64±0.0 2	99.42±1.3 1	3.65
AIRF6	200±1.82	4.54±0.12	2.88±0.08	0.70±0.0 3	99.50±1.8 0	2.54

Table no. 29: 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

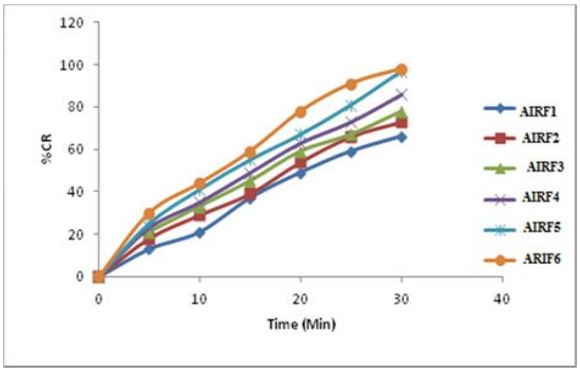


Figure No.14: In vitro drug release data of Aliskiren IR (AIRF1- AIRF6)

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 29. 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 30 .and figure 9.10. For bilayer tablet as it reflects good disintegration and dissolution.

Table no.30: Post Compression Evaluation of Empagliflozin ER

Batch code	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug 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

Table no.31: In vitro drug release data of Empagliflozin ER (EERF1-EERF6)

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

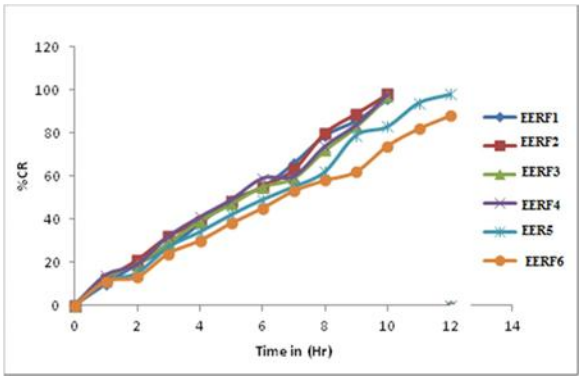


Figure No.15: In vitro drug release data of Empagliflozin ER (EERF1-EERF6)

XI. 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 Table 30. 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.

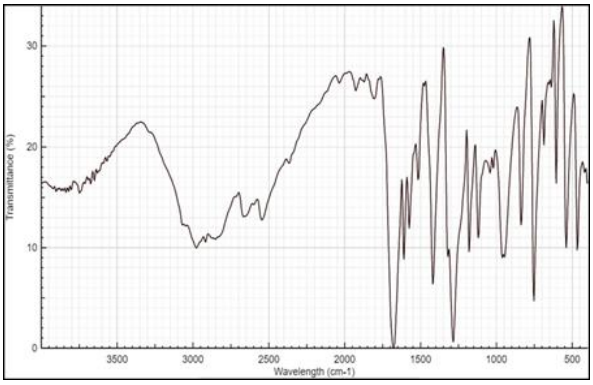


Figure no.16: IR Spectra of Bilayer Tablet

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretch	3040
3	=C-H Aromatic stretch	3041
4	=C-H Stretching	2962 2934 2876
5	-C=O stretching Conjugated vinyl bond	1706
6	-C-S linkage stretching	772

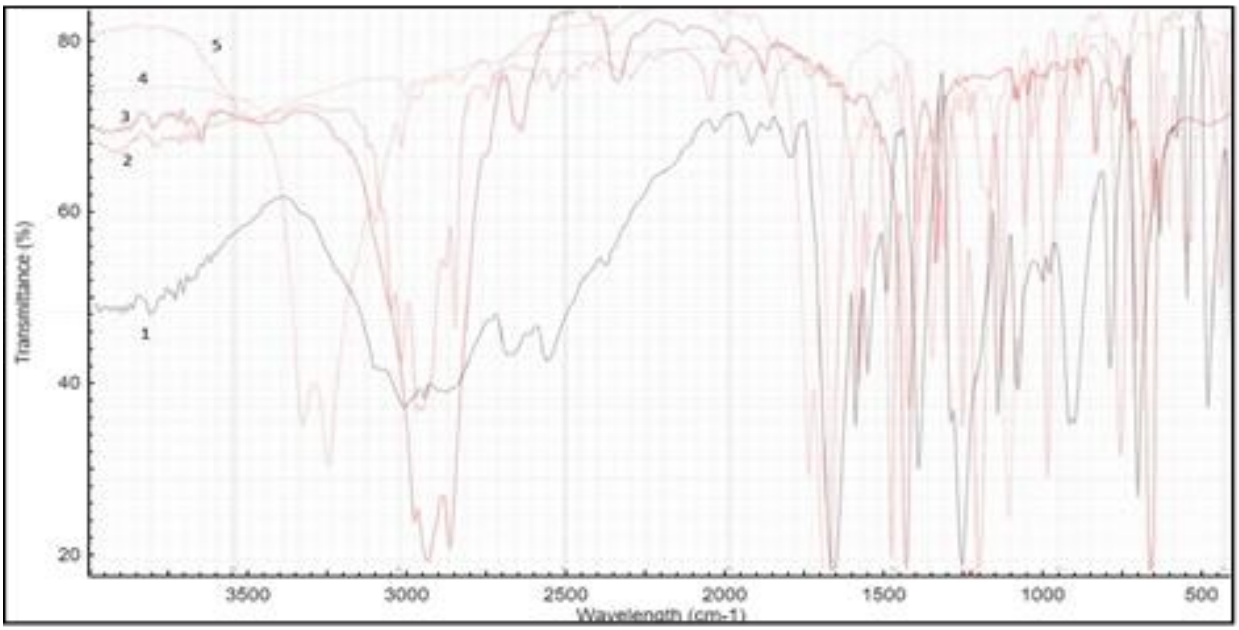


Figure no.17: Overlay Spectra of FTIR Spectrum

Post-compression parameters for bi-layered tablet

Table no.32: 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

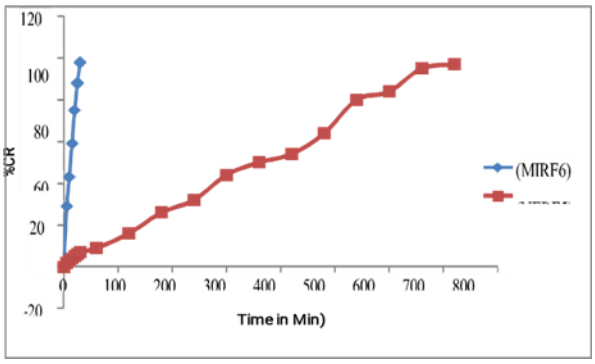


Figure No. 18: In vitro drug release data of from bilayer tablets

Table no.33: In vitro drug release data of from bilayer tablet

Time (min)	Aliskiren (AIRF6) (% drug release)	Empagliflozin (EERF5) (% drug release)
0	0	0
5	27 ± 3.57	2 ± 1.02
10	41 ± 3.33	3 ± 1.24
15	57 ± 3.6	4 ± 1.35
20	73 ± 5.11	5 ± 1.33
25	86 ± 2.77	6 ± 1.49
30	96 ± 3.73	7 ± 1.37

Time (hrs)	Aliskiren (AIRF6) (% drug release)	Empagliflozin (EERF5) (% drug release)
1	–	9 ± 3.88
2	–	16 ± 4.67
3	–	26 ± 3.61
4	–	32 ± 4.49
5	–	44 ± 4.62
6	–	50 ± 3.55
7	–	54 ± 3.46
8	–	64 ± 2.26
9	–	80 ± 4.53
10	–	84 ± 3.63
11	–	95 ± 3.57
12	–	97 ± 3.31

Table no.34: stability study data

Stability Period	40^0C / 75% RH				
	Hardness (Mean ± SD)	% Friability (Mean ± SD)	% Drug Content (Mean ± SD)	IRL (30 min)	SRL (720 min)
Initial	7.04 ± 0.68	0.39 ± 0.2	98.22 ± 0.533	99 ± 4.7	96 ± 3.33
1 month	7.06 ± 0.50	0.46 ± 0.7	98.04 ± 0.752	99 ± 7.7	95 ± 4.33
2 months	6.49 ± 0.46	0.54 ± 0.6	97.95 ± 0.793	97.8 ± 4.9	96 ± 3.33
3 months	5.84 ± 0.51	0.64 ± 0.5	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 400C / 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 34.

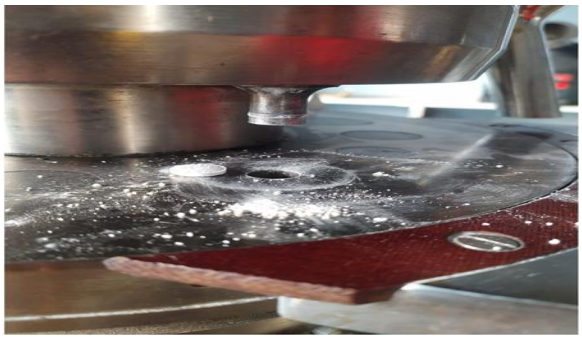


Figure: Immediate Release

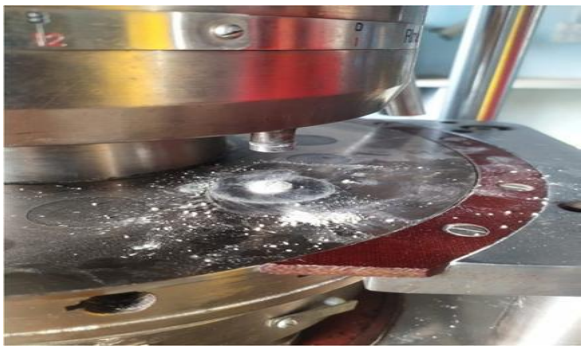


Figure: Bilayer Tablet

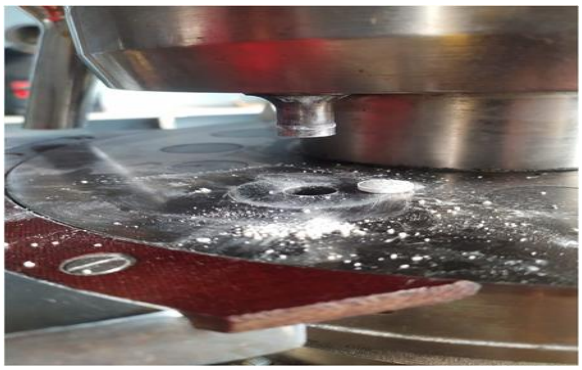


Figure: Sustained Release

XII. CONCLUSION

utilizing super disintegrants such sodium starch glycolate and croscarmellose for the immediate release layer and polymers like HPMC K4M and HPMC K100M for the sustained release layer, bi-layered tablets containing Aliskiren and empagliflozin were created in this study utilizing the wet granulation method. For the purpose of creating a bilayered tablet, the best formulations of each layer were chosen. Hardness, weight fluctuation, friability, drug content homogeneity, in vitro drug release, and drug polymer interaction were all tested on bi-layered tablets.

The aforementioned research leads to the following findings:

- FTIR analyses showed that the medication is compatible with every excipient.
- The wet granulation process was used to prepare the immediate and sustained release layers. Both layers' produced tablets were assessed for pre- and post-compression characteristics.
- For the bi-layered tablet, one formulation of each layer was chosen based on the in vitro dissolution profile data. AIRF6 from formulations for quick release, as they displayed 98. percentage of medication release in 30 minutes. 99% drug release in 12 hours was demonstrated by EERF5 from the sustained release formulation.
- The chosen immediate and sustained release layer was used to create the bilayer tablets.
- It was discovered that the produced tablets have a hardnessof7.05kg/cm.
- The prepared tablet's friability was determined to be1%.
- All of the developed bi-layered tablet formulations had the same proportion medication content.
- The bi-layered tablets' in vitro drug release pattern was identical to that of single-layer tablets.

The stability research revealed that after three months, the tablets had not changed much.

The produced bilayered tablets using super disintegrants, release retardant polymers, and various excipients were able to display all the characteristics of a Bi-layered tablet, according to the observations.

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