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APIGENIN AND BOSWELLIC ACID BILAYER TABLETS: FORMULATION AND THERAPEUTIC EVALUATION

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Abstract:

This study focuses on developing and evaluating a bilayer tablet designed to treat asthma and arthritis by combining Apigenin and Boswellic acid. Apigenin delivers immediate bronchodilatory and anti-inflammatory effects, addressing asthma symptoms, while Boswellic acid provides prolonged anti-inflammatory benefits for arthritis. Pre-formulation studies evaluated the solubility and compatibility of the active ingredients with excipients, with FT-IR analysis confirming no adverse interactions. The immediate-release (IR) layer of Apigenin was formulated using super disintegrants such as Crospovidone and Sodium starch glycolate, achieving rapid disintegration in 28.56 seconds and 99.37% release within 45 minutes. The sustained-release (SR) layer of Boswellic acid incorporated HPMC K100 and HPMC E15, ensuring a controlled release of 98.72% over 9 hours. Drug release studies revealed diffusion-based kinetics for Apigenin (Higuchi model) and consistent release for Boswellic acid (zero-order kinetics). The optimized bilayer tablet demonstrated excellent physical properties, including a hardness of 6.3 Kg/cm², friability of 0.6%, and a drug content of 98.1%. Stability tests over three months indicated no significant changes in performance, confirming the tablet's potential as an effective dual-action therapy for asthma and arthritis.

Keywords: *Apigenin, Boswellic acid, bilayer tablet, drug release kinetics.*

1. Introduction

Arthritis and asthma are chronic illnesses that greatly impact the quality of life for millions worldwide. Arthritis, marked by joint inflammation, stiffness, and pain, has several forms, with osteoarthritis and rheumatoid arthritis being the most prevalent. Osteoarthritis arises from cartilage deterioration in the joints due to wear and tear. In contrast, rheumatoid arthritis is an autoimmune condition where the immune system mistakenly attacks joint tissues. Both types result in restricted mobility and reduced quality of life due to ongoing pain, swelling, and joint deformities.[1, 2].

Asthma is a long-term respiratory condition characterized by repeated episodes of wheezing, coughing, chest tightness, and difficulty breathing. These symptoms result from airway inflammation and narrowing, often triggered by allergens, infections, or physical activity. Due to its persistent nature, asthma necessitates continuous management to avoid flare-ups that can compromise breathing and lung health.[2, 3]

Herbal remedies are increasingly explored for managing chronic conditions due to their therapeutic potential and minimal side effects. Apigenin, a flavonoid found in chamomile (Matricaria chamomilla), has shown promising anti-asthmatic properties. It helps alleviate asthma symptoms by acting as a bronchodilator, reducing airway hyperresponsiveness, and inhibiting inflammatory mediators involved in respiratory inflammation. These effects make apigenin a valuable candidate for asthma management.

Similarly, boswellic acid, extracted from the resin of Boswellia serrata, is widely recognized for its effectiveness against arthritis. This bioactive compound reduces pain and inflammation by suppressing pro-inflammatory cytokines and enzymes, improving joint mobility and overall functionality. Its anti-inflammatory properties benefit patients suffering from osteoarthritis and rheumatoid arthritis, enhancing their quality of life.

Both apigenin and boswellic acid highlight the potential of plant-based compounds as alternative therapies for chronic diseases, offering relief while minimizing the risk of adverse effects.[5,6]

A major flavonoid in chamomile (*Chamaemelum nobile, Matricaria chamomilla*), apigenin has anti-inflammatory, antioxidant, and anxiolytic properties that help with asthma, anxiety, and sleep disturbances by easing tension and tightness in the airways. Derived from the resin of Boswellia serrata, boswellic acid is a strong anti-inflammatory that inhibits 5-lipoxygenase. It is used to treat inflammatory bowel disease, asthma, chronic pain, and arthritis while improving joint health and lowering oxidative stress.[7, 8]

Role of Bilayer Tablets in the Treatment of Arthritis and Asthma

A novel approach to formulating Apigenin and Boswellic acid is the use of bilayer tablets, which optimize their therapeutic effects. These tablets combine different drug release profiles in a single dosage form, allowing for both immediate and sustained release. This method is especially effective for chronic conditions like arthritis and asthma, as it provides quick relief from symptoms followed by long-lasting management of the condition. By delivering fast-acting and extended therapeutic effects, bilayer tablets enhance treatment effectiveness and promote better patient compliance.

Immediate Release Layer: The first layer of the bilayer tablet is designed as an immediate-release layer containing Apigenin. This layer quickly delivers Apigenin's bioactive compounds, offering rapid relief from acute asthma symptoms by relaxing the airways, reducing inflammation, and mitigating oxidative stress. Apigenin's bronchodilaton and anti-inflammatory effects make it well-suited for addressing asthma exacerbations. Furthermore, the immediate-release layer can aid in the early management of inflammatory pain in arthritis, providing relief from swelling and discomfort during flare-ups.[9,10]

Layer of Sustained release : The next layer of the bilayer tablet is formulated as a sustained-release layer containing Boswellic acid. This layer ensures a slow, continuous release of Boswellic acid over an extended period, offering sustained anti-inflammatory effects for both arthritis and asthma. In the treatment of arthritis, the gradual release helps reduce chronic joint inflammation, cartilage breakdown, and persistent pain throughout the day. For asthma, the sustained release of Boswellic acid helps maintain therapeutic levels in the body, promoting long-term reduction of airway inflammation and preventing recurrent asthma attacks.[1]

2. Materials and Methods

Apigenin and Boswellic acid were purchased from Sigma Aldrich Ltd. The excipients used included, Magnesium Stearate, Sodium starch glycolate, Microcrystalline cellulose, Talc, HPMC K100, HPMC E15, Crospovidone, and PVP K30.

2.1. METHOD:

2.1.1. Drug-Excipient Compatibility Studies (FT-IR)

FT-IR analysis was performed to assess the compatibility of the drug with the excipients. A small quantity of the drug and excipients was placed on the sample holder, and the FT-IR spectrophotometer scanned the sample between 400 cm-1 and 4000 cm-1. The obtained spectra were compared, and the functional group peaks were examined. The analysis aimed to identify the main peaks of the drug, any shifts or masking of these peaks, and the formation of new peaks, which could suggest interactions between the drug and excipients.[11]

2.1.2. Identification of λmax of Apigenin

To determine the λmax of Apigenin in 0.1 N HCl, a stock solution of Apigenin was prepared in 0.1 N HCl and diluted to a concentration of 30 µg/mL. The sample was then scanned using a UV-Vis spectrophotometer across the wavelength range of 200 to 400 nm. The wavelength at which maximum absorbance occurred was recorded as the λmax. This value was used for subsequent spectrophotometric measurements and the preparation of the calibration curve.[11,12]

2.1.3. Determination of λmax of Boswellic acid. (0.1 N HCl and 6.8 pH phosphate buffer)

To determine the λmax of Boswellic acid in 0.1 N HCl and 6.8 pH phosphate buffer, a stock solution of Boswellic acid was prepared in each solvent. The stock solution was diluted to a concentration of 30 µg/mL in both solvents. The samples were then scanned using a UV-Vis spectrophotometer across the 200 to 400 nm range. The wavelength at which maximum absorbance occurred was recorded as the λmax for each solvent. These values were subsequently used for further spectrophotometric analysis and the preparation of calibration curves.[11,12]

2.2. Construction of Calibration Curve of Apigenin and Boswellic acid [12]

Apigenin: A stock solution of Apigenin in 0.1 N HCl (1000 µg/mL) was prepared and diluted to concentrations ranging from 10 to 50 µg/mL. Absorbance was measured at 280 nm using a UV-Vis spectrophotometer, and a calibration curve was constructed by plotting concentration against absorbance.

Boswellic Acid: Stock solutions of Boswellic acid in 0.1 N HCl and 6.8 pH phosphate buffer were prepared and diluted to concentrations between 10 and 50 µg/mL. The absorbance of the samples was measured at 250 nm and 263 nm, and calibration curves were generated by plotting concentration against absorbance.[11,12]

2.3. Preparation of Immediate release (IR) layer:

A DC method was followed for making tablets. The Apigenin immediate-release layer was prepared by accurately weighing Apigenin, Sodium starch glycolate, Crospovidone, Microcrystalline cellulose, Magnesium Stearate, and Talc. These ingredients were sieved using a 40-mesh sieve and then thoroughly mixed using a mortar and pestle to ensure uniformity before compression. The formulation details are provided in Table 1.

Sustained release (SR) layer fabrication:

DCT was followed for making tablets. The Boswellic acid sustained-release layer contained Boswellic acid, HPMC K100, HPMC E15, and PVP K30, Microcrystalline cellulose, Magnesium Stearate, and Talc were accurately weighed, sieved using sieve 40, and mixed in mortar and pestle to ensure uniformity before it was compressed[13]. The formulation for the preparation is given in Table 2.

2.4. Preparation of Bilayer Tablets[13,14]

Before preparing the bilayer tablets, dissolution tests were conducted separately for both the immediate-release (IR) and sustained-release (SR) layers to identify the optimal formulation. Based on the dissolution results, the selected formulations for the IR and SR layers were chosen for bilayer tablet preparation.

To begin, the sustained-release Boswellic acid layer was placed in the die cavity and compressed with a low compression force. Then, the immediate-release Apigenin layer was placed in the die cavity and compressed with the optimal force to achieve the desired tablet hardness. Each bilayer tablet was adjusted to a total weight of 1000 mg, containing 350 mg of Boswellic acid in the sustained-release layer and 350 mg of Apigenin in the immediate-release layer. The prepared bilayer tablets were then evaluated for various post-compression parameters and subjected to in-vitro dissolution studies.[12,13].

Table 1. Composition of Apigenin immediate release layer.

Ingredients (mg)	**IR1**	**1R2**	**1R3**	**1R4**	**1R5**	**1R6**
Apigenin	350	350	350	350	350	350
Sodium starch glycolate	10	20	30	_	_	_
Crospovidone	_	_	_	10	20	30
MCC	120	110	100	120	110	100
Magnesium Stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Total weight of tablets in mg	**500**	**500**	**500**	**500**	**500**	**500**

Table 2. Composition of Boswellic acid sustained release layer.

Ingredients (mg)	**SR1**	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**
Boswellic acid	350	350	350	350	350	350
HPMC K100	130	120	110	_	_	_
HPMC E15	_	_	_	130	120	110
Microcrystalline cellulose	10	20	30	10	20	30
PVP K30	6	6	6	6	6	6
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total Weight of tablets in mg	**500**	**500**	**500**	**500**	**500**	**500**

2.5. Evaluation of IR and SR Tablets:

Precompression parameters[15] like bulk density, tapped density, Carr's Index (Or) % Compressibility, Hausner`s Ratio, and Angle of Repose (θ) were determined.

Post compression parameters[15] Like Uniformity of weight, Thickness, Friability, Hardness, and *In-vitro* Disintegration time (IR)[16] were determined

2.6. Drug content[16]

2.6.1. Apigenin (IR)

To determine the drug content of Apigenin, 10 immediate-release tablets were powdered, and 100 mg of the powder was placed in a 100 mL volumetric flask. The powder was dissolved in 0.1 N HCl, sonicated for 15 minutes, and filtered using Whatman filter paper. The solution was diluted to 100 mL. Absorbance was measured at λmax 280 nm using a UV-Vis spectrophotometer, and the drug content was calculated by comparing the absorbance of the sample with that of a standard Apigenin solution.

2.6.2. Boswellic Acid (SR)

To determine the drug content of Boswellic acid, 10 sustained-release tablets were powdered, and 100 mg of the powder was transferred to a 100 mL volumetric flask. The powder was dissolved in 6.8 pH phosphate buffer, sonicated for 15 minutes, and filtered using Whatman filter paper. The solution was diluted to 100 mL. Absorbance was measured at λmax 263 nm using a UV-Vis spectrophotometer, and the drug content was determined by comparing the absorbance of the sample to that of a standard Boswellic acid solution.

2.7. *In-Vitro* Dissolution Studies (IR layer)[17]

The in-vitro dissolution of the immediate-release tablets was performed using a USP dissolution apparatus type II (paddle method). The dissolution medium consisted of 900 mL of 0.1 N HCl, maintained at 37 ± 0.5°C with paddle rotation at 50-75 rpm. Samples were withdrawn at intervals of 10, 15, 20, 30, and 45 minutes and analyzed using a UV-Vis spectrophotometer.[21].

2.8. *In-Vitro* Dissolution Studies (SR layer)[17]

The in-vitro dissolution of the sustained-release tablets was carried out using a USP dissolution apparatus type II (paddle method). A dissolution medium of 900 mL 6.8 pH phosphate buffer was maintained at 37 ± 0.5°C with paddle rotation at 50-75 rpm. Samples were withdrawn at intervals of 1, 2, 4, 6, 8, and 9 hours and analyzed using a UV-Vis spectrophotometer. [22].

2.9. Evaluation of Bilayer Tablets [18,19]

The bilayer tablets were evaluated for various parameters, including thickness (mm), hardness (Kg/cm²), weight variation (mg), friability (%), drug content (%), and disintegration time (sec). Additionally, in-vitro dissolution studies, drug release kinetics, and stability were assessed.

2.10. *In-Vitro* Dissolution Studies of Bilayer Tablet

The in-vitro drug release study of the optimized bilayer tablet, consisting of both immediate-release and sustained-release layers, was conducted using a USP Type II paddle apparatus. Each dissolution vessel contained 900 mL of 0.1 N HCl (pH 1.2), maintained at 37 ± 0.5°C with paddle rotation at 100 rpm. Samples were collected at intervals of 10, 15, 20, 30, and 45 minutes for the immediate-release layer. The dissolution medium was then replaced with 900 mL of phosphate buffer (pH 6.8), and samples for the sustained-release layer were withdrawn at intervals of 1, 2, 4, 6, 8, and 9 hours, with fresh buffer replaced to maintain sink conditions. [25].

2.11. Drug release kinetics[20,21]

The drug release kinetics were analyzed using the zero-order, Higuchi, and Korsmeyer-Peppas models to evaluate the release pattern.

2.12. Stability Studies[22]

The stability of the bilayer tablets was assessed according to ICH guidelines. The optimized tablets were stored in polypropylene bottles and kept in stability chambers at 40 ± 2°C with 75 ± 5% relative humidity for three months, as well as at room temperature. Samples were tested at one-month intervals over three months to evaluate their stability.

3. RESULTS AND DISCUSSION:

FT-IR analysis was performed, as depicted in Figures 5, 6, 7, and 8, to examine potential interactions between the drugs and excipients. The spectra of the drugs combined with the excipients were analyzed to identify any significant shifts or alterations in wave numbers that might indicate interference. The results showed no notable changes in the characteristic wave numbers of the drugs, confirming the absence of interaction between the drug and excipient molecules. Based on these findings, the selected excipients were deemed compatible and appropriate for use in the formulations.

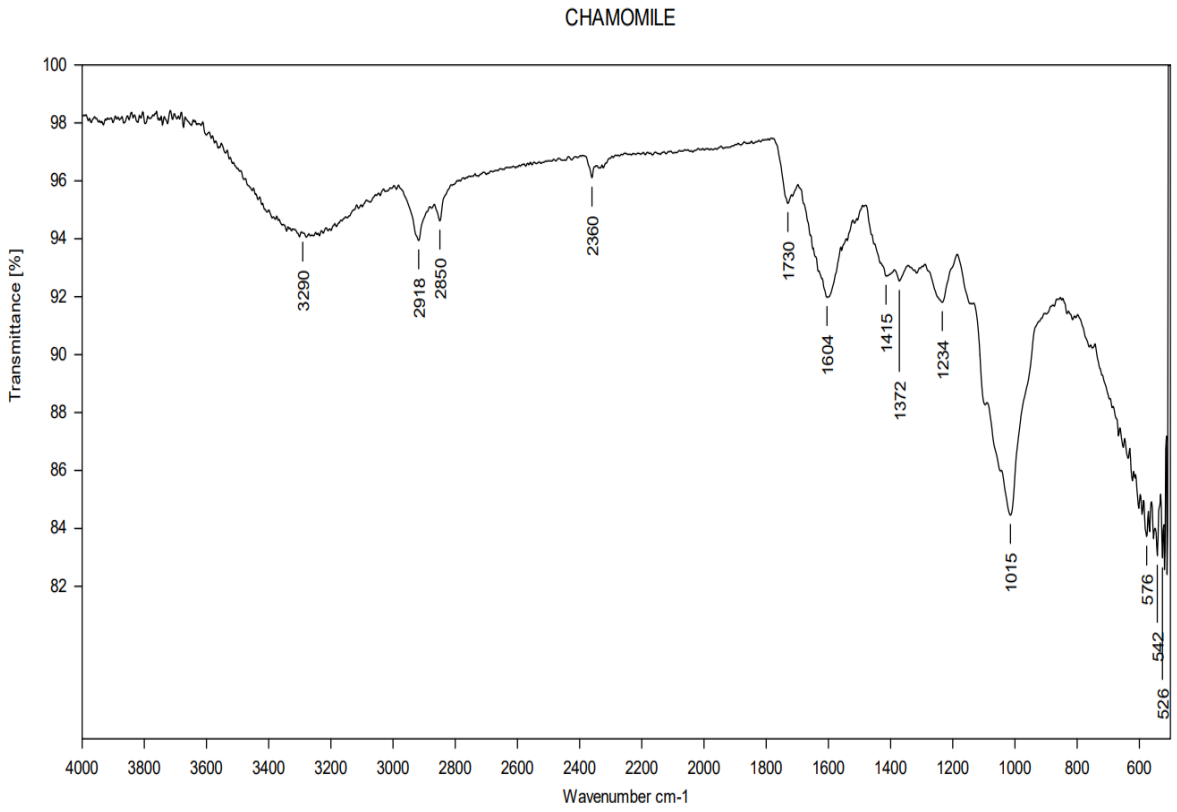


Fig.1: FT-IR spectra of pure Apigenin

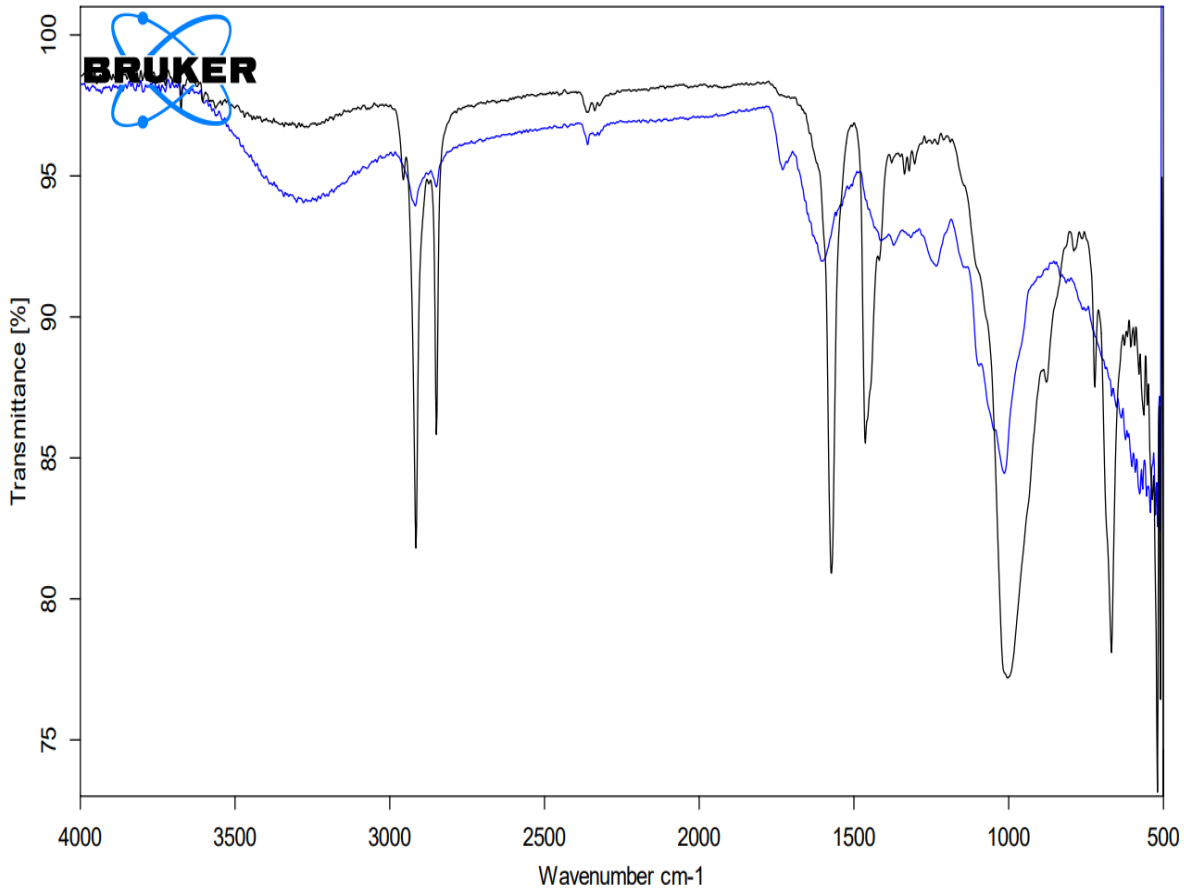


Fig.2: FT-IR spectra of Apigenin and Excipients

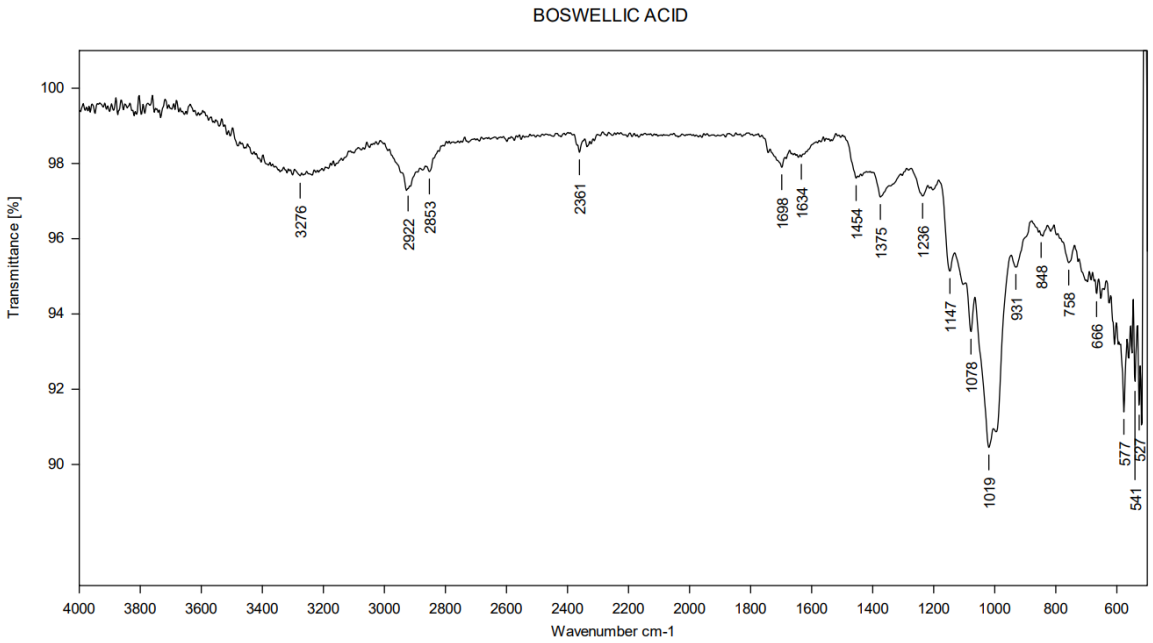


Fig.3: FT-IR spectra of pure Boswellic acid

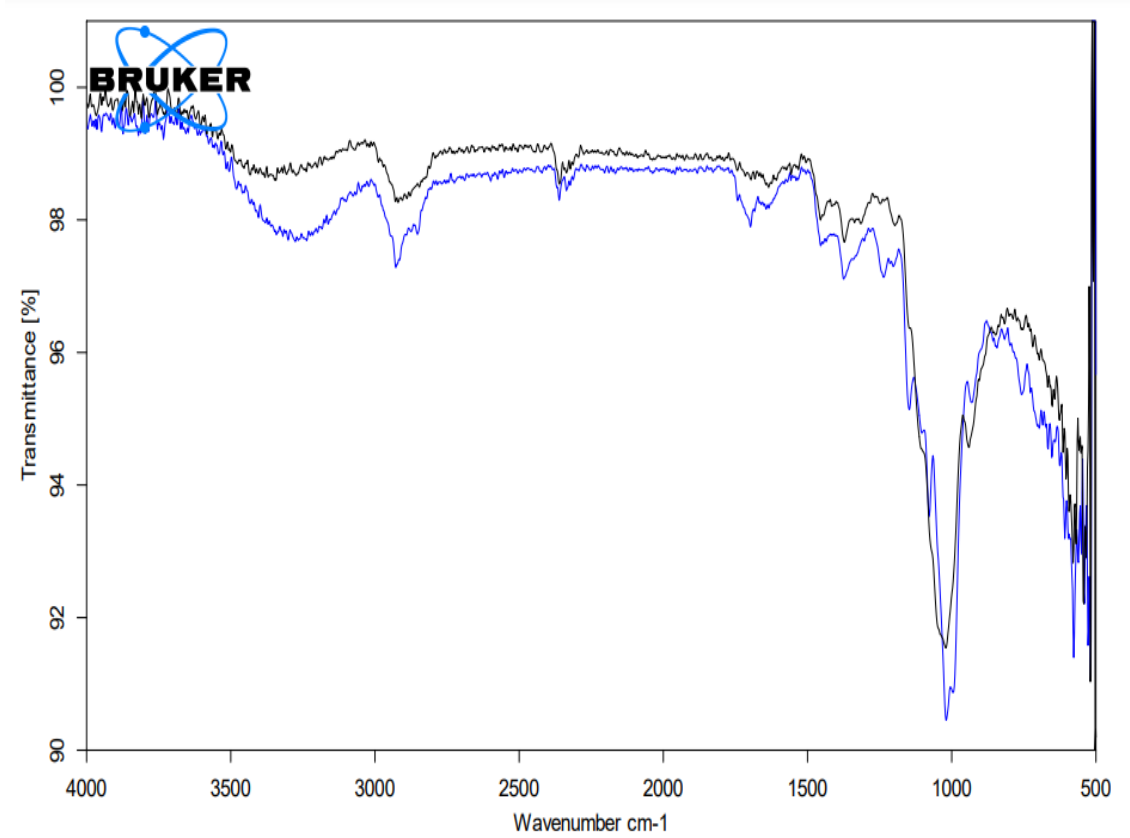


Fig.4: FT-IR spectra of pure Boswellic acid with HPMC K100 and E15

Table 3. Calibration curve absorbances of Apigenin in 0.1 N HCl solution.

Concentration (µg/ml)	Absorbance (280nm)
0	0
10	0.10±0.25
20	0.204±0.5
30	0.324±0.06
40	0.414±0.18
50	0.553±0.17

Figure 5: Calibration curve absorbances of Apigenin in 0.1 N HCl solution.

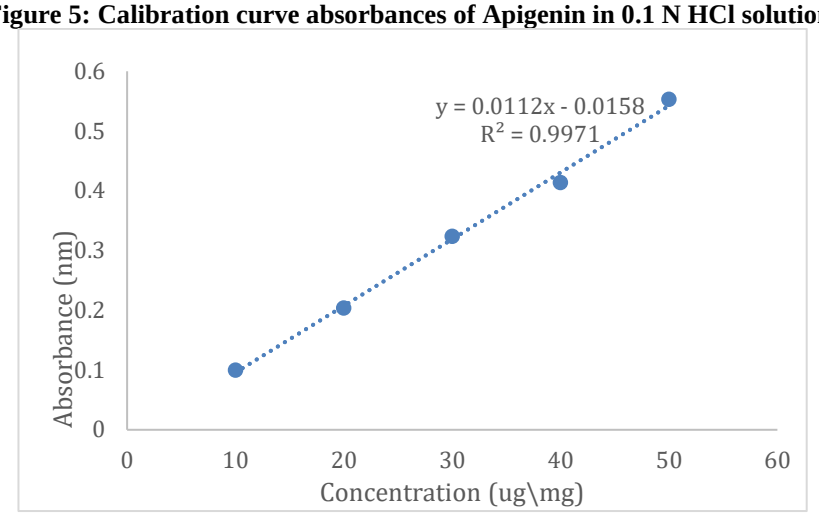


Table 4. Calibration curve absorbances of Boswellic acid in 0.1 N HCl solution

Concentration (µg/ml)	Absorbance (250)
0	0
10	0.10±0.02
20	0.224±0.05
30	0.344±0.04
40	0.401±0.08
50	0.515±0.01

Figure 6: Calibration curve absorbances of Boswellic acid in 0.1 N HCl solution

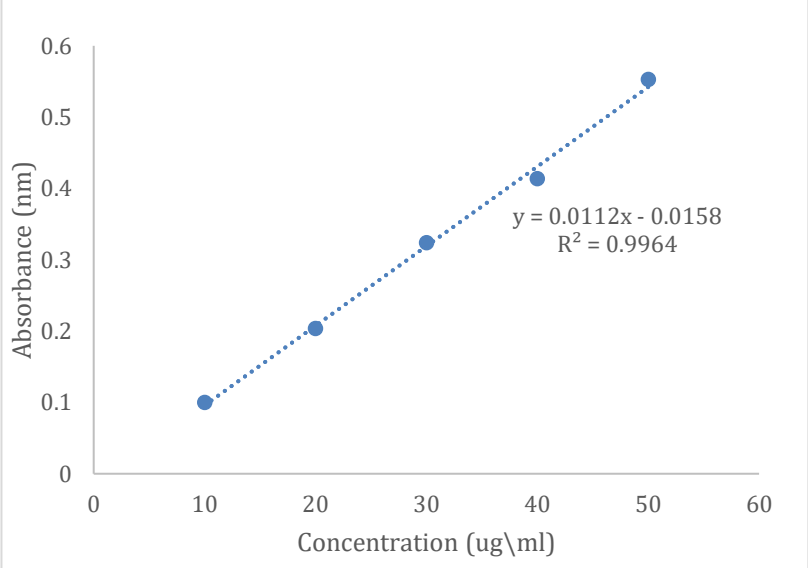


Table 5. Calibration curve absorbances of Boswellic acid in pH 6.8 phosphate buffer solution.

Concentration (µg/ml)	Absorbance (263nm)
0	**0**
10	**0.14**±0.01
20	**0.31**±0.07
30	**0.45**±0.02
40	**0.60**±0.08
50	**0.73**±0.09

Figure 7: Calibration curve absorbances of Boswellic acid in pH 6.8 phosphate buffer solution.

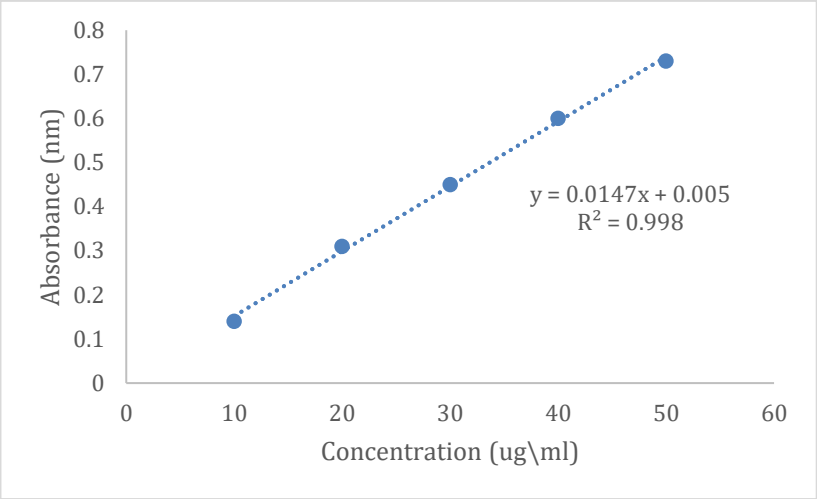


Table 6. Precompression parameters of Apigenin Immediate release layer.

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner ratio	Angle of repose (θ)
IR1	0.419±0.07	0.55±0.05	23.8±0.10	1.31±0.07	18.26±0.05
IR2	0.455±0.01	0.56±0.01	18.75±0.01	1.23±0.01	16.17±0.01
IR3	0.50±0.05	0.65±0.05	23.07±0.10	1.3±0.04	27.92±0.05
IR4	0.452±0.01	0.55±0.01	17.81±0.05	1.21±0.02	17.22±0.05
IR5	0.40±0.07	0.47±0.01	14.89±0.05	1.17±0.07	29.68±0.01
IR6	0.59±0.05	0.75±0.01	21.33±0.05	1.27±0.07	31.79±0.05

The pre-compression parameters of Apigenin Immediate Release Layer formulations (IR1-IR6) showed bulk densities from 0.40-0.59 g/cm³ and tapped densities from 0.47-0.75 g/cm³. Carr's index ranged from 14.89% (IR5) to 23.8% (IR1), with IR2, IR4, and IR5 exhibiting better flow properties. Hausner ratios (1.17-1.31) indicated good flow for IR2, IR4, and IR5. Angles of repose (16.17°-31.79°) showed IR2, IR4, and IR5 had better flowability.

Table 7. Precompression parameters for Boswellic acid sustained release layer.

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner ratio (HR)	Angle of repose (θ)
SR1	0.53±0.04	0.66±0.05	19.6±0.09	1.24±0.07	23.7±0.06
SR2	0.54±0.02	0.67±0.04	19.40±0.06	1.24±0.03	30.1±0.01
SR3	0.60±0.01	0.65±0.01	7.60±0.07	1.08±0.02	20.3±0.01
SR4	0.63±0.04	0.76±0.05	17.70±0.11	1.20±0.04	18.26±0.05
SR5	0.71±0.01	0.92±0.02	22.8±0.09	1.29±0.08	39.69±0.00
SR6	0.57±0.07	0.71±0.03	19.7±0.11	1.24±0.03	37.23±0.10

The pre-compression parameters of Boswellic acid sustained release formulations (SR1-SR6) showed bulk densities from 0.53-0.71 g/cm³ and tapped densities from 0.65-0.92 g/cm³. Carr's index ranged from 7.60% (SR3) to 22.8% (SR5), with SR3 exhibiting excellent flowability. Hausner ratios (1.08-1.29) and angles of repose (18.26°-39.69°) indicated SR3 and SR4 had superior flow properties, while SR5 and SR6 demonstrated poor flowability.

Table 8. Post compression parameters of Apigenin Immediate release layer.

Batch code	Hardness (Kg/cm^2)	Thickness (mm)	%Friability	Weight variation (mg)	Drug content %	Disintegration time(sec)
IR1	3.43±0.02	2.23±0.01	0.36%	498±0.005	95.78±0.44	40.59±8.9
IR2	3.83±0.06	2.23±0.007	0.75%	487±0.003	98.84±0.50	27.60±3.3
IR3	3.50±0.07	2.17±0.009	0.67%	502±0.007	97.26±0.15	38.56±0.88
IR4	3.76±0.05	2.27±0.21	0.53%	503±0.009	96.89±0.53	31.42±6.6
IR5	3.70±0.06	2.23±0.01	0.10%	501±0.001	98.87±0.04	22.56±0.7
IR6	3.56±0.06	2.25±0.01	0.57%	503±0.007	93.89±0.47	35.33±6.8

The post-compression parameters of Apigenin Immediate Release Layer (IR1-IR6) showed hardness values from 3.43-3.83 Kg/cm², with IR2 being the hardest. Thickness ranged from 2.17-2.27 mm, showing uniformity. Friability values were within acceptable limits (<1%), with IR5 having the lowest (0.10%). Weight variation adhered to pharmacopeia

standards (487-503 mg). Drug content ranged from 93.89% (IR6) to 98.87% (IR5). Disintegration times were under 1 minute, with IR5 disintegrating the fastest (22.56 sec), ensuring rapid drug release.

Table 9. Post compression parameters of Boswellic acid sustained release layer.

Batch code	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	Weight variation (mg)	Drug content %
SR1	4.27±0.03	2.73±0.01	2.6%	502±0.006	85.02±0.04
SR2	4.00±0.04	2.21±0.03	3.5%	504±0.002	97.16±0.12
SR3	4.37±0.01	2.81±0.009	0.6%	500±0.002	99.66±0.07
SR4	4.97±0.07	2.33±0.21	3.4%	501±0.006	96.32±0.26
SR5	4.64±0.1	2.83±0.01	3.4%	498±0.004	89.23±0.18
SR6	4.74±0.1	2.16±0.01	1.5%	499±0.01	96.02±0.30

The post-compression parameters of Boswellic acid sustained release formulations (SR1-SR6) showed hardness ranging from 4.00-4.97 Kg/cm^2, with SR4 having the highest value. Thickness varied between 2.16 mm (SR6) and 2.83 mm (SR5), indicating uniformity. Friability ranged from 0.6% (SR3) to 3.5% (SR2), with SR3 exhibiting excellent resistance. Weight variation (498-504 mg) was within pharmacopeia limits. Drug content ranged from 85.02% (SR1) to 99.66% (SR3), with SR3 demonstrating superior uniformity and SR1 the lowest content.

Table 10. *In-vitro drug* release data of Apigenin immediate release layer (% drug release).

Time in minutes	*In-vitro drug* release data of Apigenin immediate release layer % Drug release					
	IR1	**IR2**	**IR3**	**IR4**	**IR5**	**IR6**
0	0	0	0	0	0	0
5	14.70	12.32	10.27	15.27	17.02	11.67
10	28.52	26.30	22.45	30.07	34.62	24.65
15	44.02	42.73	37.02	48.27	52.65	39.20
20	66.45	63.77	55.35	67.37	68.27	58.92
30	81.52	77.85	67.60	82.57	83.57	71.70
45	94.02	90.42	80.37	96.77	99.60	86.50

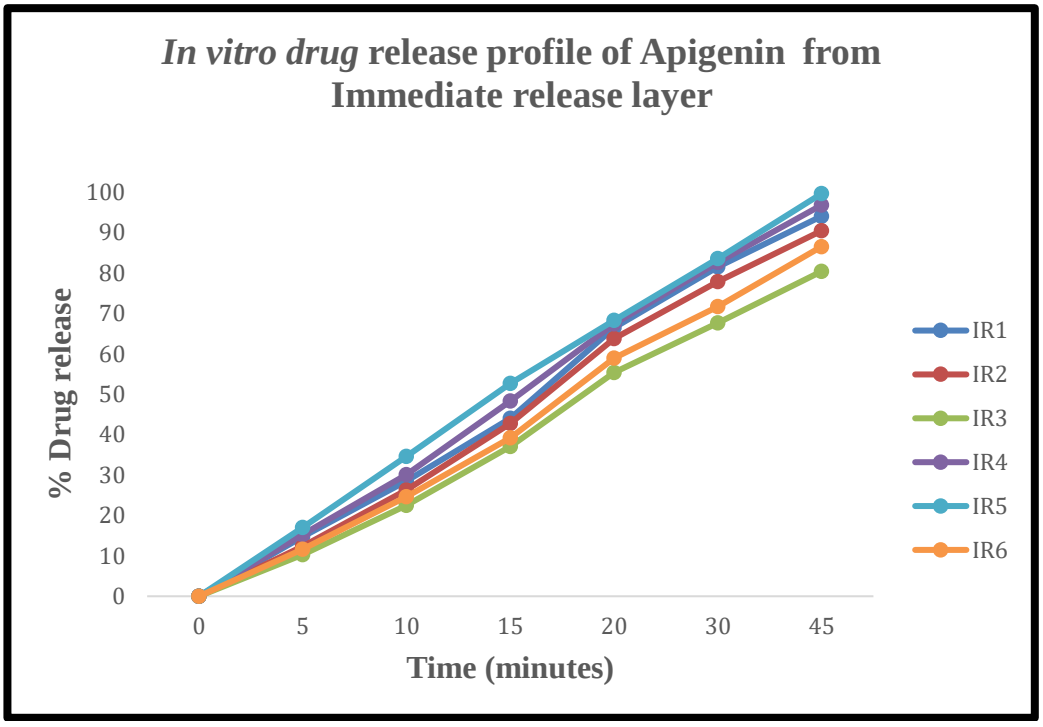


Fig.8: Drug release of Apigenin Immediate-release tablets

The *in-vitro* drug release data of the Apigenin immediate release layer demonstrates a rapid and consistent release of the drug across all formulations. At 5 minutes, the release ranges from 10.27% (IR3) to 17.02% (IR5), indicating an early burst of drug availability. By 15 minutes, over 35% of the drug has been released in all formulations, with IR5 showing the highest release (52.65%). At 20 and 30 minutes, all formulations exhibit substantial release, with IR5 achieving 83.57% at 30 minutes. The maximum release is observed at 45 minutes, where IR5 (99.60%) and IR4 (96.77%) show almost complete drug release.

Table 11. *In-vitro drug* release data of Boswellic acid from sustained release layer (% drug release)

Time in Hours	*In-vitro* release data of Boswellic acid from sustained release layer % Drug release					
	SR1	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**
0	0	0	0	0	0	0
0.25	5.47	12.97	9.97	7.72	3.97	2.47
0.5	8.47	17.47	15.97	14.47	13.72	4.72
0.75	12.97	21.97	21.97	18.97	20.47	9.22
1	15.22	25.72	24.97	25.72	22.72	12.97
2	18.97	27.97	30.22	29.47	32.47	17.47
3	21.22	30.22	39.22	38.47	37.72	27.97
4	24.22	36.97	44.47	52.72	45.97	32.47
5	27.97	47.47	52.47	62.47	50.47	38.47
6	35.47	51.97	69.22	66.97	53.47	45.22
7	38.47	60.97	93.22	72.72	61.72	51.22
8	46.75	72.97	95.47	81.01	72.97	66.22
9	50.47	88.72	97.72	89.98	82.22	78.47

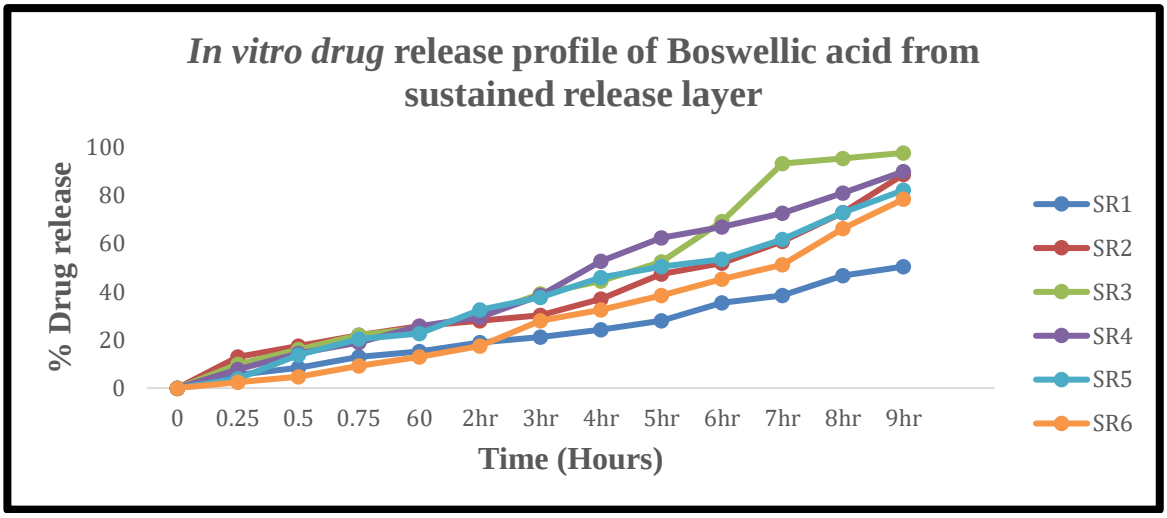
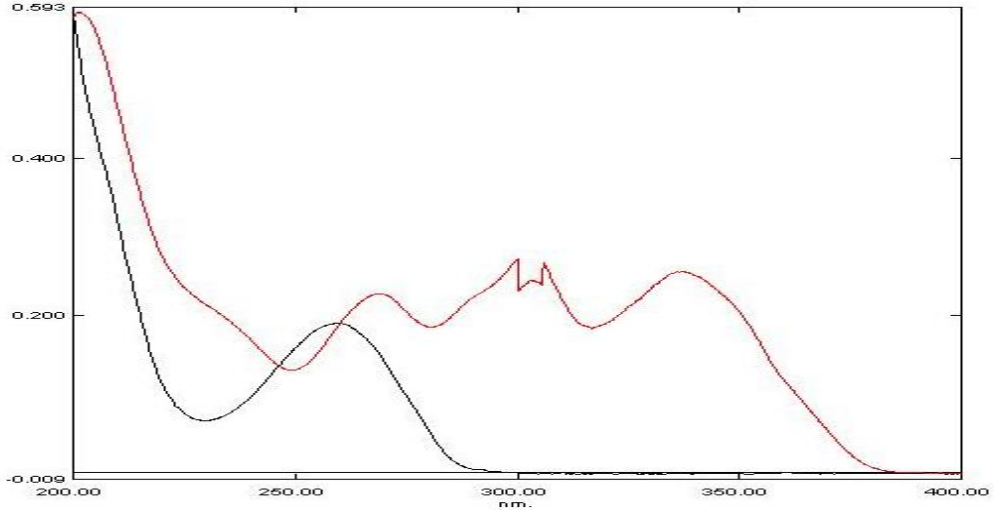


Figure 9: Drug release of Boswellic acid sustained-release tablets

The *in-vitro* release profiles of Boswellic acid from sustained release formulations (SR1-SR6) were evaluated over 9 hours. At 15 minutes, SR2 showed the highest release (12.97%), while SR6 had the lowest (2.47%). By 2 hours, SR2 continued leading (27.97%), and by 4 hours, SR4 reached 52.72%. After 5 hours, SR4 peaked at 62.47%. By 9 hours, SR3 and SR4 nearly completed release (97.72% and 89.98%), while SR6 lagged at 78.47%, indicating varied release kinetics among formulations.

Figure 10: Drug content analysis of the sample with a standard Apigenin solution.



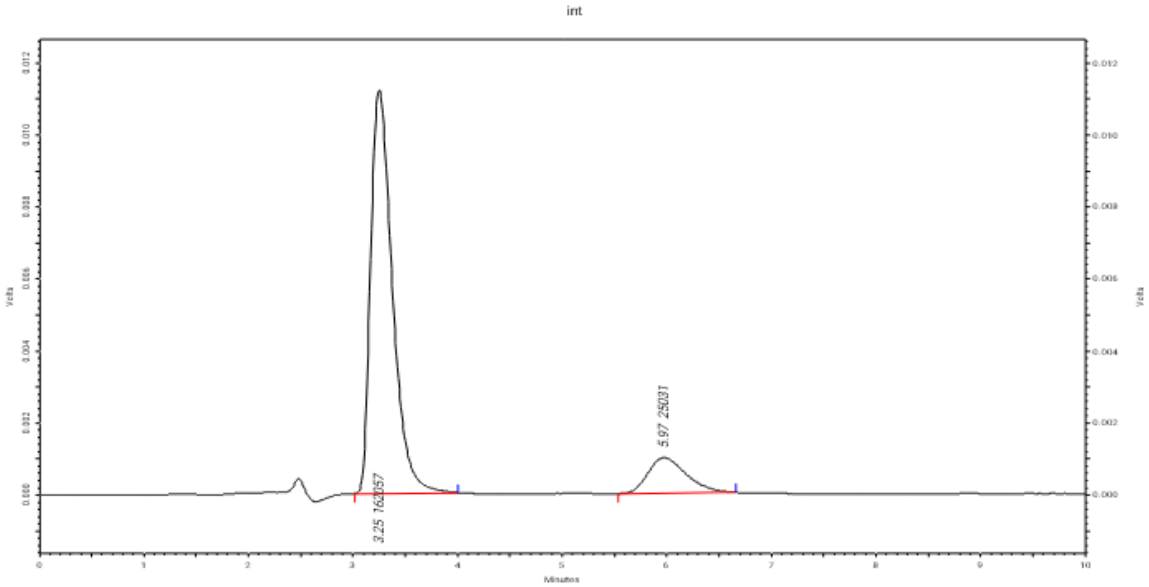


Figure 11: Drug content analysis of the sample with a standard Boswellic solution

The expected quantity of the active ingredient was present in the formulation based on the drug content analysis because the absorbance values of the Apigenin IR and Boswellic acid SR tablets fell within their corresponding standard solution values. Uniform medication content ensures that the tablets were prepared with accurate and reproducible amounts during the formulation process.

Table 12. Composition of bilayer tablet of Apigenin and Boswellic acid.

Ingredients	**BF1**
Boswellic acid	350mg
HPMC K100	110mg
Micro crystalline cellulose	30mg
PVP K30	6mg
Magnesium stearate	2mg
Talc	2mg
Apigenin	350mg
Crospovidone	20mg
Micro crystalline cellulose	110mg
Magnesium stearate	10mg
Talc	10mg
Total weight of the tablet	**1g**

Table 13. Evaluation parameters of Bilayer tablet formulation (BF1)

Batch code	**Hardness (Kg/cm^2)**	**Thickness (mm)**	**%Friability**	**Weight variation(mg)**	**Drug content%**	**Disintegration time(sec)**
BF1	6.30±0.02	3.15±0.02	0.6%	1000±0.007	98.10±0.90	28.56±2.15

The BF1 Bilayer tablet shows excellent formulation characteristics with 6.30 Kg/cm^2 hardness, 0.6% friability, and 3.15 mm thickness. It meets weight variation standards (1000 mg) and has 98.10% drug content. Disintegration occurs in 28.56 seconds, ensuring effective and timely drug release, demonstrating a well-optimized formulation.

Table 14. *In-vitro* release data of Apigenin (IR5) and Boswellic Acid (SR3) Bilayer formulation (BF1)

Time	**% drug release**	
	Immediate release layer	**Sustained release layer**
0.1N HCL buffer solution		
10	20.02	3.05
15	45.6	5.17
20	64.57	9.97
30	71.92	15.97
45	99.37	21.97
pH6.8 phosphate buffer solution		
1hr	-	25.72
2hr	-	27.97

3hr	-	30.22
4hr	-	36.97
5hr	-	49.47
6hr	-	57.97
7hr	-	71.97
8hr	-	85.97
9hr	-	98.72

Table 15: Drug Release kinetics of Apigenin (IR5) and Boswellic acid (SR3) from bilayer tablets in

Formulations	Zeroth order		First order		Higuchi		Korsmeyar- Peppas model	
	K_0	R^2	K_1	R^2	H_h	R^2	n	R^2
IR5	2.02	0.9241	0.0556	0.8903	18.948	0.9819	0.8178	0.9681
SR3	10.182	0.97	-0.1655	0.8433	35.279	0.9267	0.6109	0.9661

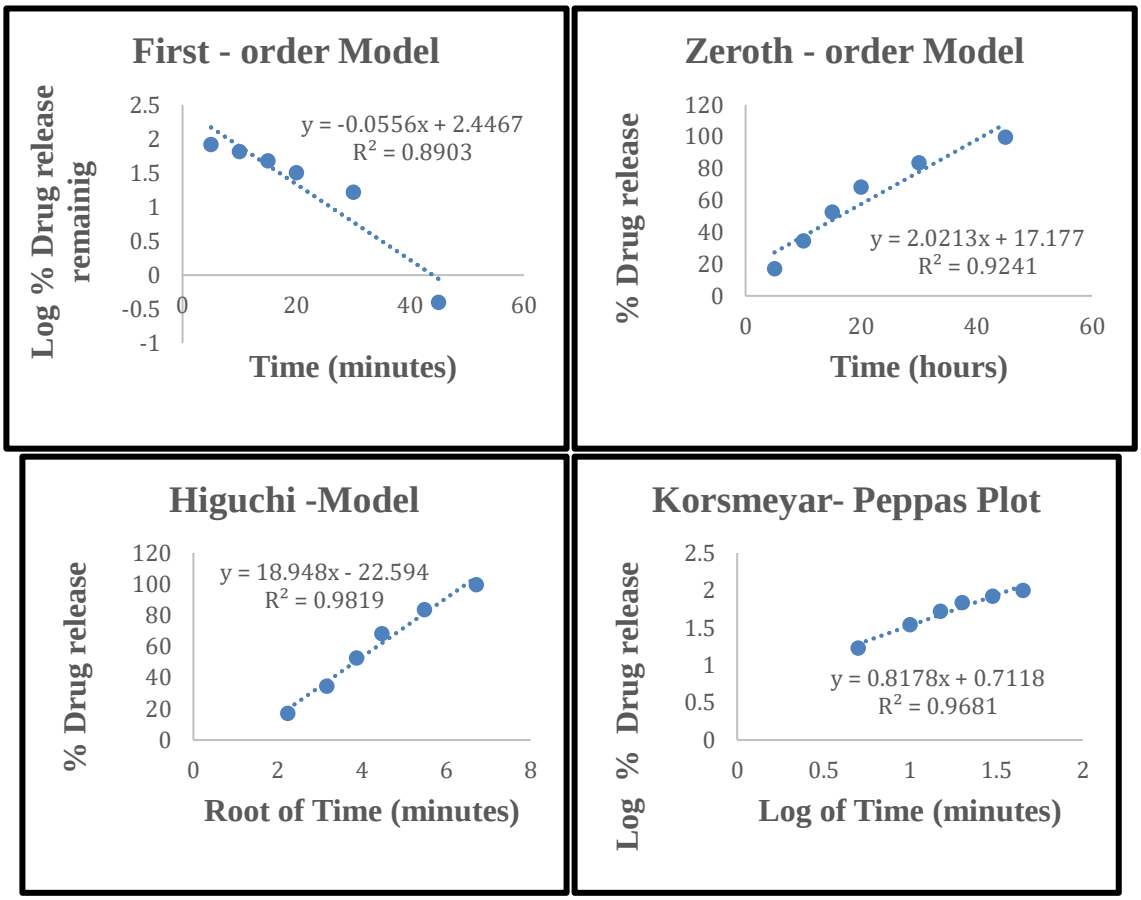
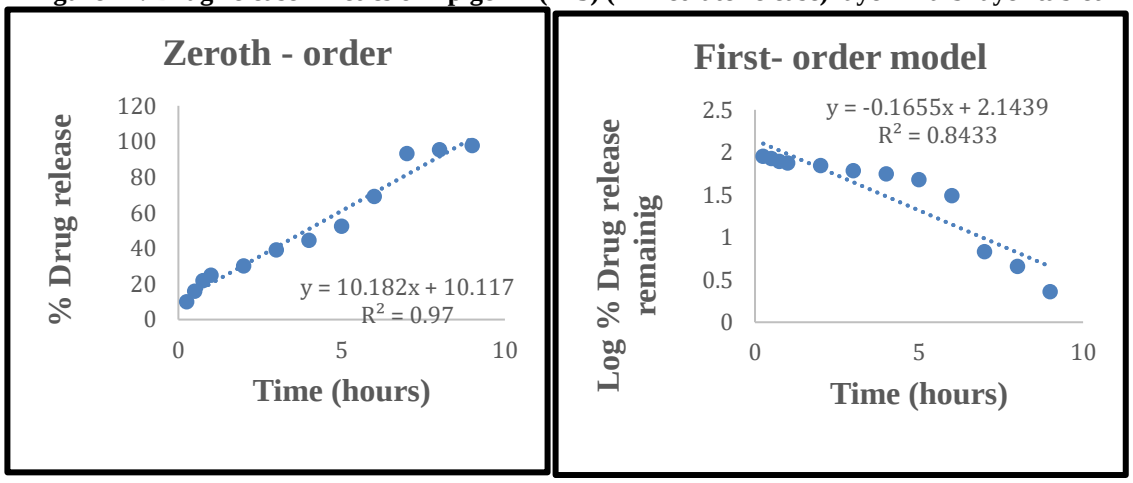


Figure 12: Drug release kinetics of Apigenin (IR5) (immediate release) layer in a bilayer tablet



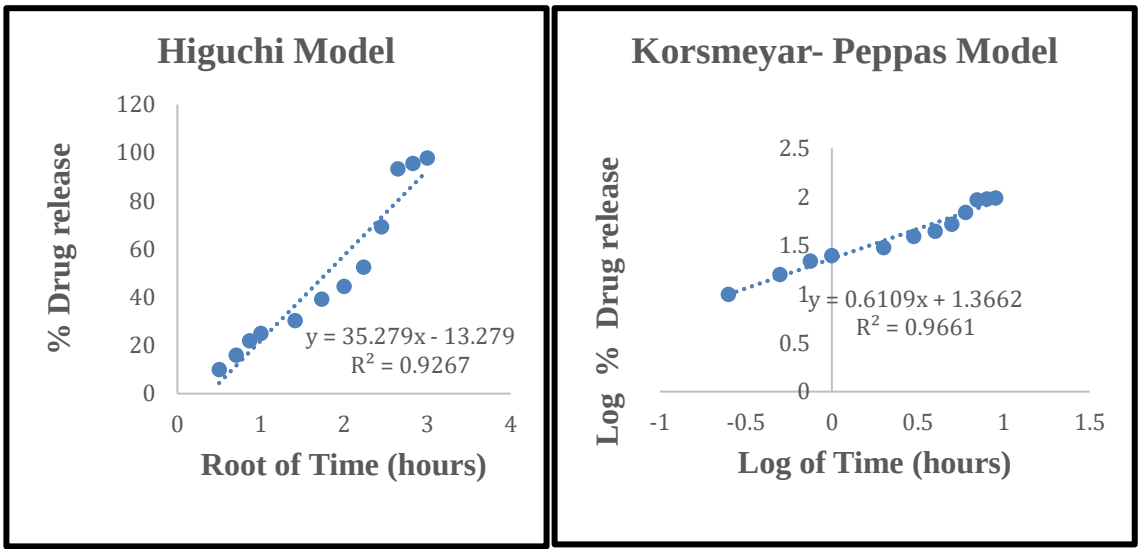


Figure 13: Drug release kinetics of Boswellic acid (SR5) (Sustained release) layer in a bilayer tablet

The drug release kinetics data suggests different mechanisms governing the release profiles of the formulations. For IR5, the highest R^2 value (0.9819) is observed with the Higuchi model, indicating that the release follows a diffusion-controlled mechanism. The Korsmeyer-Peppas model shows an "n" value of 0.8178, suggesting non-Fickian or anomalous transport, which indicates a combination of diffusion and erosion mechanisms. The Zeroth-order model also fits relatively well (R^2 = 0.9241), implying some constant release over time, but the First-order model shows a lower fit (R^2 = 0.8903).
For SR3, the drug release best fits the Zeroth-order model (R^2 = 0.97), indicating a steady, time-independent release, which is typical for sustained-release formulations. The Korsmeyer-Peppas model shows an "n" value of 0.6109, indicating that diffusion is dominant but not purely Fickian. The Higuchi model also fits well (R^2 = 0.9267), supporting a diffusion-controlled mechanism, while the First-order model has the lowest fit (R^2 = 0.8433), further confirming the preference for a constant release profile.

Table 16: Stability Studies of Bilayer Tablet

PARAMETERS	After 1month		After 2 months		After 3 months	
	Room Temp.	Accelerated condition	Room Temp.	Accelerated condition	Room Temp.	Accelerated condition
Hardness(Kg/cm^2)	6.30	6.32	6.37	6.37	6.40	6.40
Thickness(mm)	3.15	3.15	3.15	3.15	3.15	3.15
Friability (%)	0.18	0.18	0.15	0.15	0.15	0.15
In-vitro disintegration time (seconds)	29.65	30.42	30.58	31.01	31.42	31.74
Drug content (%)	98.7	98.4	98.2	98.01	97.98	97.91
Cumulative % drug release of Apigenin after 45 min	97.88	97.65	97.50	97.44	96.98	96.84
Cumulative % drug release of boswellic acid after 9 hours	98.89	98.65	98.41	98.32	98.01	97.98

The bilayer tablet containing Apigenin (IR5) and Boswellic acid (SR3) was stable over 3 months under room temperature and accelerated conditions. Key parameters like hardness, thickness, and friability remained consistent. Minor reductions in drug content and cumulative release were observed but remained within acceptable limits. Apigenin showed a slight decrease in release over 45 minutes, while Boswellic acid maintained a controlled release over 9 hours, preserving its sustained release profile.

CONCLUSION

The development and evaluation of a bilayer tablet combining Apigenin and Boswellic acid highlight its potential as an effective dual-action treatment for arthritis and asthma. The immediate-release layer of Apigenin delivered rapid relief from asthma symptoms through its anti-inflammatory and bronchodilatory properties, while the sustained-release layer of Boswellic acid provided prolonged anti-inflammatory action essential for long-term arthritis management.
Both pre-compression and post-compression evaluations of the Apigenin and Boswellic acid layers demonstrated favorable results, including good flow properties, optimal hardness, and low friability. Drug content uniformity for both active ingredients met acceptable standards, ensuring consistent efficacy. In-vitro dissolution studies revealed that Apigenin released 99% of its drug content within 45 minutes, while Boswellic acid exhibited a controlled release over 9 hours, following a zero-order kinetic model and confirming its suitability for sustained drug delivery.

The bilayer tabletmaintained stability over three months, showing minimal variations in drug content and release profiles, positioning it as a viable therapeutic option for managing both arthritis and asthma. Future studies should focus on testing the bilayer tablet in animal models to further evaluate its efficacy. This formulation holds promise as an innovative approach for addressing the needs of patients with these chronic conditions.

References:

10.53555/eijmhs.v11i1.263