Research Article

# Design and Evaluation of Herbo-Allopathic Bilayer Tablet Formulation: An Integrated Therapeutic Approach

Dr. M. V. Kumudhavalli*[1], P. Sokkalingam[2], Dr. M. Kumar[3], Dr. L. Janarthanan[4], Dr. S. Ruby[5], M. Prathikshaa[6], M. Balaji[7], S. Deepak Kumar[8]

[1]Department of Pharmacognosy, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. 0000-0001-6675-8883
[2]Department of Pharmaceutical analysis, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. 0009-0006-9133-2482
[3]Department of Pharmaceutical chemistry, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. 0000-0002-3513-2383
[4]Department of Pharmacognosy, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. 0000-0002-5011-9013
[5]Department of Pharmaceutical chemistry, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. 0000-0002-0293-7767
[6]Department of Pharmaceutical analysis, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. 0009-0002-8062-3592
[7]Department of Pharmaceutical analysis, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India.
[8]Department of Pharmaceutical analysis, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India.
**Corresponding Author**
Mr. P. Sokkalingam, Research Scholar
Department of Pharmaceutical analysis, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed University), Salem 636008, Tamil Nadu, India. , **Orcid-id :** 0009-0006-9133-2482

**Abstract:**

Diabetes mellitus, a serious metabolic disease caused by absolute or relative inadequate insulin secretion and action that leads to micro and macrovascular problems, is characterized by elevated blood sugar levels. Metformin hydrochloride is considered the medication of choice, but compliance may be impacted by its frequent dosing and gastrointestinal side effects. Herbal medications Cissus quadrangularis has anti-inflammatory, anti-hyperlipidemic, anti-diabetic, and antioxidant qualities. Thus, the goal of this research was to design, produce, and evaluate a Herbo-allopathic bilayer pill that would release Cissus extract gradually and Metformin instantly for the treatment of type 2 diabetes. The proper solvents were used to extract the C. quadrangularis stems. Physicochemical, spectroscopic, and preliminary phytochemical screening were carried out. Compatibility between drugs and excipients was also evaluated. By employing the proper excipients and the direct compression method, metformin quick release and Cissus sustained release were accomplished. Parameters were assessed both prior to and following compressions. The USP dissolving apparatus II was used to conduct the dissolution test, and the outcomes were compared to those of the commercial products. Additionally, experiments of accelerated stability were conducted. This study demonstrated the ideal physicochemical and drug release features of the bilayer tablet formulation of Metformin HCl and Cissus extract. Therefore, it was determined that combining herbal and allopathic medications will help treat type 2 diabetes more effectively with fewer side effects and higher patient compliance because of less frequent dosing.

.

**Keywords:** Diabetes mellitus; Metformin hydrochloride; Cissus quadrangularis; Herbo-allopathic formulation; Sustained-release drug delivery.

## INTRODUCTION:

### DIABETES MELLITUS:

Diabetes mellitus is a condition defined by persistently high levels of sugar (glucose) in the blood. There are several types of diabetes. The two most common are type 1 diabetes and type 2 diabetes[1].

### TABLET FORMULATION:

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single Unit and they are known collectively as solid unit dosage forms, even in the case of Sustained action preparations which, technically, contain the equivalent of several Normal doses of drug.The stringent formulation requirements of modern Medicaments, the many advantages of tablet and capsule medication, coupled With expanding health services and the commitment need for large-scale Economic manufacture, have led to a steady decline in the prescribing of powders And pills .Tablets and capsules, on the other hand, currently account for well over Two third of the total number and cost of medicines produced all over the world. Tablets are solid dosage form which is conventional as well as have many advantages over other dosage forms. Tablets are the most popular dosage form; about 70% of the total medicines are dispensed in the form of tablets. Tablets had different shapes, sizes, as well as weight depending on medicinal substances and the intended mode of administration. In this paper there are some advantages as well as some disadvantages of tablets, the basic ingredients that are commonly found in tablets, methods of tablet preparation and the various types of the tablets are briefly reviewed[2].

### BILAYER TABLET:

A Bilayer tablet is a solid oral dosage form that contains two different layers of active pharmaceutical ingredients or excipients compressed together into a single tablet unit. This type of tablet is specifically

designed to separate incompatible drugs and to provide different drug release profiles within the same dosage form. One layer of the bilayer tablet is usually formulated for immediate drug release to produce a rapid therapeutic effect, while the second layer is designed for sustained or controlled drug release to maintain the drug concentration in the body over an extended period. Bilayer tablets are widely used in combination therapy to enhance therapeutic efficacy, improve patient compliance, and achieve both immediate and prolonged action of drugs. In the formulation of a bilayer tablet containing Metformin and Cissus quadrangularis, the immediate release layer of Metformin provides a quick anti-diabetic effect, whereas the sustained release layer of Cissus quadrangularis offers prolonged herbal therapeutic benefits, making it more effective in the management of diabetes mellitus[3].

**Need for Combination Herbo Allopathic drug therapy**

Combination drug therapy has become an important strategy in the management of chronic diseases such as diabetes mellitus, obesity, metabolic syndrome, and associated complications. Monotherapy with synthetic antidiabetic drugs may not always provide complete therapeutic benefits because diabetes is a multifactorial disorder involving hyperglycemia, oxidative stress, inflammation, insulin resistance, and metabolic imbalance. Therefore, integrating herbal medicines with conventional drugs can provide synergistic therapeutic effects and improve overall treatment outcomes[4].

Metformin is considered the first-line oral antidiabetic drug for the treatment of Type 2 diabetes mellitus. It primarily acts by reducing hepatic glucose production, increasing insulin sensitivity, and enhancing peripheral glucose utilization. Although metformin effectively controls blood glucose levels, long-term therapy may be associated with gastrointestinal side effects, vitamin B12 deficiency, reduced patient compliance, and inadequate control of oxidative stress and inflammation. Long term use of metformin may causes calcium deficiency. Order to rectify this bilayer tablet may be use full for diabetic mellitus.

Cissus quadrangularis is a medicinal plant widely used in traditional medicine systems such as Ayurveda and Siddha. The plant contains several bioactive phytoconstituents including flavonoids, triterpenoids, β-sitosterol, ascorbic acid, carotenoids, calcium and phenolic compounds. These constituents possess antioxidant, anti-inflammatory, anti-obesity, hypoglycemic, and bone-healing properties.

Cissus quadrangularis and metformin can be combined in a herbo-allopathic bilayer tablet to provide complementary therapeutic effects in the management of Type 2 diabetes mellitus and associated bone-health concerns. The metformin layer provides the conventional antidiabetic effect by reducing hepatic glucose production and improving insulin sensitivity, while the Cissus quadrangularis layer provides phytoconstituents such as flavonoids, β-sitosterol, phenolic compounds, carotenoids, and minerals including calcium. The calcium and other bioactive constituents present in Cissus quadrangularis may contribute to calcium availability and bone mineralization, while the plant's antioxidant and anti-inflammatory properties may provide additional supportive benefits. In a bilayer tablet, the two components can be formulated as separate layers with controlled drug release, allowing metformin to provide its antihyperglycemic action and Cissus quadrangularis to provide sustained herbal activity. This approach may offer an integrated therapeutic strategy combining glycemic control, antioxidant protection, and support for calcium utilization and bone health.

Combination therapy may also improve therapeutic efficacy in patients suffering from obesity-associated diabetes. Cissus quadrangularis has been reported to exhibit anti-obesity and lipid-lowering effects, which can help manage metabolic syndrome and cardiovascular risk factors commonly associated with diabetes mellitus. Thus, the combination provides multidimensional therapeutic benefits beyond blood glucose control.

## MATERIAL AND METHODS

**MATERIAL:** The collected Plant was identified and authenticated by the botanist Dr. A. Balasubramanian (consultant central siddha research) executive director ABS botanical garden, Salem, Tamil Nadu. Metformin HCL was procured from Biocon Pvt Limited.

**METHODS:**

**1. Method of extraction:** Continuous hot percolation process by using “Soxhlet apparatus” for Cissus Quandrangularis Plant

**2. solvent used:** Petroleum ether manufactured by OXFORD range of laboratory chemicals; Ethanol manufactured by OXFORD range of laboratory chemicals and distilled water. 2.Materials used: Cissus Quandrangularis

**Standard curve for metformin:**

The 100 mg of ethanolic extract of Cissus quadrangularis was dissolved in ethanol, from which dilutions were made to obtain lower concentrations. These were scanned in a UV spectrometer in the range of 200–400 nm. The maximum absorbance was taken as the λmax value, and further screening was carried out.

**Development and evaluation bilayer tablet formulation**

**Table No 1: Sustained Release (SR) Layer Formulation – Cissus quadrangularis**

| Ingredients (mg) | F1 | F2 | F3 |
|---|---|---|---|
| Cissus quadrangularis extract | 300 | 300 | 300 |
| HPMC K100M | 80 | 100 | 120 |
| Lactose | 90 | 70 | 50 |
| Polyvinylpyrrolidone K30 (PVP K30) | 20 | 20 | 20 |
| Magnesium stearate | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 |
| Total Weight (mg) | 500 | 500 | 500 |

**Table No 2: Immediate Release (IR) Layer Formulation – Metformin**

| Ingredients (mg) | F1 | F2 | F3 |
|---|---|---|---|
| Metformin HCl | 500 | 500 | 500 |
| Microcrystalline Cellulose (MCC) | 90 | 85 | 80 |
| Sodium starch glycolate | 15 | 20 | 25 |
| Polyvinylpyrrolidone K30 (PVP K30) | 20 | 20 | 20 |
| Magnesium stearate | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 |
| Total Weight (mg) | 500 | 500 | 500 |

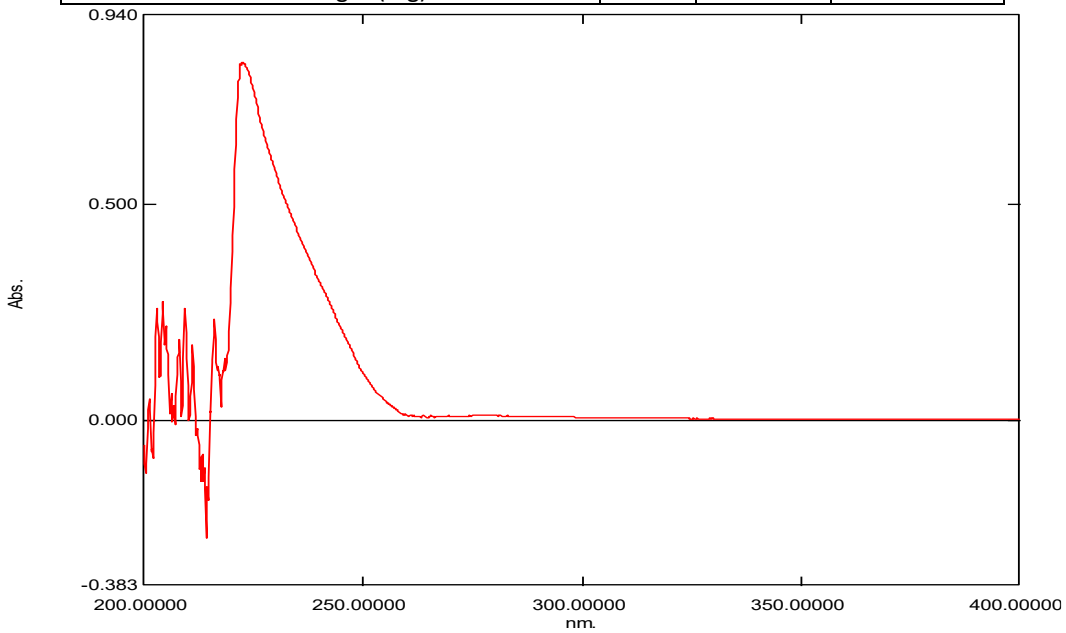



**Figure No 1: (λ) max of Cissus quadrangularis L**

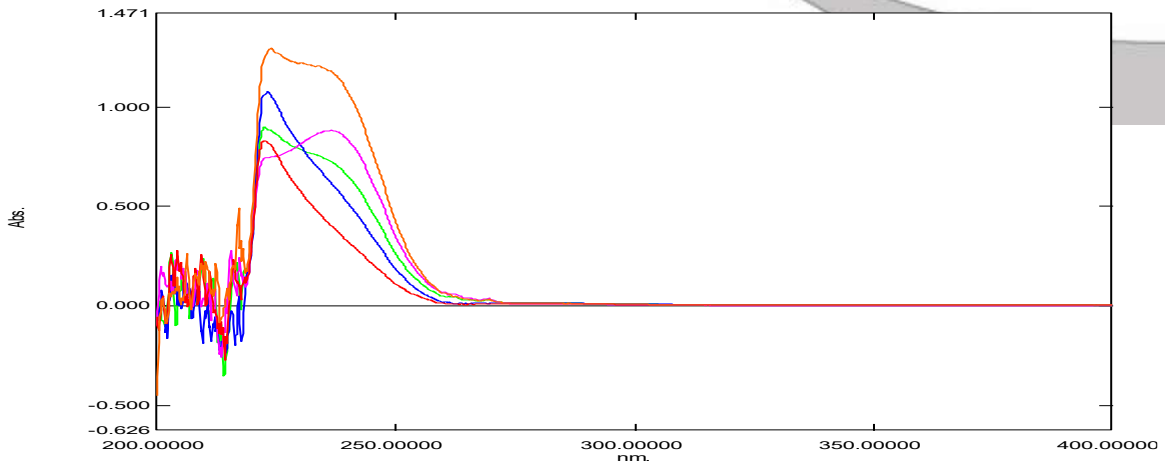
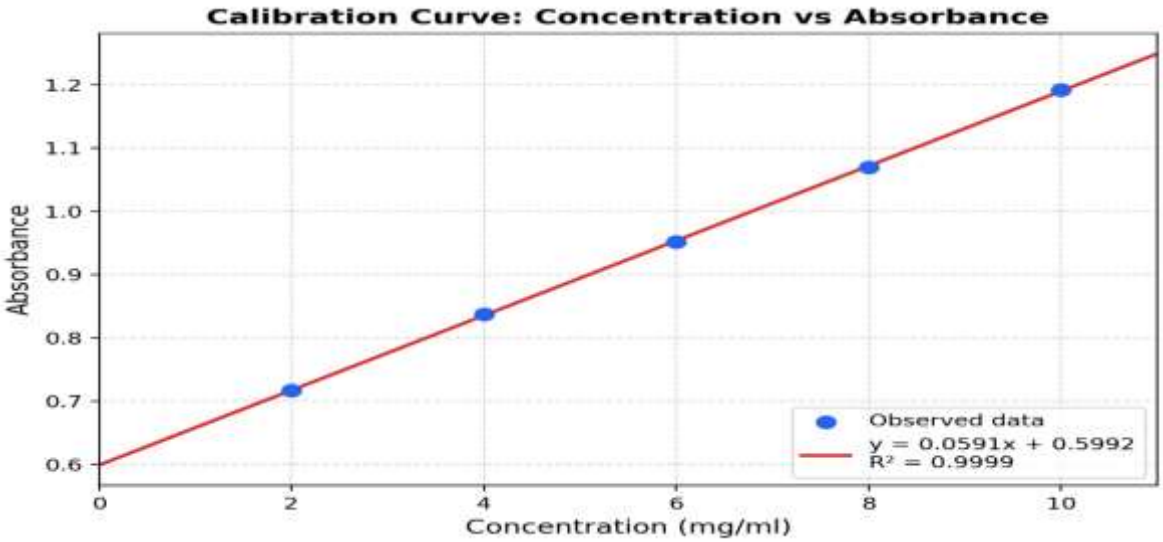



**Figure No 2: Overlay spectrum of Cissus quadrangularis L**




**Fig, NO 3 :Standard (λ) max was calibration curve Cissus quadrangularis**

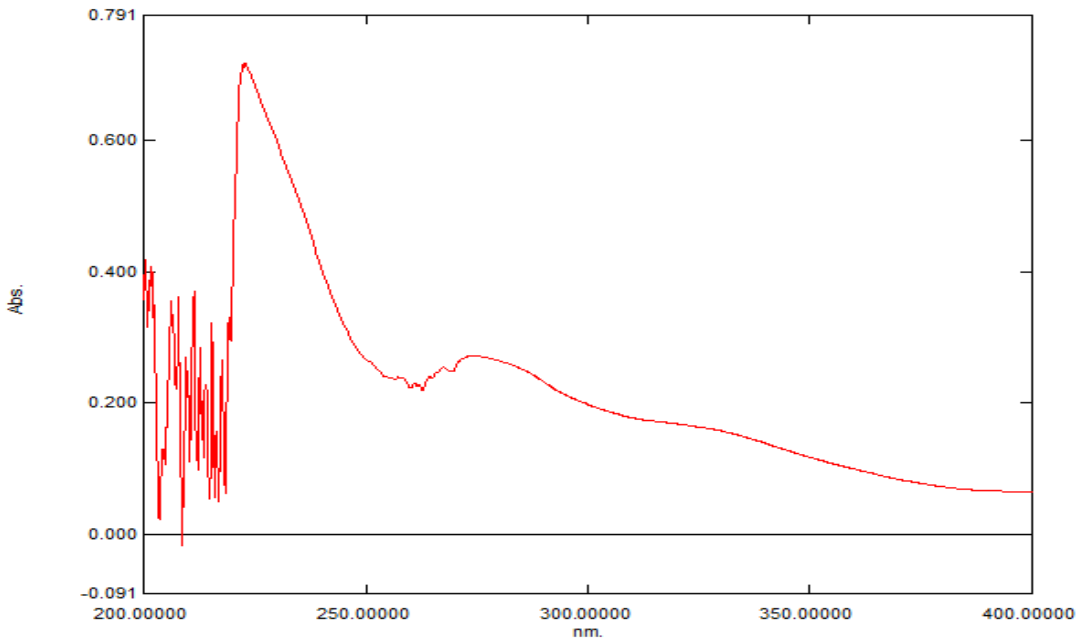


**Figure No 4 : (λ) max Spectrum of Metformin HCL**

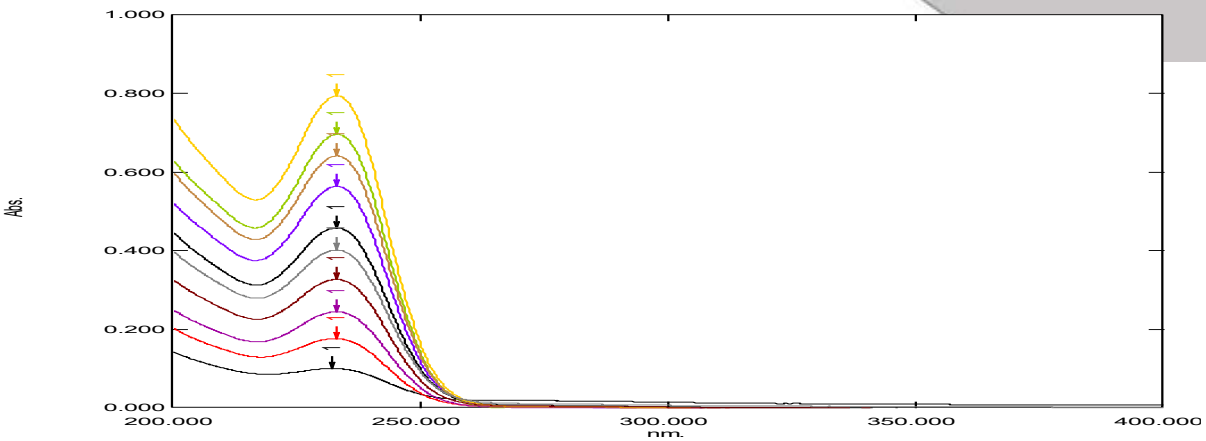
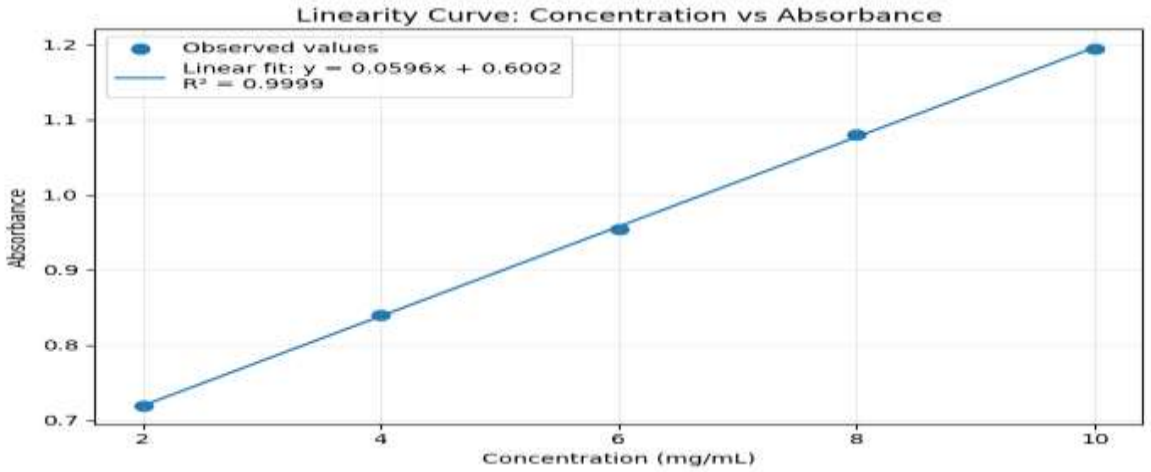



**Figure No 5 :Overlay Spectrum of Metformin HCL**




**Fig, NO 6 : Standard calibration curve of Metformin HCL**

**ATFTIR**

The spectrum was recorded in the wavelength region of 4000 to 400cm-1. A sample of The api was directly filled into the cavity of the sample holder and an IR spectrum was recorded using an ATR-FTIR spectrophotometer

**Cissus quadrangularis L**

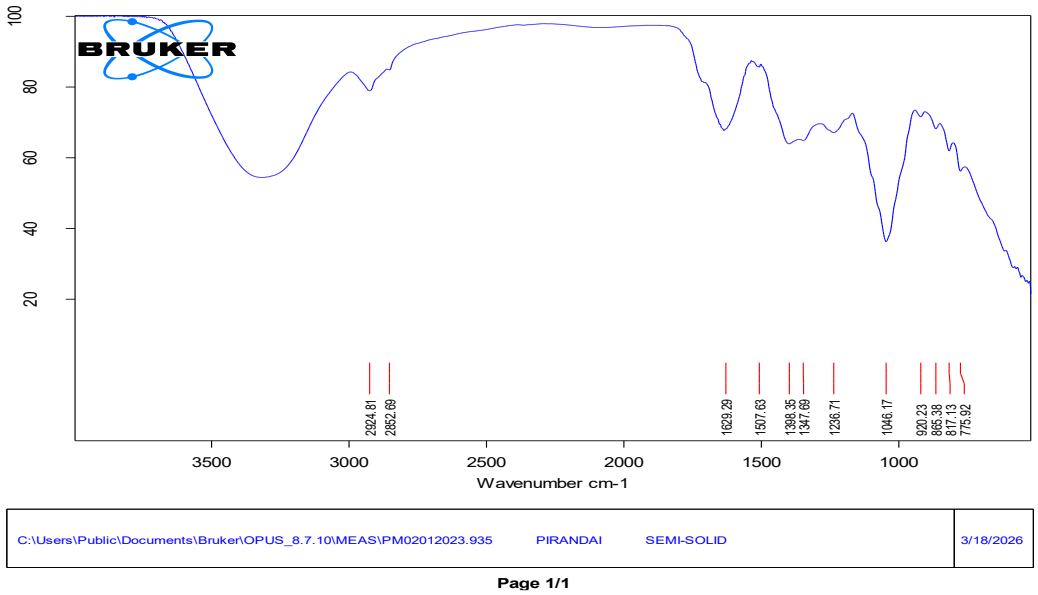


**Figure No 7: ATR-FTR spectrum of Cissus Quandrangularis**

**METFORMIN:**

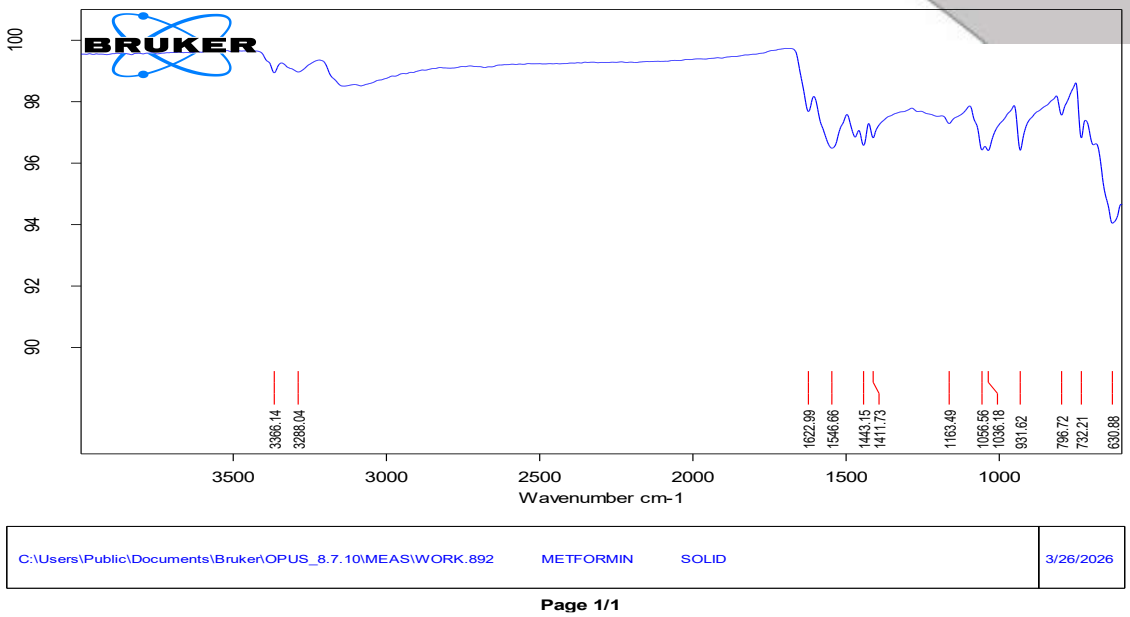



**Figure No 8 : ATR-FTR spectrum of Metformin HCL**

## EXTRACTION PROCEDURE[6]

**1.Petroleum ether extract**: The shade dried coarsely powdered Plant of Cissus Quandrangularis each (100g) was extracted was petroleum ether (60-80°C) until the extraction was completed. Distillation was used to eliminate the solvent after the extraction was completed. Light green was obtained. After that, the residue was placed in a desiccator.

**2.Chloroform Extract:** The marc left after Petroleum Ether extraction was dried and extracted with 2-3 liters of Chloroform (50.5-61.5°C) by continuous hot percolation using Soxhlet apparatus. After completion of extraction, it was filtered and the solvent was removed by distillation under reduced pressure. The extract was stored in desiccators. A brown color residue was obtained.

**3. Ethanol extract:** The marc left after $CHCl_3$ extraction was dried and then extracted with ethanol 95%v/v (75-78 °C), until the extraction was completed. Distillation was used to eliminate the solvent after extraction was completed. Light green residue was obtained. After that, the residue was placed in a desiccator.

**4.Aqueous Extract:** The marc left after Ethyl Acetate extraction was dried and macerated with 2-3 liters of Chloroform Water (0.25%) in mouthed bottle for three days. After completion of extraction it was filtered and the solvent was removed by distillation under reduced pressure. The extract was then store in desiccators. A black colour residue was obtained. All the above extracts were used for identification of constituents by Phytochemical tests, separation and isolation of plant constituents by "Chromatographic" studies. From the weight of drug, the extract content was calculated

$$\text{Extractive Value (\%)} = \frac{\text{Wt. of Extractive}}{\text{Wt. of Drug}} \times 100$$

**Sustained-Release Layer – Cissus quadrangularis by Direct Compression Method**

The required quantities of Cissus quadrangularis extract, microcrystalline cellulose, HPMC, and other excipients were accurately weighed using an electronic balance[7]. All ingredients were separately passed through sieve No. 30 to remove lumps and obtain a uniform particle size. The Cissus quadrangularis extract was mixed with microcrystalline cellulose by geometric dilution, followed by the gradual incorporation of HPMC as the sustained-release polymer. The powder mixture was blended thoroughly for 10–15 minutes to ensure uniform distribution of the herbal extract and polymer. Magnesium stearate was then added as a lubricant and mixed gently for 3–5 minutes to avoid over-lubrication. The final blend was evaluated for flow properties, including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The prepared blend was transferred into the hopper of a rotary tablet compression machine and compressed at an appropriate compression force to obtain a uniform and mechanically strong sustained-release layer. The prepared Cissus quadrangularis layer was

subsequently combined with the metformin layer during bilayer tablet compression and evaluated for post-compression parameters and sustained drug-release characteristics[8].

**Immediate-Release Layer – Metformin by Wet Granulation Method**

The required quantities of Metformin, lactose, HPMC, and microcrystalline cellulose were accurately weighed and mixed uniformly in a mortar and pestle for 10–15 minutes. Magnesium stearate was weighed separately and kept aside for lubrication. Purified water or a suitable aqueous binder solution was slowly added to the powder mixture with continuous stirring to form a damp mass. The wet mass was kneaded properly to obtain a uniform consistency and was passed through sieve No. 20 to produce wet granules of suitable size. The granules were dried in a tray dryer or hot-air oven at 40–50°C until the moisture content was below 5%. The dried granules were again passed through sieve No. 20 to remove aggregates and obtain uniform, free-flowing granules. Finally, the dried granules were lubricated with magnesium stearate by gentle mixing for approximately 5 minutes and passed through sieve No. 72 to ensure uniform distribution before compression into the immediate-release layer of the bilayer tablet[9].

**Figure No 9 :Bilayer Tablet**

**PHYSICOCHEMICAL PARAMETER:**

The physicochemical characteristics of Cissus quadrangularis obtained in the present study are summarized in Table No: 8.3

**Table No 3 :PHYSICOCHEMICAL PARAMETER**

| S/No | Parameter | Result |
|---|---|---|
| 1. | Loss on drying | 88.77 |
| 2. | Water extract (%) | 21.75 |
| 3. | Alcohol extract (%) | 4.74 |
| 4. | Petroleum ether extract (%) | 1.74 |
| 5. | Total ash value | 20.34 |
| 6. | Acid insoluble ash (%) | 1.10 |
| 7. | Water soluble ash (%) | 1.46 |

## DISCUSSION

Physicochemical analysis of the powdered Cissus quadrangularis revealed that the material had a value of extractives in water, alcohol, and petroleum ether, indicating the presence of various phytoconstituents. Thus, the ash values indicated the amount of inorganic matter present in the crude drug. The physicochemical parameters help in understanding the quality of the crude drug, which is necessary for the preparation of the sustained-release layer of the designed bilayer tablet

## RESULTS AND DISCUSSION:

**EVALUATION:**

**WEIGHT VARIATION:**

**Table No 4 :WEIGHT VARIATION**

| S/no | Weight of individual weight(y) | Average weight (x) | (x-y) | % Deviation (x-y/x) ×100 |
|---|---|---|---|---|
| 1. | 0.20 | 0.2 | 0 | 0 |
| 2. | 0.21 | 0.2 | -0.01 | -0.05 |
| 3. | 0.21 | 0.2 | -0.01 | -0.05 |
| 4. | 0.19 | 0.2 | 0.01 | 0.002 |
| 5. | 0.18 | 0.2 | 0.02 | 0.1 |
| 6. | 0.20 | 0.2 | 0 | 0 |
| 7. | 0,21 | 0.2 | -0.01 | -0.05 |
| 8. | 0.19 | 0.2 | 0.01 | 0.002 |
| 9. | 0.21 | 0.2 | -0.01 | -0.05 |
| 10. | 0.20 | 0.2 | 0 | 0 |
| Average= | 0.2 | | | ± 0.096 % |

Average weight of 10 tablet= 2.23
Average weight = 2.23/10=0.223gm
% deviation = 0.22-0.21/0.22 × 100
= 0.01 /0.22 × 100
= 0.045 × 100
= 4.5%

## DISCUSSION:

The tablets demonstrated acceptable weight uniformity with only minor variation among individual units. The calculated average tablet weight was 0.223 g, indicating consistency in the compression process and satisfactory control during tablet manufacture

**Friability**

prepared tablet: Friability testing was carried out using a Roche friabilator to evaluate the resistance of the tablets to abrasion and mechanical stress. Ten tablets were accurately weighed before the test, rotated for the specified number of revolutions, and reweighed after removal of dust. Percentage friability was calculated using the standard equation:
Initial weight of 10 tablets: 2.23
final weight of 10 tablets: 2.20
% of Friability = Initial weight of tablet- final weight of tablet / Initial weight of tablet × 100
= 2.23 -2.20 / 2.23 × 100
= 0.02 / 2.23 × 100
= 0.0008 × 100
= 0.8%

- % of friability of prepared tablet = 0.8
- The tablet does not obey the I.P limit >1% so the tablet Pass the friability test for tablets.

**DISCUSSION:**

The prepared tablets exhibited a friability value of 0.8%, indicating satisfactory resistance to mechanical abrasion. Since the observed friability was below the pharmacopoeial acceptance limit of 1.0%, the formulation demonstrated adequate mechanical durability for routine handling and transportation.

**HARDNESS**

**Prepared tablet:**
Tablet hardness was evaluated using a Monsanto hardness tester to determine the mechanical strength of the compressed bilayer tablets. Three tablets were randomly selected, and the crushing strength required to fracture each tablet was recorded

**Table No 5 :HARDNESS**

| S/No | Initial | Final | Hardness |
|---|---|---|---|
| 1. | 0 | 3 | 3 kg/cm² |
| 2. | 0 | 3 | 3 kg/cm² |
| 3. | 0 | 4 | 4 kg/cm² |

Average of the hardness of tablets= 3+3+4/3
= 10/3
= 3.3 kg/cm²

**DISCUSSION:**
The average hardness of the prepared tablets was found to be 3.3 kg/cm², indicating sufficient mechanical strength to withstand handling, packaging, transportation, and storage while maintaining acceptable tablet integrity.

**DISINTEGRATION TEST:**
Disintegration testing was performed to evaluate the time required for complete tablet disintegration under prescribed experimental conditions. The test was conducted using a standard tablet disintegration apparatus maintained under pharmacopoeial conditions.
Uncoated tablets = 5-15 mins
prepared tablets = 7 mins

- The disintegration test for the given tablet was found to be 7 mins
- As, it obey the IP standard.it passes disintegration test

**DISCUSSION:**
The prepared bilayer tablets exhibited a disintegration time of 7 min, indicating satisfactory performance of the immediate-release layer. The observed value complied with the acceptable limits for uncoated tablets reported in the present investigation and confirmed the suitability of the formulation for rapid initial drug release.

**DISSOLUTION:**
1.Determine concentration from calibration curve: 40 µg/mL
2.Amount of drug dissolved:
Drug Released (mg)= Concentration(µg/mL) ×Volume(mL) / 1000
= 40×900/1000
=36mg

3.Percentage Drug Release:
%Drug Release= Drug Released (mg)/ Label Claim (mg) ×100
If Metformin label claim = 500 mg:
%Release= 36 / 500 ×100
=7.2%

**DISCUSSION:**
The dissolution study indicated a calculated drug concentration of 40 µg/mL, corresponding to 36 mg of dissolved drug and an estimated 7.2% drug release based on the reported calculation. The obtained data provide preliminary information regarding the release behaviour of the developed formulation under the experimental conditions described in the study.

## SUMMARY AND CONCLUSION

The research was carried out to develop and evaluate a herbo-allopathic bilayer tablet of Metformin hydrochloride and Cissus quadrangularis extract for the management of Type 2 Diabetes Mellitus.
The purpose of the research work is to reduce the adverse effect caused by the allopathic drug such as joint paints caused due to the prolonged use of metformin for the diabetic patient. The plant extract of cissus quadrangularis having the phytoconstituents helps to reduce the joint pain and maintain calcium decrease in the body. Hence the study was to caused to formulate the bilayer formulation. The study was conducted on the rationale to provide the rapid onset of action of Metformin hydrochloride and the prolonged efficacy provided by Cissus quadrangularis extract. The plant extract was authenticated and subjected to physical, chemical identification tests and preliminary phytochemical screening. Solubility studies, uv-vis spectroscopy analysis, ATR-FTIR compatibility studies were done as a part of pre-formulation studies to evaluate the physicochemical properties of the drug, herbal extract and polymer used. Bilayer tablets of Metformin hydrochloride and Cissus quadrangularis extract were prepared by direct compression method using various polymers to obtain an immediate release of Metformin hydrochloride from the upper layer of the tablet and sustained release of Cissus quadrangularis extract from the lower layer of the tablet. Pre-compression and post-compression parameters like flow properties, weight variation, tablet hardness, thickness, friability, disintegration time, drug content, in-vitro dissolution and accelerated stability studies were performed to check the suitability and compatibility of the herbal preparation with the synthetic drug. The pre-compression and post-compression parameters of the optimized batch were found to be satisfactory and were well within the pharmacopoeial limits. It was concluded that the herbo-allopathic bilayer tablet formulation could be helpful in the management of Type 2 Diabetes Mellitus. The bilayer tablet of Metformin hydrochloride and Cissus quadrangularis extract might help to reduce the dose of each formulation, improve the bioavailability of the drug, increase the level of patient compliance and decrease side effects and toxicity caused due to the synthetic drug. The combined effect of the herbal extract and synthetic drug could help to reduce the progression of the disease and lead to better control over the disease. In summary, the research concluded the successful development of a herbo-allopathic bilayer tablet of Metformin hydrochloride and Cissus quadrangularis extract for the management of Type 2 Diabetes Mellitus.

**ACKNOWLEDGEMENT**
The authors are thankful to Vinayaka Mission's College of Pharmacy for providing the necessary laboratory for the completion of the research work Funding Sources: The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest**: The author(s) do not have any conflict of interest. Data Availability Statement This statement does not apply to this article.

**Ethics Statement:** This research did not involve human participants, animal subjects, or any material that requires ethical approval.

**Informed Consent Statement**: This study did not involve human participants, and therefore, informed consent was not required.

**Clinical Trial Registration**: This research does not involve any clinical trials. Author's contribution Dr. M.V. Kumudhavalli: Project Supervision, Data Analysis, writing, Review and editing; P.Sokkalingam: Project conduction, methodology , Writing- original draft

## REFERENCES:

1. Ubhe TS, Gedam P. A brief overview on tablet and it's types. Journal of Advancement in Pharmacology. 2020 Oct 27;1(1):21-31.
2. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM. Review of bilayer tablet technology. International journal of pharmaceutics. 2014 Jan 30;461(1-2):549-58.
3. Ebadi AG. Synergistic approaches in diabetes management: The role of anti-diabetic drugs and herbal medicine in therapeutic strategies. Nepal Journal of Medical Sciences. 2025 Jun 30;10(2):68-82.
4. Powers AC, Niswender KD, Evans-Molina C. Diabetes mellitus: diagnosis, classification, and pathophysiology. Diabetes. 2022;1000(415):3195-204.
5.Bhawana M, Deepak P, Suraj G, Akash G, Ramnarayan YS, Ashok NK. Chemical Detoxification of Therapeutic Hybrid Complexes Prepared by the Compatible Combination of Ayurvedic Herb and Allopathic Drug. Current Indian Science. 2023 Jan;1(1):E050423215447.

6.Kaur J, Ghoshal G, et al. LC/MS guided identification of metabolites of different extracts of Cissus quadrangularis. Food Chem Adv. 2022;1:100084. doi:10.1016/j.focha.2022.100084
7.Taylor KMG, Aulton ME, editors. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 6th ed. Amsterdam: Elsevier; 2022.
8.Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1987.
9. Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 4th ed. New York: Marcel Dekker; 2002.